

UNIVERSITY OF NICOSIA

From Awareness to Clinical Practice: Protein
Knowledge, Dietary Behavior, and Implementation of a
Plant-Dominant Low-Protein Diet (PLADO) in Cypriot
Renal Patients.

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PhD (Doctor of Philosophy) in Nutrition and Dietetics

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Abstract

Chronic kidney disease (CKD) represents a growing global public health challenge, with dietary management constituting a cornerstone of conservative treatment. Traditional low-protein diets (LPDs), although effective in slowing CKD progression, often rely heavily on animal-based protein sources, contributing to increased dietary acid load, phosphorus burden, and reduced long-term adherence. Emerging evidence supports plant-dominant dietary strategies; however, region-specific clinical application within Mediterranean populations remains limited. The present multi-phase study aimed to evaluate the clinical effectiveness and implementation feasibility of a culturally adapted plant-dominant low-protein diet (PLADO) in slowing CKD progression among Cypriot patients, compared to a conventional low-protein dietary approach.

The research design comprised four integrated phases: (1) a comprehensive literature review establishing the scientific rationale for PLADO; (2) development and validation of a questionnaire assessing protein-related knowledge, dietary behaviors, and perceptions; (3) a cross-sectional baseline analysis evaluating Mediterranean diet adherence, anthropometric indices, and CKD prevalence; and (4) a nine-month controlled intervention study involving 60 adults with CKD allocated to either a PLADO group or a conventional KDOQI-based low-protein diet group. Renal biomarkers—including estimated glomerular filtration rate (eGFR), serum creatinine, and serum urea—were measured alongside metabolic and inflammatory parameters such as serum phosphorus, potassium, lipid profile, acid–base balance, hemoglobin, albumin, and C-reactive protein (CRP). Multivariable logistic regression and ROC curve analyses were performed where applicable.

The questionnaire phase revealed significant variability in nutrition literacy, with notable knowledge gaps among younger and less-educated participants. Higher Mediterranean diet adherence was independently associated with lower odds of CKD (OR = 0.81, $p < 0.001$). In the intervention phase, the PLADO group demonstrated clinically meaningful improvements in key renal biomarkers, including greater reductions in serum creatinine and urea levels and a more pronounced increase in eGFR compared to the conventional low-protein diet group. Notably, inflammatory status improved substantially in the PLADO group, with marked reductions in CRP levels, suggesting potential anti-inflammatory effects of plant-dominant protein sources. Improvements were also observed in lipid profile parameters and acid–base

balance, while electrolyte stability indicated metabolic safety and absence of clinically significant hyperkalemia. Although not all outcomes reached statistical significance, the direction and magnitude of biomarker changes consistently favored the PLADO intervention.

Overall, this study provides preliminary clinical and contextual evidence supporting the feasibility, safety, and potential nephroprotective properties of a culturally adapted plant-dominant low-protein diet within a Mediterranean CKD population. By integrating biomarker monitoring, nutrition literacy assessment, and sustainability considerations, the findings contribute to the evolving field of precision renal nutrition. Larger randomized controlled trials are warranted to confirm long-term efficacy and generalizability, but the present research establishes an important foundation for implementing plant-dominant dietary strategies in CKD management.

Keywords: Chronic Kidney Disease (CKD); Plant-Dominant Low-Protein Diet (PLADO); Renal Biomarkers; Mediterranean Diet; Dietary Protein Restriction; eGFR; Inflammation; Nutrition Literacy; Sustainable Diets; Acid–Base Balance; Logistic Regression; Clinical Nutrition Intervention.

Dedication

To my renal patients, whose trust and strength gave meaning to this work.

To my mentors, especially Prof. Eleni Andreou, for their guidance, insight, and for challenging me to think beyond limitations. Thank you for everything.

To my mother, who carried everything so I could stand where I am today. I love you mom.

To my husband, who walked beside me through the most demanding and transformative years of this journey. Thank you for your patience, your strength, and your unwavering belief in me.

And to the version of myself who began this journey, for the courage to start and the determination to finish.



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I am equally thankful to the members of my advisory and examination committee for their valuable feedback, constructive comments, and thoughtful discussion that strengthened the quality and the scientific depth of this work.

My sincere appreciation goes to the nephrologists, dietitians, students, and academia personnel who contributed to the validation of the questionnaire and supported the implementation of the PLADO intervention. Their clinical expertise was essential to ensure the methodological robustness and real-world applicability of this research.

I would like to also thank the renal patients who participated in this study as well as everyone who volunteered. Their trust, commitment, and willingness to engage in a 6-month dietary intervention made this research possible. Their willingness to participate in a nutritional educational study remain the main foundation of this work.

Special thanks are extended to all the students who contributed to the all the phases of the study.

I owe my deepest gratitude to my mother, who has been the foundation of everything I have achieved. Through her tireless hard work, strength, and firm dedication , she created every opportunity that shaped my academic journey. From the beginning of my life, she chose me, raised me, and shaped me with unconditional love and courage. She supported my journey far beyond what words can capture, Sending me to UK for my bachelor's degree, standing behind me though two years of master's studies, and walking silently beside me through five demanding years of doctoral research. She never complained, never hesitated, and never allowed me to doubt that I was capable of more. Every opportunity I was given was built on her strength. Every milestone I reached was rooted in her belief. This achievement rests on the years she carried everything so that I would never have to carry it alone. This PhD is as much hers as it is mine.

To my husband, thank you for walking beside me through the most challenging and transformative years of this journey. Your patience, encouragement, and quiet strength gave me stability when the path felt overwhelming. Thank you for believing in me, for celebrating every milestone, and for reminding me of who I am beyond academia. Thank you for carrying the everyday burdens so I could carry this dream. For the warm meals waiting for me after long days, and for the warmth you bring into my life.

This thesis represents more than academic achievement; it reflects resilience, sacrifice, partnership, and love. I carry forward not only the knowledge gained through this research, but the strength and gratitude shaped by this journey.



Declaration

I declare that the work in this thesis was carried out in accordance with the regulations of the University of Nicosia. This thesis has been composed solely by myself except where stated otherwise by reference or acknowledgment. It has not been previously submitted, in whole or in part, to this or any other institution for a degree, diploma or other qualifications.

Signed


Date .11/06/2026.....



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Abbreviation Index

ACE: Angiotensin-Converting Enzyme, 28

ACR: Albumin-to-Creatinine Ratio, 17, 25, 26

AER: Albumin Excretion Rate, 25; Albuminuria, 25

AGEs: Advanced Glycation End Products, 38

ARBs: Angiotensin Receptor Blockers, 28, 58, 78

BCAAs: Branched-Chain Amino Acids, 87

BIA: Bioelectrical Impedance Analysis, 47

BMI: Body Mass Index, 31, 39

BSA: Body Surface Area, 23

BUN: Blood Urea Nitrogen, 50, 119

CHRIS: Cooperative Health Research in South Tyrol, 273

CI: Confidence Intervals, 159

CKD: Chronic Kidney Disease, 2

CKD-MBD: Chronic Kidney Disease – Mineral and Bone Disorder, 33

CKD-PM: CKD-Progression Model, 21

CKM: Cardiovascular-Kidney-Metabolic, 51

CO₂: Carbon Dioxide, 40

CRF: Chronic Renal Failure, 17

CRM: Cardio-Renal-Metabolic, 51

CRP: C-reactive Protein, 35; C-Reactive Protein, 20

CT: Computed Tomography, 22

CVD: Cardiovascular disease, 27

DALY: Disability-Adjusted Life Year, 30

DASH: Dietary Approaches to Stop Hypertension, 56

DEXA: Dual-energy X-ray Absorptiometry, 47

DIAAS: Digestible Indispensable Amino Acid Score, 94

DIALECT-1: DIAbetes and LiFEstyle Cohort Twente-1, 260

DKD: Diabetic Nephropathy, 19

DSI: Dialysis Symptom Index, 30

EAA: Essential Amino Acids, 87

EAR: Estimated Average Requirement, 94

EFA: Exploratory Factor Analysis, 139

eGFR: Estimated Glomerular Filtration Rate, 23

eGFRcr-cys: Estimated Glomerular Filtration Rate by Creatinine and Cystatin C, 23

EKFC: European Kidney Function Consortium, 24

EOSS: Edmonton Obesity Staging System, 47

ESAs: Erythropoiesis-Stimulating Agents, 79

ESPEN: European Society for Clinical Nutrition and Metabolism, 82

ESRD: End-Stage Renal Disease, 2

FFM: Fat-Free Mass, 47

FGF23: Fibroblast Growth Factor-23, 34

FM: Fat Mass, 47

GBD: Global Burden of Disease, 30

GBM: Glomerular Basement Membrane, 18

GeSY: General Healthcare System of Cyprus, 76

GFAT: Gluteofemoral Fat, 47

GFR: Glomerular Filtration Rate, 2

HDL: High-Density Lipoprotein Cholesterol, 39

HTN: Hypertension, 44

IL-: Interleukin-, 20

IL-1: Interleukin-1, 35

IL-6: Interleukin-6, 35

ISRNM: International Society of Renal Nutrition and Metabolism, 144

KA: Ketoacids, 87

KDIGO: Kidney Disease; Improving Global Outcomes, 2

KDOQI: Kidney Disease Outcomes Quality Initiative, 2

KDQOL: Kidney Disease Quality of Life, 29

KFRE: Kidney Failure Risk Equation, 22

KRT: Kidney Replacement Therapy, 22

LPD, 62; Low-Protein Diet, 3

MESA: Multi-Ethnic Study of Atherosclerosis, 70

mGFR: Measured Glomerular Filtration Rate, 23

MNT: Medical Nutrition Therapy, 61

MPS: Postprandial Muscle Protein Synthesis, 92

MRI: Magnetic Resonance Imaging, 47

MUFA: Monounsaturated Fatty Acids, 39

MUST: Malnutrition Universal Screening Tool, 145

NCD: Non-communicable Disease, 12

NCDs, 74

NHANES: National Health and Nutrition Examination Survey, 34; National Health Nutrition Examination Survey, 49

NHHR: Non-HDL to HDL Cholesterol Ratio, 42

NICE: National Institute for Health and Care Excellence, 39; National Institute of Health and Care Excellence, 29

NT-proBNP: N-terminal pro-B-type natriuretic peptide, 54

OR: Odds ratios, 159

PAL: Physical Activity Level, 49

PDCAAS: Protein Digestibility-Corrected Amino Acid Score, 94

PEW: Protein-Energy Wasting, 64, 79

PLADO, 67; Plant-Dominant Low-Protein Diet, 4

pmp: Per Million Population, 31

POS-r: Palliative Outcome Symptom-Scale renal, 30

PREVEND: Prevention of Renal and Vascular End-stage Disease, 49

PTH: Parathyroid hormone, 33

PUFA: Polyunsaturated Fatty Acids, 39

RAAS: Renin-Angiotensin-Aldosterone System, 38

RAS: Renin-Angiotensin System, 44

RCT: Randomized Controlled Trial, 66

RCTs: Randomized Controlled Trials, 4

RDA: Recommended Dietary Allowance, 94

RDNs: Registered Dietitian Nutritionists, 61

ROS: Reactive Oxygen Species, 19

RRT: Renal Replacement Therapy, 20

SAH: S-Adenosyl-Homocysteine, 3

SAT: Subcutaneous Adipose Tissue, 48

SF: Self-Reported, 30

SFAs: Saturated Fatty Acids, 40

SGLT2: Sodium-glucose cotransporter-2, 35

SHARP: Study of Heart and Renal Protection, 78

SMI: Skeletal Muscle Mass Index, 65

sVLDP: Very-Low-Protein Diet Supplemented with Ketoanalogues, 4

T2DM: Type 2 Diabetes Mellitus, 22

TBK: Total Body Potassium, 47

TID: True Ileal Digestibility, 95

TLGS: Tehran Lipid and Glucose Study, 70

TNF- α : Tumor Necrosis Factor- α , 35

TOHP: Trials of Hypertension Prevention, 56

UA/CR: Urine Albumin/Creatinine Ratio, 22

UACR: Urinary Albumin-to- Creatinine Ratio, 2

US: United States, 49, 85

VAT: Visceral Adipose Tissue, 48

VLPD, 62; Very Low-Protein Diet, 87

WHO: World Health Organization, 32

WHR: Waist-to-Hip Ratio, 46

WHtR: Waist-to-Height Ratio, 46

CHAPTER 1 INTRODUCTION

1.0 BACKGROUND AND RATIONALE

Chronic Kidney Disease (CKD) is a condition that affects more than 10% of the total population globally, which contributes to more than 800 million people. It is a progressive disease that occurs commonly in the general adult population, especially in people with diabetes and hypertension (Kalantar-Zadeh *et al.*, 2021). It is one of the leading causes of mortality around the world due to increased levels of diabetes, hypertension, and obesity (Maringhini and Zoccali, 2024). It is defined by constant abnormalities of kidney function or structure that have a negative impact on health; therefore, a progressive decrease of excretory kidney function can impact body homeostasis. Renal failure can be fatal if kidney transplant is not accessible, which is observed in several regions worldwide (Romagnani *et al.*, 2025).

A significant burden on healthcare systems across the world is the progression of CKD due to patients with impaired kidney function facing an increased risk of mortality, morbidity, and impairment of quality of life (Kovesdy, 2022). Studies reported that direct healthcare costs for renal failure will increase rapidly in the upcoming years, which will lead to renal failure facing severe economic challenges. This leads to the conclusion that early diagnosis and proactive management could decrease the disease progression rate (Chadban *et al.*, 2024).

Organizations such as Kidney Disease: Improving Global Outcomes (KDIGO) or Kidney Disease Outcomes Quality Initiative (KDOQI) developed criteria in order to define and diagnose CKD. Based on KDIGO, the two main criteria to define and diagnose CKD are glomerular filtration rate (GFR) below 60 mL/min per 1.73 m² for more than 3 months, with or without kidney damage, and persistent kidney damage for more than 3 months, defined by structural or functional abnormalities of the kidney, caused by either pathological abnormalities or markers of kidney loss (blood or urine abnormalities) (Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group, 2024). Normal kidney function is presented when eGFR is above 90 mL/min/1.73 m², whereas when eGFR is lower than 15 mL/min/1.73 m², kidney dysfunction is observed, therefore characterizing renal failure to stage 5 or end-stage renal disease (ESRD), where renal transplant or dialysis is needed (Satyanarayana R. Vaidya and Narothama R. Aeddula, 2025).

However, during the early stages of renal failure, eGFR from 89 to 45 mL/min/1.73 m², the disease goes unrecognized by both patients and healthcare practitioners due to the disease being asymptomatic. The main diagnostic criteria for kidney functioning are biomarkers such as eGFR and urinary albumin-to-creatinine ratio (UACR), serum creatinine, serum urea, 24-hour

urine creatinine, and urinary protein (Tangri *et al.*, 2023). Thus, stages 3 and 4 are important to diagnose early to determine how rapid the progression of the disease is. Early diagnosis and early management are they key strategies in reducing CKD progression rate and therefore improving patients' outcomes (MacLaughlin, Friedman and Ikizler, 2022).

Another economic burden of CKD is the use of expensive drug treatments, including erythropoiesis-stimulating agents, phosphate and potassium binders, and calcium mimetics, as well as renal replacement therapies such as hemodialysis, peritoneal dialysis, and kidney transplant in more advanced stages of renal failure (Wang *et al.*, 2016). Based on these, the importance and use of effective disease management strategies were developed. One of the main strategies is nutritional and dietary management. Patients with impaired kidney function should receive individualized meal plans from expert clinician dietitians that are tailored to the severity of CKD, focusing on salt, phosphate, potassium, and protein intake (Ikizler, Talat Alp and Cuppari, 2021).

More specifically, the main focus of nutrition therapy in renal failure management is protein restriction. Several studies, trials, and meta-analyses conducted showed evidence of the effectiveness of limiting protein intake as well as other nutritional interventions on kidney outcomes. Higher dietary protein intake is known to increase the kidneys' workload, leading to glomerular filtration, increased renal pressure, and rapid increase in kidney damage progression (Ko, Gang-Jee *et al.*, 2020). Therefore, a low-protein diet (LPD) is often recommended for patients with CKD to reduce kidney stress, with the total protein intake being from 0.6 g/kg/day to 0.8 g/kg/day, with more than half of the total protein being high-biological value. The source of protein for LPDs is mainly animal-based protein in order to reduce the risk of malnutrition or anemia that may occur when reducing the total protein intake (Pereira, C. D. *et al.*, 2024). The use of animal-based products in LPDs is mainly due to their increased biological value, which contributes to the presence of essential amino acids. Studies reported that in dialysis patients with low albumin levels, when consuming high-protein meals during dialysis combined with lanthanum carbonate administration, serum albumin levels increased by 0.2 mg/dL while maintaining serum phosphorus within target value (Rhee *et al.*, 2017). However, animal sources are rich in sulfur-containing amino acids (methionine, cysteine), which increase the acid load in the body and produce toxic products, such as homocysteine and s-adenosyl-homocysteine (SAH), which contribute to the development of metabolic acidosis (Jiao *et al.*, 2024).

Another guideline was the effect of a very-low-protein-diet (sVLPD) supplemented with essential amino acids and keto-analogues in CKD progression and management. This diet is described by restricting protein intake more than the conventional LPD. Total protein intake of sVLPD is from 0.3 to 0.4 g/kg/day. A recent study that compared these two diets, sVLPD and LPD, found that sVLPD is nutritionally safe and could delay the dialysis initiation in some patients with CKD (Garneata *et al.*, 2016).

Moreover, an alternative to these diets with a 0.7 g/kg/day protein intake vegan diet has emerged, which aims to increase consumption of vegetables and fruits. This led to the development of a plant-dominant low-protein diet (PLADO). Thus, other nutritional recommendations of PLADO include low sodium intake, not exceeding 3 g/day; high fiber intake, contributing to 25-30 g/day; and adequate energy intake, 30-35 kcal/kg/day. The increase of shifting from animal-based products to vegetarian products has been encouraging for several reasons. For instance, plant-based products, especially fruits and vegetables, are kidney-protective; plant-based fats, such as olive oil, have anti-atherogenic effects (Haring *et al.*, 2017). Moreover, vegetarian proteins are high in antioxidants and phytochemicals, and there is evidence suggesting their protective role in developing insulin resistance and inflammation in individualized with CKD (Garibotto *et al.*, 2017). Lastly, one common complication in these patients is elevated phosphorus levels, especially those who consumed animal-based diets due to their higher animal phosphate content; therefore, consuming more plant phosphates has a lower bioavailability, which enables better phosphorus control in the blood (Michail and Andreou, 2025). In addition, plant-based diets have been shown to improve cardiovascular health, blood sugar management, and lipid profiles, all of which are beneficial for patients with CKD, who are at high risk of cardiovascular comorbidities (Carrero *et al.*, 2020). However, despite the beneficial properties of these diets, LPD, sVLPD, and PLADO, adherence is the main challenge for several people with CKD due to them being restrictive and culturally difficult to adopt with many patients' food preferences.

Despite the emerging increase of research regarding PLADO in patients with CKD, there are limited randomized controlled trials (RCTs) assessing the effectiveness of the diet for a longer period of time. Thus, research investigating the use of vegetarian, vegan, or plant-based diets in CKD populations has been focused on Western countries that follow Western dietary guidelines, with less attention to the cultural adaptation of such diets in the Mediterranean countries, such as Cyprus.

The population in Cyprus mainly follows Mediterranean guidelines, which include the use of vegetables, legumes, and olive oil that are highly consumed; however, there is a significant number of animal-based products in the Cypriot culture, such as lamb, poultry, and fish. Therefore, this leads to the unique opportunity to investigate the relation and adaptation of PLADO and how it could be implemented into local dietary habits without causing significant changes to the traditional food culture or complications regarding CKD.

Considering all of the above, the current study aimed to assess the feasibility, effectiveness, and cultural acceptability of a PLADO nutritional intervention, which is intended to meet the needs and wants of the Cypriot population. PLADO's adaptation to Cypriot culinary traditions, this research will further investigate whether this dietary approach can improve renal function, reduce any complications, and improve the overall quality of life in Cypriot individuals with CKD, across all stages.

Moreover, this study was developed to reduce the burden of dietary adherence of standard LPDs by improving it and making it more individualized. Thus, insights from the study will provide important information regarding the cultural adaptation of vegetarian-protein renal diets, which is also a potential implication for other countries in the Mediterranean as well as similar populations that face challenges regarding CKD management.

Chapter 1 introduces renal failure and its importance regarding public health concern and highlights the importance of dietary interventions, such as protein restriction, in CKD management. Moreover, the following chapter emphasizes the need for adapting dietary interventions in the culture, especially following a specific dietary guideline, such as PLADO, by investing in its effectiveness, feasibility, and cultural acceptability. Thus, it addresses the gap in research by providing evidence that could inform dietary guidelines for patients with CKD across all stages in the Mediterranean regions. Lastly, results of the research have the potential to impact nutrition practices and improve renal care outcomes for populations facing similar dietary and health challenges.

1.1 PROBLEM STATEMENT AND RESEARCH JUSTIFICATION

Current nutritional recommendations for chronic kidney disease (CKD), including protein restriction strategies and plant-forward dietary patterns, are largely derived from studies conducted in North American and Northern European populations. Mediterranean countries, including Cyprus, remain underrepresented in interventional and longitudinal CKD nutrition

research. Given the substantial influence of cultural dietary practices on food selection, protein sources, and long-term adherence, the direct transferability of existing evidence to the Cypriot context remains uncertain.

Although emerging literature supports the potential benefits of plant-dominant low-protein diets (PLADO) in slowing CKD progression, improving metabolic parameters, and reducing dietary acid load, robust evidence from Mediterranean populations is limited. More specifically, there is insufficient data evaluating the feasibility, adherence, and biomarker response to PLADO within dietary patterns traditionally characterized by mixed plant–animal protein intake, such as the contemporary Cypriot diet.

Conventional low-protein diets (LPDs) implemented in clinical practice in Cyprus often emphasize high-biological-value animal protein sources to prevent protein-energy wasting. However, this approach may inadvertently increase dietary phosphorus burden, net endogenous acid production, and cardiovascular risk—factors known to contribute to CKD progression and morbidity. Furthermore, restrictive dietary prescriptions may reduce dietary variety and compromise long-term adherence, thereby limiting clinical effectiveness.

Accordingly, there is a critical need to evaluate whether a culturally adapted plant-dominant low-protein dietary model can achieve renal protective benefits while maintaining acceptability and adherence within the Cypriot CKD population. This study seeks to address this gap by systematically examining the feasibility, clinical efficacy, and implementation potential of PLADO in Cypriot patients across CKD stages, thereby generating context-specific evidence to inform regional dietary guidelines and optimize nutritional management strategies.

1.2 GAPS IN CURRENT RESEARCH

Renal failure has become a significant global health concern, with increasing prevalence and a growing burden on healthcare systems. While much research has focused on the impact of dietary interventions in managing CKD, significant gaps remain in our understanding of how specific diets and nutritional strategies affect CKD progression over time.

1.2.1. Lack of Long-term Intervention Studies

One of the most notable gaps in current research on renal nutrition is the lack of long-term intervention studies examining the effects of dietary changes on CKD progression. While many short-term clinical trials have shown positive effects of dietary modifications, such as protein

restriction, plant-based diets, and phosphorus control, there is insufficient evidence regarding their long-term efficacy in delaying disease progression and improving outcomes such as kidney function and quality of life for patients with CKD. Thus, most studies conducted so far are either cross-sectional or relatively short duration, often lasting only a few months (Palmer *et al.*, 2017). As a result, the long-term effects of several nutritional interventions on the clinical outcomes of patients with CKD are largely unknown. Longitudinal studies that track the effects of dietary changes over several years are necessary to provide stronger evidence about the potential of diets to prevent CKD progression to ESRD or the need for dialysis. However, long-term studies in renal nutrition are difficult to conduct due to challenges such as patient adherence, nutritional compliance, and variations in disease progression (Beto, Schury and Bansal, 2016). Although advancements in technology, such as genetic profiling, biomarkers, and digital health platforms, can overcome these challenges by allowing for better tracking of patients and providing more precise measurements of dietary adherence and clinical outcomes. Thus, these studies should focus on multiple aspects, including kidney function, proteinuria, nutrient deficiencies, and cardiovascular health. Moreover, exploring the impact of dietary changes on health-related quality of life, and psychosocial factors will provide a more holistic understanding of how nutrition influenced the overall well-being of patients with impaired kidney function.

1.2.2. Personalized Nutrition in CKD

Personalized nutrition is an emerging field that seeks to tailor dietary recommendations to individuals based on factors such as genetics, metabolism, and clinical characteristics. In CKD, personalized nutrition could significantly improve patient outcomes by recognizing the diverse needs and responses of different individuals. For instance, patients with CKD are genetically and metabolically heterogeneous, meaning that a dietary intervention that benefits one patient might not benefit another. Research into nutrigenomics and nutrimetabolomics is essential. These approaches could lead to more targeted, individualized dietary recommendations, considering genetic variants that affect protein metabolism, electrolyte balance, and inflammation (Zeisel, 2007). Moreover, patients with CKD vary widely based on their disease stage, comorbidities, age, gender, and lifestyle factors. Personalized nutrition takes these clinical factors into account, which may help address the chronic malnutrition seen in patients diagnosed with CKD and reduce the risk of complications such as cardiovascular disease, malnutrition, and muscle wasting. Technology advancements such as artificial intelligence, and bioinformatics provide opportunities to analyze large datasets to create more personalized

nutrition models for people with impaired kidney function (Wu, X. *et al.*, 2025). Further research into the role of personalized nutrition in CKD is crucial to develop effective interventions that consider the biological diversity of patients and their specific nutritional needs.

1.2.3. Effectiveness of Plant-Based Diets in CKD

Recent years, evidence-based research have been highlighting the importance of following more plant-based diets in preventing and managing diseases caused by lifestyle habits, including renal failure (Katz and Meller, 2014). Reducing animal protein and adding more plant-based foods in peoples' diets may decrease dependence on nephroprotective medications, reduce CKD complications, and potentially decrease the disease's progression rate, therefore better patient survival rates (Marrone *et al.*, 2025). There are some concerns regarding implementing plant-based diets such as increased potassium levels and protein deficiency, however when implementing correctly by clinical dietitians the overall risk-benefit ratio tends to increasingly support the adoption of vegetarian plant-based diets.

While there is growing evidence supporting the benefits of plant-based diets for overall health there is need for more rigorous research specifically examining the efficacy of plant-based diets in managing CKD at all stages. Plant-based diets, especially those focusing on vegetarian or vegan approaches, have been shown to offer several benefits in health, but more studies are needed to confirm their long-term impact on kidney function and disease progression. Existing research on plant-based diets in CKD has been limited to small studies, observational studies, and short-term interventions. Larger multicenter clinical trials are needed to evaluate the long-term impact of plant-based diets on kidney function, proteinuria, and overall health in patients with CKD (Kaimori *et al.*, 2025). These trials should focus on several stages of CKD and examine how dietary modifications influence dialysis initiation, ESRD progression, and cardiovascular risks. Thus, people with kidney dysfunction from different ethnic groups may respond differently to plant-based diets due to genetic and cultural factors. It is crucial to conduct studies across diverse populations to understand how vegetarian diets can be optimized for different groups (Norton *et al.*, 2016). For instance, the Mediterranean diet, which emphasizes in plant-based foods, may be more appropriate for European countries, while Asian or African populations may require more tailored plant-based interventions due to differences in dietary habits and nutritional needs. Plant-based diets may help to reduce phosphorus levels, blood pressure, and inflammation, all of which are contributing factors in CKD management. Further research into the mechanisms behind these effects, such as reduced acid load, improved

vascular health, and microbiome modulation, is needed to build a comprehensive understanding of how plant-based diets can be used effectively in CKD treatment.

The exploration of unexplored areas in renal nutrition indicates several opportunities for advancing our understanding of CKD and its management through diet. The need for more long-term intervention studies, the potential of personalized nutrition, and the need for more robust research into the effectiveness of plant-based diets all offer significant contribution for further investigation. Addressing these gaps in research will help refine dietary interventions, improve clinical outcomes for patients with impaired kidney function, and contribute to the development of evidence-based guidelines for nutritional management in CKD.

Ethnic and cultural variability further complicates interpretation of existing findings. Dietary patterns differ substantially across populations, and genetic and sociocultural factors may influence metabolic response to plant-based interventions (Norton et al., 2016). For example, Mediterranean dietary traditions emphasize plant-based foods yet also incorporate significant animal protein intake. Whether structured plant-dominant low-protein diets (PLADO) can be effectively adapted within Mediterranean populations remains insufficiently investigated.

1.3 RESEARCH AIM AND OBJECTIVES

The primary aim of this study is to evaluate the clinical effectiveness and implementation feasibility of a culturally adapted plant-dominant low-protein diet (PLADO) in slowing the progression of chronic kidney disease (CKD) among Cypriot patients, compared to a conventional low-protein dietary approach.

The specific objectives of the study are:

1. To determine the effect of PLADO on renal function decline, as assessed by changes in estimated glomerular filtration rate (eGFR), serum creatinine, and urea levels over the intervention period.
2. To evaluate the impact of PLADO on metabolic and biochemical parameters relevant to CKD progression, including serum phosphorus, potassium, acid–base balance, and inflammatory markers.
3. To compare dietary adherence rates, dietary satisfaction, and intervention feasibility between PLADO and conventional low-protein diet groups.

4. To assess the effect of PLADO on patient-reported outcomes, including quality of life and dietary acceptability.
5. To identify cultural, social, and economic determinants influencing adherence to PLADO within the Cypriot context.

1.4 RESEARCH QUESTIONS & HYPOTHESES

- **Primary Research Question**

Does a culturally adapted plant-dominant low-protein diet (PLADO) result in a slower decline in renal function compared to a conventional low-protein diet among Cypriot patients with CKD?

- **Secondary Research Questions**

1. What are the effects of PLADO on CKD-related metabolic and biochemical markers?
2. Does PLADO improve dietary adherence and patient satisfaction compared to conventional renal diets?
3. Does PLADO improve patient-reported quality of life?
4. What cultural and socioeconomic factors influence adherence to PLADO in Cyprus?

Hypotheses of the study:

H1 (Primary Clinical Hypothesis): Patients following PLADO will demonstrate a significantly slower decline in eGFR compared to those following a conventional low-protein diet over the intervention period.

H2 (Metabolic Hypothesis): Patients following PLADO will demonstrate significantly lower serum urea and phosphorus levels, and improved acid–base balance, compared to controls.

H3 (Patient-Reported Outcomes Hypothesis): Patients following PLADO will report significantly higher dietary satisfaction and quality of life scores compared to those following a conventional renal diet.

H4 (Adherence Hypothesis): Dietary adherence rates will be significantly higher in the PLADO group compared to the conventional low-protein diet group.

H5 (Implementation Hypothesis – If Using Regression Models): Cultural dietary preferences and food accessibility will significantly predict adherence to PLADO within the Cypriot population.

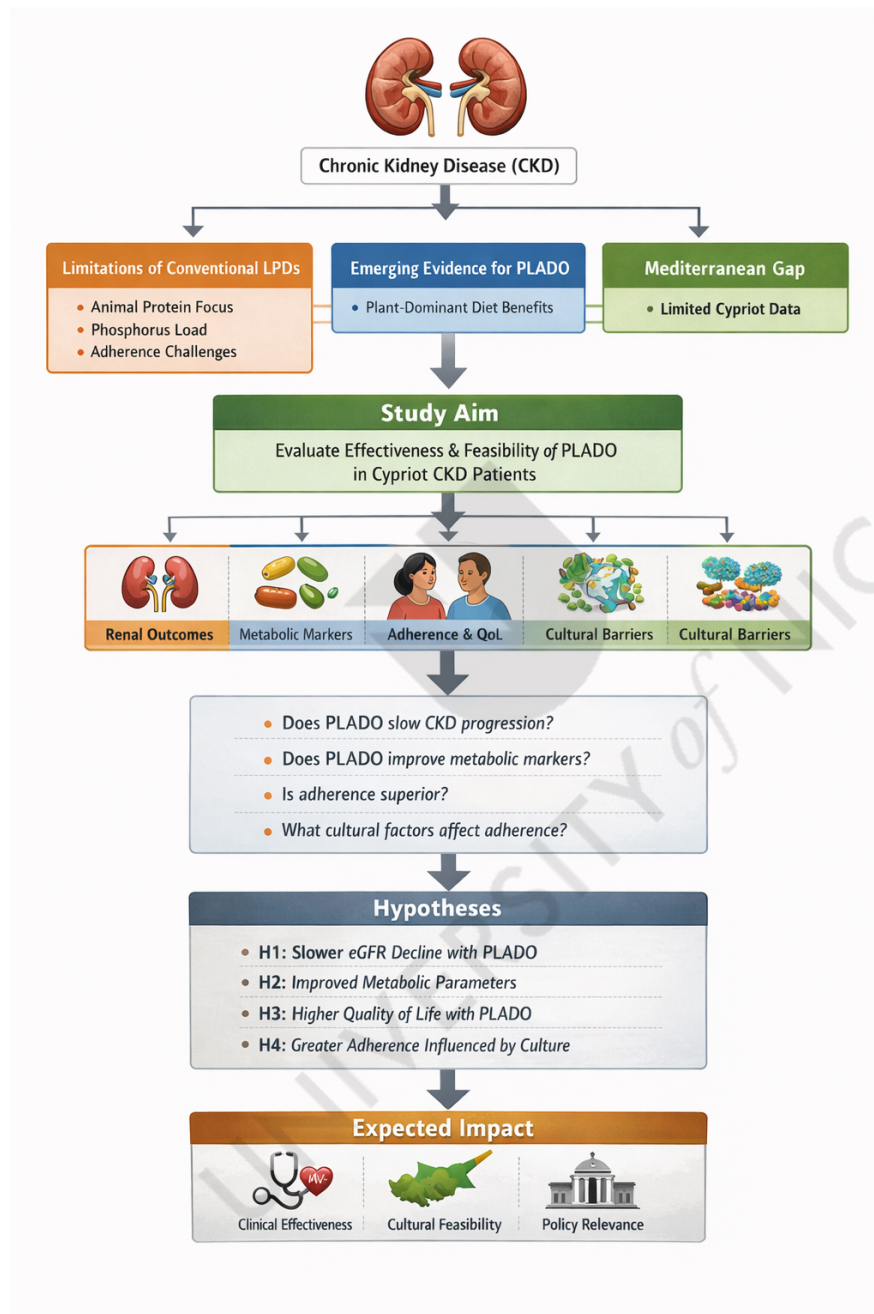


Figure 1.1: Graphical Aim, Objective, Research Questions, and Hypothesis.

1.5 SIGNIFICANCE OF STUDY

1.5.1. Impact on Clinical Nutrition and Nephrology

This study contributes to the advancement of clinical nutrition and nephrology by generating context-specific evidence on the effectiveness and feasibility of a plant-dominant low-protein diet (PLADO) in the management of chronic kidney disease (CKD). While low-protein dietary strategies are widely recommended in CKD care, uncertainty remains regarding optimal protein sources, long-term adherence, and cultural adaptability.

By systematically evaluating renal outcomes, metabolic parameters, and adherence within a Cypriot population, this research provides empirical data that may refine dietary prescription practices in nephrology. The findings may support a shift from predominantly animal-based low-protein models toward more plant-dominant approaches where clinically appropriate. Furthermore, the study contributes to understanding how traditional Mediterranean dietary patterns can be adapted within a structured renal nutrition framework, thereby bridging the gap between evidence-based dietary therapy and culturally grounded eating practices.

In addition, by integrating clinical outcomes with patient-reported measures and implementation considerations, this study extends beyond biochemical efficacy to address real-world applicability, an area often underrepresented in renal nutrition research.

1.5.2. Implications for Public Health and Policy

Beyond its clinical contribution, this study holds relevance for public health planning in Cyprus and similar Mediterranean contexts. Chronic kidney disease represents a growing non-communicable disease (NCD) burden with significant economic and healthcare implications. Nutritional strategies that are both effective and culturally sustainable may serve as cost-effective interventions to delay CKD progression and reduce reliance on dialysis and other high-cost treatments.

If plant-dominant dietary models are shown to be clinically beneficial and feasible, the findings may inform the development of national dietary guidelines, renal nutrition protocols, and structured dietary counseling programs. Moreover, the promotion of plant-forward dietary patterns aligns with broader public health objectives, including cardiovascular risk reduction, metabolic disease prevention, and sustainable food system development.

By generating localized evidence, this study supports data-driven decision-making in clinical and public health nutrition, potentially contributing to more culturally responsive and economically sustainable CKD management strategies.

1.6 ORIGINALITY OF THE STUDY

This study contributes original knowledge to the field of renal nutrition by addressing clinical, cultural, and implementation gaps in the application of plant-dominant low-protein dietary strategies for chronic kidney disease (CKD).

First, while plant-based and low-protein dietary approaches have been explored in Western populations, Mediterranean cohorts—particularly the Cypriot population—remain substantially underrepresented in interventional CKD nutrition research. To the best of current knowledge, no structured clinical investigation has evaluated the implementation of a culturally adapted plant-dominant low-protein diet (PLADO) within a Cypriot CKD cohort. This study therefore generates context-specific evidence that accounts for regional dietary traditions, food availability, and sociocultural influences on adherence.

Second, this research advances existing literature by integrating clinical effectiveness and implementation evaluation within a single framework. Rather than assessing biochemical outcomes in isolation, the study simultaneously examines renal function markers, metabolic parameters, dietary adherence, patient-reported outcomes, and cultural determinants of compliance. This multidimensional approach extends beyond conventional dietary intervention trials, which often focus solely on renal biomarkers without considering behavioral feasibility or long-term sustainability.

Third, the study critically evaluates the assumption that conventional low-protein diets relying predominantly on high-biological-value animal protein are the optimal approach in CKD management. By systematically comparing PLADO with traditional low-protein dietary practice, the research explores whether plant-dominant protein distribution can achieve renal-protective benefits while potentially reducing dietary phosphorus load, metabolic acidosis, and cardiovascular risk factors.

Finally, the study provides translational value by generating evidence that may inform regional dietary guidelines and clinical nutrition protocols in Mediterranean settings. The integration of cultural adaptation within a renal dietary model offers a framework that may be transferable to other populations with similar dietary patterns.

Collectively, this research advances the scientific understanding of plant-dominant protein strategies in CKD by combining clinical, metabolic, microbiological, and sociocultural dimensions within a single, context-specific investigation.

1.7 CONCLUSIONS

This thesis is structured to systematically develop the conceptual foundation, methodological rigor, and empirical evaluation required to address the research aims and hypotheses outlined in this study.

Chapter 1 establishes the clinical and scientific background of chronic kidney disease (CKD), articulates the research problem, defines the study aims and hypotheses, and presents the originality and justification of the investigation within the Cypriot context.

Chapter 2 provides a critical and analytical review of the literature on CKD pathophysiology, nutritional management strategies, protein-restriction paradigms, and the emerging evidence surrounding plant-dominant low-protein diets (PLADO). Particular emphasis is placed on identifying methodological limitations, gaps in Mediterranean populations, and inconsistencies in existing interventional studies.

Chapter 3 describes the research design and methodological framework of the study, including participant recruitment, intervention protocol, dietary assessment tools, biomarker analysis, microbiota evaluation (if applicable), statistical procedures, and ethical considerations. This chapter also outlines the rationale underpinning the chosen analytical approach.

Chapter 4 presents the empirical findings of the study, including renal function outcomes, metabolic biomarkers, adherence measures, patient-reported outcomes, and microbiota analyses.

Chapter 5 discusses the results in relation to the study hypotheses and situates the findings within the broader scientific literature. Mechanistic interpretations, clinical implications, and contextual relevance to Mediterranean dietary practices are critically examined.

Chapter 6 concludes the thesis by summarizing the principal contributions, acknowledging methodological limitations, and proposing directions for future research and clinical application.

CHAPTER 2 LITERATURE REVIEW

1.0 LITERATURE REVIEW

The management of CKD is a complex and multifaceted challenge, that requires a thorough understanding of both the disease's pathophysiology and the impact of various interventions in slowing its progression. As CKD progresses, early diagnosis and timely intervention are critical to prevent the advancement to ESRD, where dialysis or kidney transplantation is required. One of the crucial aspects of managing renal failure, especially in its early and moderate stages, is dietary intervention, as dietary habits directly affect kidney function, metabolic balance, and overall patient outcomes.

In this literature review, several research on dietary management in CKD, with a particular focus on LPD and the emerging interest in plant-based nutrition will be explored. Traditional dietary strategies have primarily focused on protein restriction, given the kidneys' role in filtering nitrogenous waste products from dietary protein. However, the shift towards exploring PLADO has opened new possibilities in CKD management. Plant-based diets have shown promise in reducing the renal workload, acid load, and inflammation, all of which are contributing factors in slowing renal failure progression. Despite the growing research, there remains a significant gap in knowledge about the specific application of PLADO for Mediterranean populations, particularly Cypriot patients with kidney dysfunction, whose dietary habits and cultural preferences may impact the acceptance and feasibility of such interventions.

This review begins with an overview of CKD, focusing on its stages, diagnosis, and progression, and examines how dietary management has evolved as a cornerstone in the treatment of the disease. Thus, this review then goes in depth into protein intake and its biochemical effects on renal function, followed by comparison between plant-based and animal-based proteins in the context of CKD management. Lastly, Mediterranean diet in CKD management will be explored, with a focus on how PLADO can be adapted to local dietary habits in Cyprus and similar Mediterranean countries.

By synthesizing existing research, this chapter aims to provide a comprehensive understanding of the current landscape of dietary interventions in CKD, highlighting the potential of plant-based nutrition, and identifying the gaps that the present study will address. In doing so, it sets the foundation for the research objectives outlined in the subsequent chapters and justifies the need for further investigation into culturally appropriate, plant-based strategies for CKD management.

2.0 OVERVIEW OF CHRONIC KIDNEY DISEASE (CKD)

2.0.1. Definition of CKD

Renal failure is characterized by the presence of kidney damage or an eGFR of less than 60 mL/min/1.73 m², persisting for 3 months or more (Satyanarayana R. Vaidya and Narothama R. Aeddula, 2025). Historically, the term Chronic Renal Failure (CRF) was commonly used in medical literature to describe long-term loss of kidney function. Although, modern nephrology guidelines have adopted the broader term Chronic Kidney Disease, which encompasses all stages of progressive kidney dysfunction and allows earlier identification and management of kidney damage. Therefore, the terms CKD and CRF may appear interchangeably in older studies, although CKD is not the preferred terminology in clinical practice and research (Bindroo, Quintanilla Rodriguez and Challa, 2026). The relationship and terminology differences between CKD and CRF are summarized in table 2.1.

Kidney damage refers to pathologic abnormalities in the native kidney, established via imaging, biopsy, or deduced from clinical markers such as increased albuminuria, albumin-to-creatinine ratio (ACR) more than 30 mg/g (3.4 mg/mmol), or urinary sediment alterations; decreased kidney function leads to eGFR reduction, which can be estimated from the serum concentration of creatinine (Navaneethan *et al.*, 2021).

Table 2.1: Comparison Between Chronic Kidney Disease and Chronic Renal Failure Terminology in Clinical Practice.

Aspect	Chronic Kidney Disease (CKD)	Chronic Renal Failure (CRF)
Terminology	Modern and preferred term in current nephrology guidelines	Older terminology historically used in medical literature
Definition	Persistent abnormalities of kidney structure or function for >3 months, with health implications	Refers to long-term loss of kidney function; historically used to describe the same chronic condition
Medical Usage	Standard terminology recommended by modern guidelines and literature	Gradually being replaced by the term CKD in contemporary publications

Staging System	Classified using CKD stages (G1–G5) based on eGFR and albuminuria	Same disease spectrum; current staging systems apply equally
Treatment Approach	Managed according to CKD guidelines (blood pressure control, renin–angiotensin system blockade, SGLT2 inhibitors, etc.)	Treatment strategies are identical because the condition described is the same
Patient Communication	Considered clearer and less alarming terminology	The word “failure” may sound more severe or alarming to patients

Kidneys, ureters, and urethra are consisted in the urinary system. The main function of the renal system is to filter approximately 200 liters of fluid a day from renal blood flow, along toxins, metabolic waste products, and excess ions to be excreted while maintaining important substances in the blood stream (Ogobuiro and Tuma,2025). Main homeostatic kidney functions are, waste ammonia (NH_3) removal and fluid/electrolyte balance, metabolic acid-base balance, production or modifications of hormones to maintain blood pressure, calcium and potassium homeostasis, and production of red blood cells (Murray, I. V. and Paolini,2025). When CKD is present, each residual working nephron works overload, compensatory hypertrophy, causing excess generation of ammonia due to trying to eliminate waste acid in the form of ammonium (NH_4^+). Therefore, total ammonia nitrogen (combination of ammonia and ammonium) leads to complement activation, resulting in tubule-interstitial inflammation, injury and fibrosis (Zha and Qian, 2017).

The first step in urine production is glomerular filtration, which is a passive process where hydrostatic pressure pushes fluid and solute through a membrane without requiring energy. The composition of the glomerular filtration barrier is the (1) pedicles of podocytes (visceral epithelium of Bowman’s capsule), (2) glomerular basement membrane (GBM) or basal lamina (produced by both endothelial and epithelial cells), and (3) the fenestrated endothelium of glomerular capillaries (Arif and Nihalani, 2013). Filtering plasma in order to maintain ionic and osmotic homeostasis is the main function of the barrier. Larger macromolecules (albumin and hemoglobin, as well as larger proteins such as immunoglobulins) cannot pass through the barriers, whereas small and medium-sized solutes (ions), potassium and sodium, and sugar

molecules pass through the barrier as glomerular filtrate, which then travels through the renal tubules and the collecting duct to produce urine. However, when homeostasis maintenance is needed, certain molecules (sugars), within the filtrate, can be resorbed in the tubules and returned to the bloodstream (Murray, I. V. and Paolini, 2025).

2.0.1.1 CKD Progression Pathophysiology

Renal failure progression rate depends on the main disease as well as other contributing factors including diet, smoking, or comorbidities. Studies have shown elevated oxidative stress biomarkers in individuals with CKD, indicating that elevated systemic oxidative stress. There is a positive association between CKD and systemic complications due to the combination of oxidative stress, chronic inflammation, and endothelial dysfunction (Duni *et al.*, 2019). Renal failure is a medical condition caused by different disease pathways that permanently change the kidney structure and function over months or years. The disease is classified into five stages based on GFR, with stage 1 representing minimal kidney damage and stage 5 indicating ESRD. Diagnosis of renal disease is based on evidence of chronic decreased kidney function and impaired renal structure. Current guidelines around the world define CKD as a threatening condition with a mostly asymptomatic evolution, shown by a decrease of GFR of less than 60 mL/min/1.73 m², or markers of kidney damage, such as albuminuria (ACR > 30 mg/g), or both, lasting at least 3 months, regardless of the underlying cause (Inker *et al.*, 2014).

Oxidative stress, inflammation, neutrophil gelatinase-related lipocalin, matrix metalloproteinases, and uremic toxins form CKD pathogenesis. Oxidative stress is a process caused by increased amounts of reactive oxygen species (ROS) and nitrogen species and is characterized by imbalances in the pro-/antioxidant balance. Mitochondrial dysfunction, which causes low energy metabolism and enhanced mitochondrial ROS, is the leading cause of increased oxidative stress in renal failure. Thus, in diabetic nephropathy (DKD) patients, mitochondrial overproduction of ROS is linked with mitochondrial impairment, therefore leading to cellular damage and worsening renal failure (Galvan, Green and Danesh, 2017). Glomerular injury, proteinuria, interstitial fibrosis, chronic inflammation, and microvascular dysfunction are caused by oxidative stress. Kidneys need an overconsumption of oxygen, marking it as a high metabolic rate organ, in order to support the energy requirements of tubular reabsorption of filtered solutes; therefore, when oxidative stress is present, kidneys are more susceptible to impairment (Frąk *et al.*, 2022). Important biomarkers of oxidative assessment are protein carbonyls, which have been linked with CKD state, and their presence of elevated

concentrated levels is notably compared to other biomarkers; however, the gold standard oxidative stress injury measurement is plasma total F2-isoprostanes, a by-product of lipid peroxidation. Even at early stages of renal failure, there have been reported increased levels of oxidative stress, which is associated with the progression to ESKD (Schei *et al.*, 2017). As previously reported, inflammation has been associated with oxidative stress in patients with CKD. Inflammatory markers, including high-sensitivity C-reactive protein (CRP), interleukin-(IL-) 6, fibrinogen, and tumor necrosis factor- α , have been correlated with renal disease. Thus, other contributing factors regarding CKD progression include apoptosis, necrosis, and fibrosis of damaged renal tissues, which were associated with inflammatory cytokines. Lastly, another contributing factor for oxidative stress includes uric acid production during purine degradation. Uremic toxins are present in individuals with CKD, increase the inflammation as well as oxidative stress (Gyurászová *et al.*, 2020). Therefore, increased levels of oxidative stress in kidney patients have reported autonomic dysfunction due to lower heart rate variability.

A population-based cohort study conducted in Canada, studied CKD progression and regression by age in patients with CKD. Results showed the annual incidence of CKD increased with advancing age, from 180 per 100 000 population younger than 65 years to 7250 per 100 000 in those 85 years or older (Liu, P. *et al.*, 2021). Another cohort study measured the progression and relationship between CKD to renal replacement therapy (RRT). Results showed that RRT initiation and progression rates were 0.97 and 3.50 per 100 patient-years respectively: with females having a significant lower progression and RRT initiation rates. However, progression rate was not dependent on CKD stage whereas RRT rate was (Marks *et al.*, 2014).

2.0.1.2 CKD Progression Models

Renal failure progresses rapidly around the world, which leads to several models of disease progression to be developed. A study by Cook and Bies (2016) reported that “disease progression modeling includes the use of mathematical formulas as quantitative descriptors of the time course of disease status.” Thus, in order to predict the risk of complications for long periods of time, long-term changes in biomarkers and risk factors are included in the model. Recent systematic review examined existing CKD models that predict disease progression based on albuminuria or reduction of eGFR (Cao and Singh, 2020). Several prediction models were developed in order to estimate the probability of renal failure progression, using predictors such as age, eGFR, serum albumin level, and presence of comorbidities. Reduction

of eGFR or need for dialysis or kidney transplant are the main outcomes those models assess for CKD progression. However, results from several modeling methods failed to conclude sufficient participants to monitor patient heterogeneity; therefore, there is a need for extensive, high-quality data inputs (Sugrue *et al.*, 2019). Based on literature, a recent CKD progression model (CKD-PM) has been developed, validated, and presented bellow as a pictorial representation of this model. The regression model included several risk equations from different sources, including a large range of demographic and clinical variables, risk factors, comorbidities, and complications that may occur in CKD. Thus, treatment with target treatment effects was also achieved in the CKD-PM, which was achieved based on disease-specific risk equations instead of treatment-specific risk equations (Ramos *et al.*, 2024).

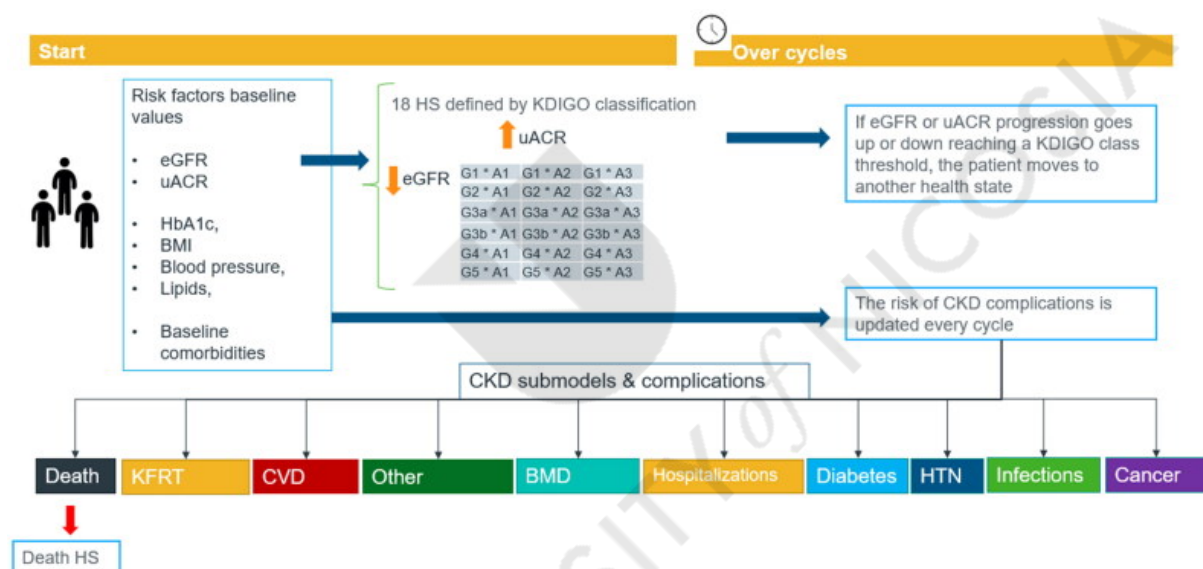


Figure 2.1: CKD progression model diagram.

BMD: bone and mineral disorders; BMI: body mass index; CKD: chronic kidney disease; CVD: cardiovascular disease; CVM: cardiovascular mortality; eGFR: estimated glomerular filtration rate; ESKD: end-stage kidney disease; HbA1c, glycated hemoglobin; HS: health state; HTN: hypertension; KDIGO: kidney disease improving global outcomes; KRT: kidney with replacement therapy; uACR: urine albumin-creatinine ratio. (Ramos *et al.*, 2024)

Another progression model to assess the risk of CKD progression and the need for renal therapy (dialysis or kidney transplant) using artificial intelligence was developed in Columbia. The study included patients with CKD stages 3 to 5, with a 5-year follow-up. Results showed that the time-to-event model predicted three outcomes (CKD progression, reduction of eGFR, need for renal therapy) of CKD progression (Isaza-Ruget *et al.*, 2024).

Another CKD progression model is the Kidney Failure Risk Equation (KFRE) model which was developed to predict kidney replacement therapy (KRT), in the UK, using age, gender, eGFR, and urine albumin/creatinine ratio (UA/CR) (Ahmed, Salman *et al.*, 2021). Based KFRE model, another study was conducted in order to evaluate the tool with timing of CKD referrals. Results showed that KFRE tool can decrease referral rates while also being an effective method to help timely referrals. Thus, when used in triage, the tool aid with identifying patients who were at low risk of developing renal failure, thereby preventing unnecessary referrals. This method allows the patients to remain in primary care for extended periods of time, ultimately conserving healthcare resources and decreasing patients' stress and wait times (Li, K. *et al.*, 2024). Considering one of the main risk factors of CKD, type 2 diabetes mellitus (T2DM), a tool known as Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation, which assesses the risk equation for diabetic patients and CKD development and progression rate. The main outcomes assessed were whether major kidney-related events occurred (doubling of serum creatinine, KRT, or renal death), and new-onset albuminuria (Jardine *et al.*, 2012).

2.0.2. CKD Diagnosis

The loss of nephrons function and the steady degeneration of the renal parenchyma are the main characteristics of renal failure. Diagnosing CKD is a difficult process that requires a thorough grasp of many diagnostic tools and indicators. The CKD progression highlights the importance of early and accurate diagnosis to reduce the impact of patient's health and quality of life. Traditional indicators, innovative biomarkers, and imaging modalities are used to diagnose renal dysfunction. Early detection, stages 1 to 3, can influence the development of renal failure and decrease any possible complications. Traditional markers include blood creatinine which is used to calculate eGFR (Biljak *et al.*, 2017). Additionally, albuminuria (presence of albumin in urine) is also a key marker for CKD diagnosis, as albumin is not normally found in urine. Thus, measuring the concentration of urine albumin is preferred to measuring the concentration of urine total protein, therefore, use of urine albumin is the preferred test to detect proteinuria which will improve the sensitivity, quality, and consistency of early detection and management of CKD (Chouhan, Kaple and Hingway, 2023). Thus, medical imaging is essential in diagnosing CKD, such as computed tomography (CT) scan, X-ray, magnetic resonance imaging, and ultrasonography (Kanno *et al.*, 2014).

GFR measures the volume of fluid filtered in a minute, which is dependent on the net filtration pressure, the total available surface area for filtration, and filtration membrane permeability (Ogobuiro and Tuma, 2025). Originally, it had been reported to estimate the glomerular function using the amount of filtered fluid by renal glomeruli per unit of time. However, measures of the total of all glomerular capillaries in the human kidney were reflected, instead of measuring one single-nephron glomerular function. Thus, the filtration rate of the glomerular function cannot be directly measured, although it can be measured from the clearance measurements or estimated from endogenous filtration markers in the blood (Levey, Inker and Coresh, 2014).

It can be estimated based on formulas using biological biomarkers and demographic variables such as gender, age, and sometimes weight, height, and/or ethnicity. For instance, when the GFR formula using gender as a variable showed the same estimated GFR even though both genders had different creatinine levels of 0.7 mg/dL and 0.9 mg/dL for female and male, respectively (Pottel *et al.*, 2017). Moreover, over the years, serum creatinine was used to estimate GFR; it has been available around the world and has been standardized and inexpensive (Delanaye, Cavalier and Pottel, 2017). However, the relation between serum creatinine and cystatin C and GFR is opposite and inflated, which means that even a small change in serum creatinine will lead to a large change in GFR. On the contrary, major change in serum creatinine concentration will result in a minor change in GFR (Delanaye and Cohen, 2008). Thus, another reason that serum creatinine is not the best marker to estimate GFR is that serum creatinine concentration depends on muscular mass, as it is a catabolite of the muscular molecule creatine. Calculation of creatinine clearance by a 2-hour urine collection has been more complicated which resulted to urine collection of filtered creatinine, known as measured glomerular filtration rate (mGFR), being replaced by estimated glomerular filtration rate (eGFR) (Zsom *et al.*, 2022). Thus, KDIGO clinical guidelines classified the majority proportion of the population into different GFR stages based on eGFR by the use of creatinine and cystatin C (eGFR_{cr-cys}); therefore, suggesting that in order to stage and diagnose renal failure, cystatin C should be added to creatinine to estimate GFR (Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group, 2024)

Moreover, body size is a contributing factor affecting GFR; it is indexed relative to an average body surface area (BSA) of 1.73m² and expressed as mL/min/per 1.73 m². Other contributing factors are, measurement time of day, protein intake, pregnancy, extracellular fluid status, blood pressure extremes, use of antihypertensive agents, and the presence and severity of kidney damage (Levey, Inker and Coresh, 2014).

In 1976, the first published GFR equation included serum creatinine, age, gender, and weight by Cockcroft and Gault, as shown below. Increase in its popularity was due to being relatively easy to use and to calculate. The formula measures the creatinine clearance expressed in mL/min; therefore, it does not measure GFR, which is expressed in mL/min/1.73 m² (Cockcroft and Gault, 1976).

$$Ccr = \{((140 - age) \times weight) / (72 \times SCr)\} \times 0.85 \text{ (if female)}$$

After several equations developed, the latest equation, formed in 2021, was published by the European Kidney Function Consortium (EKFC) which aimed to overcome the limitations regarding age and race modeling. The equation can apply to people from ages 2 to 90 years and serum creatinine levels from 0.45 to 5.54 mg/dL (Zhao *et al.*, 2023). Thus, it contains Q values which correspond to the median serum creatinine values for the age- and gender-specific populations. The full equation is presented bellow in table 2.2.

Table 2.2: EKFC equation.

Age	SCr/Q	EKFC equation
2-40 years	<1	107.3 x (SCr/Q) ^{-0.322}
	≥1	107.3 x (SCr/Q) ^{-1.132}
>40 years	<1	107.3 x (SCr/Q) ^{-0.322} x 0.990 ^(Age-40)
	≥1	107.3 x (SCr/Q) ^{-1.322} x 0.990 ^(Age-40)

Note: Abbreviations: SCr: serum creatinine concentration; Q value calculations for ages 2-25 years: Males: $\ln(Q) = 3.200 + 0.259 \times \text{Age} - 0.543 \times \ln(\text{Age}) - 0.00763 \times \text{Age}^2 + 0.0000790 \times \text{Age}^3$; Females: $\ln(Q) = 3.080 + 0.177 \times \text{Age} - 0.223 \times \ln(\text{Age}) - 0.00596 \times \text{Age}^2 + 0.0000686 \times \text{Age}^3$; Q value calculations for ages >25 years:

Males: $Q = 80 \mu\text{mol/L}$ (0.90 mg/dL); Females: $Q = 62 \mu\text{mol/L}$ (0.70 mg/dL); SCr and Q are reported in $\mu\text{mol/L}$ (to convert to mg/dL, divide by 88.4).

Considering the above, all equations that have been developed are a relatively an approximate estimation. An accurate GFR measurement in specific populations and/or specific clinical situations might be needed.

As mentioned above, CKD is defined as kidney damage or $\text{eGFR} < 60 \text{ mL/min/1.73 m}^2$ for 3 months or more. Thus, kidney dysfunction can be presented by the presence of albuminuria, known as an albumin-to-creatinine ratio $> 30 \text{ mg/g}$ in two of three spot urine specimens. The severity of the disease is classified into five stages based on the GFR level, as well as albuminuria levels, presented in figure 1.2. Diagnosis of CKD is known as the existence of an abnormality in renal structure or activity persisting for more than 3 months. Table 2.3 shows the criteria for CKD are divided into two categories: (a) markers of kidney damage and (b) decreased eGFR. Markers of kidney loss include (1) albumin excretion rate ($\text{AER} > 30 \text{ mg/24 hours}$); (2) albumin-to-creatinine ratio ($\text{ACR} > 30 \text{ mg/g}$); (3) urine sediment abnormalities; (4) electrolyte and other anomalies due to tubular disorders; (5) abnormalities detected by histology; (6) structural anomalies detected by screening; and (7) history of renal transplant. A value lower than or equal to $60 \text{ mL/min/1.73 m}^2$ is characterized as a decrease in eGFR (Satyanarayana R. Vaidya and Narothama R. Aeddula, 2025).

Table 2.3: Classification for CKD.

Markers of renal dysfunction	• Albuminuria ($\text{ACR} \geq 30 \text{ mg/g}$ ($\geq 3 \text{ mg/mmol}$)). • Urine sediment abnormalities. • Urine sediment abnormalities. • Electrolyte and other anomalies due to tubular disfunctions. • Structural anomalies detected by screening. • Abnormalities detected by histology. • History of renal transplant
Decrease of eGFR	$\text{eGFR} < 60 \text{ mL/min per } 1.73 \text{ m}^2$ (stage 3 – 5)

Diagnosis of CKD includes stage assessment, defining the cause, and examining the progression rate of the disease. Once the diagnosis is determined, the following step is to determine the stage of renal failure. Proteinuria or albuminuria is also an important biomarker for assessing CKD. Proteinuria occurs when the volume of filtered protein surpasses the proximal tubule's ability to reabsorb it, caused by a damaged glomerular filtration barrier. Around 70% of the excreted protein, when albuminuria occurs, is albumin. The standard procedure to measure urinary protein excretion is with a timed urine collection, typically a 24-hour urine collection; however, the risk of collection errors, added costs, and the inconvenience for patients reduced the clinical usefulness of this method. This led to a more practical method, measuring protein concentration on a single urine sample and reporting it as a ratio to the urine creatinine concentration (Kobayashi *et al.*, 2019). The normal level of urine albumin-to-creatinine ratio (ACR) is below 30 mg/g, whereas “microalbuminuria” is presented when ACR values are from 30 to 300 mg/g, and severe albuminuria is when ACR values are above 300 mg/g. Moreover, it is important to confirm the chronicity of at least three months before CKD diagnosis is confirmed, regardless of an abnormal eGFR or the presence of elevated ACR values. An abnormal test should be retaken again after a minimum interval of 90 days, which is essential due to kidney measurements (GFR and proteinuria) having fluctuations over time.

Figure 2.2 illustrates the prognosis of CKD by GFR, and albuminuria categories based on KDIGO guidelines. Thus, it shows all CKD stages and all three categories of albuminuria (Aklilu, 2023).

Prognosis of CKD by GFR and Albuminuria Categories				Albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30-299 mg/g 3-29 mg/mmol	≥300 mg/g ≥30 mg/mmol
GFR categories (mL/min/1.73 m ²) Description and range	G1	Normal or high	≥90			
	G2	Mildly decreased	60-90			
	G3a	Mildly to moderately decreased	45-59			
	G3b	Moderately to severely decreased	30-44			
	G4	Severely decreased	15-29			
	G5	Kidney failure	<15			
Green: low risk (if no other markers of kidney disease, no CKD); Yellow: moderately increased risk; Orange: high risk; Red, very high risk. KDIGO 2012						

Figure 2.2: eGFR and Albuminuria Categories.

Note: CKD is defined as abnormalities of kidney structure or function, persistent for at least 3 months, with complications to health. CKD is classified based on “Cause” (table 2.3), Glomerular Filtration Rate (GFR) stages (from G1 to G5), and “Albuminuria” category (A1-A3). Green boxes indicates low risk; yellow boxes indicate moderately elevated risk; orange boxes indicate high risk; red boxes indicate very high risk (Levin and Stevens, 2014).

Early stages of CKD, stage 1 and stage 2, is when kidney damage is present although kidney function is relatively normal or with mild kidney dysfunction. In these stages, GFR is typically from 90 mL/min/1.73 m² to 60 mL/min/1.73 m² and the disease may go unnoticed without specific testing for proteinuria or urinary abnormalities (Evans *et al.*, 2022).

More advanced stages, stage 3a and stage 3b represents moderate CKD, where GFR drops from 59 to 44 mL/min/1.73 m², indicating more significant kidney dysfunction. At these stages, patients may begin to experience symptoms such as fatigue, fluid retention, and high blood pressure, which indicate that kidneys are no longer functioning normally; however, symptoms may not occur in all patients which might lead to be undiagnosed. However, within these stages the disease can be managed through careful monitoring of renal function, maintaining normal blood pressure as well as glucose control, and electrolyte balance. Interventions such as dietary modifications, blood pressure control, and management of comorbidities (such as diabetes or cardiovascular disease (CVD)), are crucial to slow the disease progression (Tangri *et al.*, 2023).

Renal failure progresses to stage 4, where GFR is between 29 to 15 mL/min/1.73 m², kidney function is significantly lower, and symptoms become more noticeable. This stage is often

characterized by elevated levels of creatinine, urea, and the presence of albuminuria, indicating a decline in the kidney's ability to filter waste products. Individuals with CKD may experience worsening symptoms such as fatigue, edema, and difficulty concentrating caused by the accumulation of metabolic waste products. Interventions at this stage primarily focus on dialysis preparation (e.g. fistula, AV graft) and renal protective measures such as protein restriction, sodium restriction, and the use of angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) to protect kidney function and control blood pressure (Lambert *et al.*, 2022).

Lastly, stage 5 represents ESRD, where GFR drops below 15 mL/min/1.73 m², kidneys can no longer maintain vital functions such as fluid balance, waste filtration, and electrolyte regulation. This stage is characterized by uremic symptoms, including nausea, vomiting, confusion, shortness of breath, and loss of appetite, all of which result from the production of waste products in the blood. At this point, patients require dialysis or a kidney transplant to sustain life. Dialysis can be either hemodialysis or peritoneal dialysis, both of which help to artificially remove waste and excess fluid from the blood. Kidney transplant is the ideal solution for suitable candidates, offering the potential for restored kidney function, but it is not always available or suitable for every patient (Wulczyn *et al.*, 2022).

The progression from stage 1 to stage 5 is not always linear, and many factors, including comorbid conditions, such as diabetes and hypertension, influence the rate at which kidney function decreases (Altamura *et al.*, 2023). More specifically, a recent systematic analysis examined the global, regional, and national burden of CKD from 1990 to 2017. Results showed that kidney failure has both direct and indirect effect on global health due to it being a direct cause of global morbidity and mortality and is an important risk factor for CVD (GBD Chronic Kidney Disease Collaboration, 2020). The increase of prevalence of diabetes mellitus, hypertension, and obesity, causes the global upsurge in CKD development due to them being major risk factors (Kofod *et al.*, 2023)(Kalantar-Zadeh *et al.*, 2021)(Nair *et al.*, 2022)(Gregg and Hedayati, 2018). Additionally, certain ethnic groups, such as African Americans, Hispanics, and South Asians, are more likely to develop CKD due to genetic and environmental factors (Hounkpatin *et al.*, 2020). Approximately 850 million people around the world are estimated to have CKD, mostly in low-income and lower-middle-income countries, and a large proportion of these individuals lack access to kidney disease diagnosis, prevention or treatment. Moreover, 1 in 3 people with diabetes and 1 in 5 with hypertension in high-income countries have been diagnosed with renal failure, which leads to the suggestion that focusing on the control of

diabetes and cardiovascular disease will decrease the growing burden of CKD (Francis *et al.*, 2024).

For a better understanding of CKD, the primary cause of renal disease should be determined to lower the risk of progression rate and implement disease-specific management strategies. Two major diseases have been associated with the most rapid GFR reduction, with the first being polycystic kidney disease and the second being diabetes, with both diseases reducing GFR by 2-3 mL/min/year (Ryu *et al.*, 2023).

2.0.2.1 Detection and Screening

Renal failure is often asymptomatic, and some people might not develop any severe symptoms until their kidney function is in an advanced condition. However, when CKD progress to advanced stages, severe adverse clinical outcomes have been observed. Renal dysfunction can be detected with simple and inexpensive tests, and the use of several treatments to slow the rate of GFR decline while reducing cardiovascular complications. Therefore, combining these considerations screening asymptomatic people will be easier to perform. Screening aims to improve early detection of CKD associated with an increased risk of possible complications. Based on early detection, National Institute of Health and Care Excellence (NICE) suggested a protocol for screening, diagnosing, and managing CKD. The protocol follows: (1) patient demographics (presence of: diabetes, hypertension, episode of acute kidney disease in last three months, and cardiovascular disease; family history; etc.); how to screen: eGFR and urine ACR; when eGFR is above 60 mL/min/1.73m² or ACR is lower than 3 mg/mmol, then there is no CKD present, however, if those biomarkers are different then the biomarkers would be repeated within 1 week to eliminate acute kidney disease; if the markers are consistent within the week, the biomarkers should be repeated after 3 months; if eGFR is below 60 mL/min/1.73m², then (2) CKD is diagnosed; (3) risk assessment takes place, using KDIGO table graph combining eGFR and ACR categories, as well as performing the KFRE; (4) the patient is referred to a nephrologist; (5) CKD management: blood pressure control, medication to slow CKD progression, medication to reduce cardiovascular risks when appropriate, and detection of CKD complications such as anaemia; and (6) close monitoring by assessing eGFR and ACR (Martinez *et al.*, 2021).

As mentioned above, at early stages of CKD, patients report no symptoms, however; the most common symptoms are fatigue, weakness, pain, sleep disturbances, and itchy skin. However, several methods such as Kidney Disease Quality of Life (KDQOL)-36, Palliative Outcome

Symptom-Scale Renal (POS-r)-13, and Dialysis Symptom Index (DSI)-10 were developed in order to do symptom assessment (Clark-Cutaia *et al.*, 2022). KDQOL-36 includes the self-reported (SF)-12 (which assesses the impact of health on an individual's everyday life) plus four questions on the burden of kidney failure, 12 questions for symptoms/problems, and eight questions regarding the effects of kidney disease; thus, the questionnaire has been mainly evaluated in the United States for dialysis patients (Peipert *et al.*, 2019). POS-r-13 was developed in London, United Kingdom, and can be used in teaching and research as well as in clinical practice; therefore, it can be considered a multidimensional assessment tool. This instrument has two versions: the self-reported scale, which is intended for patients, and the proxy used by health professionals, whereas KDQOL-36 is mainly used for patients. Thus, the questionnaire has been adapted and validated in several countries, such as Portugal, Italy, Spain, Germany, France, China, and others; however, it has not been translated neither Greece nor Cyprus. Patient POS is based on 12 questions and is recommended for healthcare facilities caring for chronically ill patients who require palliative and long-term care, such as dialysis patients (Grochowicka *et al.*, 2024). Lastly, DSI-10 has been developed since 2004 in the US for dialysis patients and included 30 questions. The questionnaire is patient-centred and has been developed to assess the physical and emotional symptoms in patients with CKD undergoing haemodialysis (Weisbord *et al.*, 2004). All three instruments measure the symptoms in dialysis patients; however, there has not been any instrument developed assessing symptoms in patients with earlier stages of CKD. Assessing symptoms in earlier stages will help early diagnosis of the disease, therefore decreasing the CKD progression rate.

2.0.3. Prevalence

Renal failure has been a major public health concern around the world for several years. It has been characterized as a leading public health complication with its prevalence estimated at 13.4% (Elendu *et al.*, 2023). CKD incidence, prevalence, mortality, and disability-adjusted life year (DALY) have rapidly increased over the last 30 years, mainly due to increased population and aging. DALY measures the assessment of disease burden; while DALYs decrease, there is a reduction in both years of life lost and years lived with disability. Data from the Global Burden of Disease (GBD) reported that in 1990, CKD-DALY was ranked in the 29th position, and by 2019 reached the 18th position; therefore, understanding and investigating contributing factors that influence CKD's burden is important and has a significant impact on global health (Murray, C. J. L., 2022).

More specifically, the number of newly diagnosed CKD cases has increased significantly from 7.8 million to 18.9 million in 2019 (GBD 2021 Diseases and Injuries Collaborators, 2024). In addition, Lv and Zhang (2019) estimated the number of patients with ESKD requiring kidney replacement therapy to be between 4.402 and 7.083 million. Moreover, reports showed that by 2040, CKD will be the fifth-ranked cause of mortality, due to the increase of the death rate contributing to 41.5% from the years 1990 to 2017 (Kovesdy and Kalantar-Zadeh, 2016).

Furthermore, it is important to estimate the disease burden among individuals by contributing factors of renal prevalence. These factors include age, gender, race, and comorbidities such as diabetes mellitus and hypertension (Kovesdy, 2022). Geographic region also has an important role in the burden of CKD. In low- and middle-income countries, 78% of patients with kidney dysfunction were accounted for; a higher renal failure burden was observed in Southeast Asia, Central and South America, and the Middle East and North Africa, while in high-income Asia and Europe, CKD burden was lower (Qin *et al.*, 2024). Elevated body mass index (BMI), dietary risks, and decreased physical activity, shown in high socio-demographic index countries, have a greater impact on CKD burden, whereas countries with low socio-demographic index environmental risks, including air pollution and water contamination, are more significant (Guo, J. *et al.*, 2025). Reports investigating the importance of geographic regions by income level with CKD age-standardized prevalence showed that high-income countries had an 8.6% and 9.6% for males and females, respectively, whereas low- and middle-income countries' results were higher with 10.6% and 12.5% for males and females, respectively (Mills *et al.*, 2015).

In the EU, 36% of the population reported to have at least one chronic condition. In Cyprus, data from 2019 reported that two in five adult Cypriots contributed to 39% (OECD/European Observatory on Health Systems and Policies, 2023). It is the second leading cause of death in Cyprus, with the incidence rate of kidney failure being 204 per million population (pmp), which is considered high prevalence, whereas other countries in the EU have a lower incidence rate as shown in figure 2.3. Data from 2022, the total incident counts in Cyprus were 277 of whom 197 were male and only 80 were females. However, CKD prevalence in females is higher than in men, whereas in the Cypriot population, the incidence is noticeably lower in females. Regarding the age group from 0 to 19 years, only one incident occurred, with the highest incidence percentage, 42%, found in Cypriot aged above 75 years, whereas ages from 65 to 74 years reported a total of 30% incidence, and ages from 45 to 64 years and 20 to 44 years reported 22% and 5%, respectively. Regarding the incidence of kidney transplants in Cyprus, were 306 pmp, contributed by the total of 277 participants, and the mean age was 69.6. Thus,

when diabetes was the primary renal disease incidence of the individuals who had kidney transplants was 118 pmp. Moreover, primary renal disease incidence pmp was 298.4, caused by diabetes and hypertension at 37.8% and 15.9%, respectively (ERA Registry, 2022). This is also shown in an earlier study assessing Cypriot multimorbidity prevalence which reported that elevated cholesterol and blood pressure reaching 44.7% and 37.5%, respectively (Kyprianidou *et al.*, 2020).

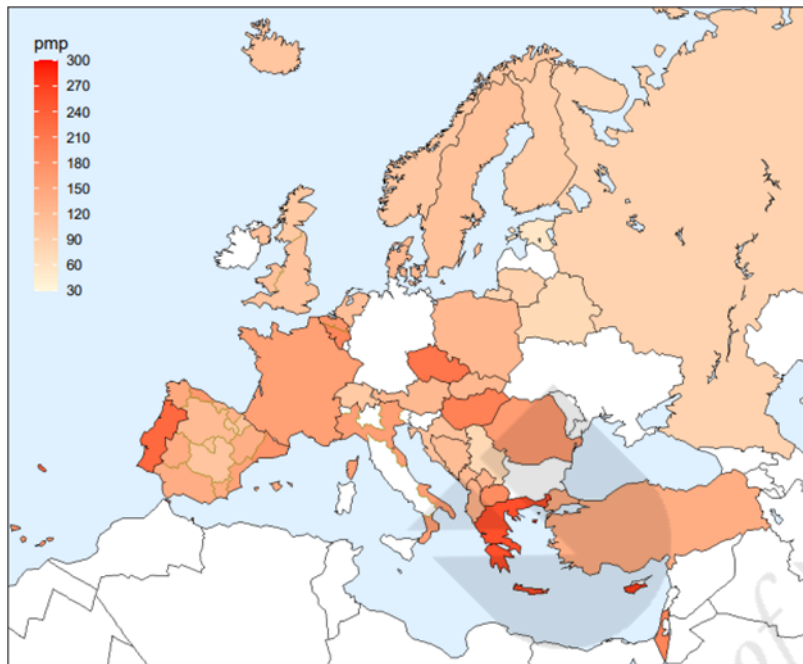


Figure 2.3: Incidence per million population by country / region, unadjusted.

Note: Shows the incidence per million population by country with color. Highest the color highest the prevalence rate. Modified by (ERA Registry, 2022).

Moreover, a recent study by Kyprianidou *et al.*, (2023) reported that a significant proportion of the Cypriot population is affected by at least one noncommunicable disease (NCD). Chronic diseases with persistent durations caused by a combination of genetic, physiological, environmental, and behavioral factors are the main definition of NCDs. The most prevalent NCDs within the population are hyperlipidemia, hypertension, and thyroid disease.

Based on the World Health Organization (WHO), by 2030 it is estimated that life expectancy will increase, stating that multimorbidity is a new global health challenge. Part of renal failure's prevalence can be multimorbidity, which is defined by the presence of two or more continuing diseases. The main impacts of multimorbidity are the increase in treatment and medication burden, poor quality of life, and worsening outcomes (Tonelli *et al.*, 2015). Moreover, a study by Huang *et al.*, (2021) reported that increased risk of developing other comorbidities in people

with CKD at any stage was associated with increased symptoms of anxiety, such as depression or anxiety. Thus, hospitalization rates in individuals with kidney dysfunction with two or more comorbid conditions were increased twice or three times compared to patients with kidney impairment with no other conditions (Sullivan, Michael K. *et al.*, 2021). Contributing factors of multimorbidity include socio-demographic factors and status, age, gender, education, BMI, lifestyle (dietary and physical activity), smoking, as well as psychological and environmental aspects (Bezerra de Souza *et al.*, 2021). Assessing multimorbidity in patients with CKD reported that 96% of the participants had multimorbidity, with two main prevalent diseases being hypertension and musculoskeletal disorders at 55% and 40%, respectively, at all renal failure stages (Hawthorne *et al.*, 2023). Moreover, regarding Cyprus multimorbidity prevalence, a study conducted by reported that the multimorbidity prevalence rate was higher in females than males, with hyperlipidemia and hypertension being the most prevalent diseases at 44.7% and 37.5%, respectively. Thus, results reported that patients with three morbidities were significantly associated with females, smoking status, aging, and higher BMI. This is supported by following a diet increased in fat and calories is associated with increased levels of obesity, which coexist with gastrointestinal reflux and elevated cholesterol levels (Kyprianidou *et al.*, 2020).

A link between cardiovascular events and mortality with eGFR independent of age, gender, and other risk factors is observed. Individuals with mild to moderately reduced eGFR face structural and functional changes consistent with CKD-associated cardiomyopathy (Edwards *et al.*, 2015). Cardiovascular complications are the most common causes of death in dialysis patients. Increased death rate caused by cardiovascular disease, most patients with progressive renal impairment die before reaching kidney failure (Zoccali *et al.*, 2023). Kidneys have an important role in maintaining fluid balance and blood pH in their homeostatic range by excretion of nitrogenous waste, regulation of blood ions, blood volume regulation, and hormone production. Thus, kidneys secrete several endocrine hormones such as renin, erythropoietin, 1,25 dihydroxy vitamin D3, as well as autocrine and paracrine hormones (e.g. prostaglandins, endothelin, adrenomedullin etc.). When kidneys dysfunction affects the metabolic excretion of many endocrine hormones such as insulin, parathyroid hormone (PTH), thyroid hormones, and sex hormones (Kaka *et al.*, 2022). Moreover, Chronic Kidney Disease – Mineral and Bone Disorder (CKD-MBD) is associated with a systemic disorder of mineral and bone metabolism which is developed by either one or a combination of biochemical imbalances, bone abnormalities, and vascular or other soft tissue calcification. The main serum

biochemistry imbalance are increases in fibroblast growth factor 23 (FGF23) and parathyroid hormone and decreases in 1,25 dihydroxy vitamin D (calcitriol) and soluble α -Klotho, allowing serum calcium and phosphate to stay normal for long periods of time. The synthesis and the secretion of PTH are continuously stimulated in CKD which then results in secondary hyperparathyroidism (Drüeke, 2025). Elevated phosphorus in the blood is associated with significant pathophysiology in renal failure, that contributes to the high rates of mortality observed in CKD. Phosphorus homeostasis is lost in renal disease due to failure to excretion. Regulation of phosphate balance during CKD before loss of balance occurs is complicated. Loss of calcitriol production capacity is an important factor leading to a decrease in calcium absorption, hypocalcemia and stimulation of PTH secretion. Elevated PTH levels reduce the fraction of the filtered phosphate load and maintains phosphate excretion at normal levels. Thus, protein levels increase in CKD as the GFR decreases (Hruska *et al.*, 2008). Osteoporosis is a skeletal disorder which is defined by the loss of bone strength predisposing to an increased risk of fracture. Prevalence of osteoporosis in patients with CKD from stages 3 to 5, is 31.8% (Hsu, C., Chen and Chen, 2020), and based on National Health and Nutrition Examination Survey (NHANES III) participants with eGFR <60 mL/min osteoporosis was twice more common than in patients with eGFR higher than 60 mL/min (Nickolas, McMahon and Shane, 2006).

Progression of CKD is a complex process that involves multiple mechanisms that contribute to the gradual loss of kidney function. These mechanisms are interrelated and understanding them is crucial for identifying potential therapeutic targets and interventions to slow CKD progression.

2.0.4. Mechanisms of CKD progression

2.0.4.1 Glomerular hyperfiltration

Glomerular hyperfiltration is a pathophysiological event caused by an increased glomerular capillary pressure and glomerular size and loss of tubuloglomerular feedback. Diminished sodium chloride delivery to the macula densa which leads to deactivation of tubuloglomerular feedback and vasodilation of efferent arterioles. Therefore, tensile stress occurs from increased hydrostatic pressure perpendicular to the capillary wall. Increased sodium chloride availability at the macula densa causes afferent arteriolar vasoconstriction, decreasing GFR and distal sodium delivery. Excess glomerular filtration of glucose in diabetes will increase sodium-glucose cotransporter-2 (SGLT2) expression and activity, resulting in glomerular hyperfiltration. Glomerular hyperfiltration increases CKD progression through mechanical

stress, leading to podocyte loss, albuminuria and tubular injury, as well as tubular work overload. A decrease in albuminuria/proteinuria and a decrease in GFR are the main clinical parameters in the CKD diagnosis, glomerular hypertrophy precedes the development of such clinical parameters and represents a superior indicator for CKD progression (Kanbay *et al.*, 2024).

Inflammation and Oxidative Stress

As mentioned above, patients with impaired kidney function suffer from many complications such as high blood pressure, CVD, anemia, metabolic acidosis, altered immune response, mineral and bone abnormalities, and neurological complications. Among these complications, the loss of cardiovascular function and infections caused by an altered immune response have also been linked to increase the risk of morbidity and mortality in patients with impaired kidney function. In these conditions, inflammation and oxidative stress have a vital role to play (Kochi *et al.*, 2018). These patients typically suffer from chronic inflammation and have severely altered antioxidative systems which worsen progressively with the stage of renal failure. Inflammation and oxidative stress work as defending mechanisms against infections. However, if not properly regulates, they may initiate several deleterious effects, such as overproduction of cytokines and increase in pro-inflammatory and oxidative stress mediators (Libetta *et al.*, 2011). Several studies have evaluated the relation between inflammatory markers and CKD mortality and showed that inflammatory markers have linked with many complications of renal failure such as malnutrition, coronary artery calcification, atherosclerosis, atrial fibrillation, heart failure and left ventricular hypertrophy. Important markers of inflammation in CKD are C-reactive protein (CRP), interleukin-6 (IL-6), interleukin-1 (IL-1), tumor necrosis factor- α (TNF- α), adipokines, adhesion molecules and the CD40 ligand (Rapa *et al.*, 2019). In patients with CKD, increased levels of oxidative stress have been observed, due to the lack of their physiological defence mechanisms which cause oxidative damage to nucleic acids which results in increases risk for onset of subsequent tumours (Descamps-Latscha, Drüeke and Witko-Sarsat, 2001). Oxidative stress is frequently observed in ESRD and is a not-traditional risk factor for all causes of mortality. Therefore, oxidative stress is an important diagnostic and prognostic factor and is a target for CKD prevention and treatment. Increased levels of oxidative stress have been reported in the early stages of renal failure, which increases the progression of ESRD; and is further increased in haemodialysis patients (Liakopoulos *et al.*, 2017). Antioxidant therapies have a positive impact in decreasing oxidative stress, lowering uremic and cardiovascular toxicity and improving survival rate. Some anti-inflammatory

interventions are change in the lifestyle factors, such as higher aerobic exercise and dietary interventions; however, the adherence for individuals with CKD is often poor, which leads to pharmacological therapy as a potential alternative (Mena *et al.*, 2009). The use of statins and angiotensin-converting enzyme inhibitors have been shown to have an anti-inflammatory effect (Rapa *et al.*, 2019).

Several vitamins and minerals, as well as plant-derived metabolites are considered as a possibility of using compounds with anti-inflammatory and antioxidants benefits in the treatment of CKD. Patients with impaired kidney dysfunction present with weaker antioxidative defence mechanisms due to dietary restrictions on fruits and vegetables which results in lower levels of vitamins C and E (Jankowska *et al.*, 2016).

2.0.4.2 Fibrosis and Tubulointerstitial Damage

Renal fibrosis is described by renal interstitial fibroblast proliferations which results in aberrant and excessive deposition of extracellular matrix which then leads to the destruction of the normal renal tubules and interstitial structures. Tubulointerstitial fibrosis is associated with the decline kidney function and can predict CKD progression; therefore, it has been recognized as the most reliable predictor of CKD (Wong and Pollock, 2014). Fibrosis impacts several kidney compartments starting in the tubulointerstitial area and then damage the vasculature and glomeruli which then contributes to the development of arteriosclerosis and glomerulosclerosis (Humphreys, 2018). When a significant portion of the kidney tissue becomes fibrotic several complications occur such as increased blood pressure, serum creatinine, and urinary albumin excretion (Reiss *et al.*, 2024). Fibrosis has a major role in some infectious conditions and also has a protective role in cases of major tissue destruction such as renal infarctions, pyelonephritis, and myocardial infarction. In addition, key factors that increase fibrosis are renin-angiotensin system, parathyroid hormone, FGF23, Klotho, microRNAs, and vitamin D metabolism, have a great negative impact in kidney and cardiac in patients with impaired kidney function (Panizo *et al.*, 2021). The assessment of renal fibrosis is mainly assessed by kidney biopsy, and it is considered as a gold standard measurement, although renal biopsy is invasive and can cause complications such as bleeding, pain or infection (Rende *et al.*, 2023). Effective detection models can help in guiding clinical treatment plans and assessing the effectiveness of new antifibrotic agents (Reiss *et al.*, 2024).

2.0.4.3 Proteinuria

A sign of kidney damage is presented by persistent amounts of proteins in the urine, which then when combined can estimate GFR. Proteinuria can also identify a subgroup of patients with high risk of progressive renal failure and increased cardiovascular morbidity (Brantsma *et al.*, 2008). However, the presence of protein in urine is a strong relation that a patient is likely to develop progressive decline of kidney function, even when GFR is relatively normal (Gorriz and Martinez-Castelao, 2012). Proteinuria is a marker of renal outcome, independent of other risk factors. Regardless of the initial cause of kidney damage, the loss of nephrons adds additional strain on the remaining nephrons, which triggers adaptive hemodynamic changes to support kidney function. The resulting glomerular capillary hypertension has a negative impact to the permeability of proteins which then causes them to be filtered in excessive amounts. This mechanical stress leads to elevated production of angiotensin II (Ang II) and angiotensin AT1 receptors in the podocytes. Increased levels of Ang II can damage the expression of nephrin, an important protein in the glomerular slit diaphragm (Gagliardini *et al.*, 2013). Abnormal proteinuria was defined as the excretion of more than 150 mg of protein per day; although early renal disease is reflected by lesser degrees of proteinuria, particularly increased amounts of albuminuria. Albuminuria is defined as the elimination of urinary albumin excretion above 30 mg per 24 hours, equivalent to 20 mg/min in urine collected over a determined period or 30 mg/g creatinine in a single sample. However, some scientific societies, such as KDOQI, suggests a limit of 17 mg/g and 25 mg/g for males and females respectively (Ren, F. *et al.*, 2021). Factors influencing urinary albumin excretion include intense physical exercise, menstruation, urinary tract infections, hematuria, fever, hypertension, glycemic disturbances, or heart failure, are contributing factors and should be considered before diagnosing albuminuria (Gorriz and Martinez-Castelao, 2012).

2.0.4.4 Hyperglycemia (in Diabetic Nephropathy)

Patients often have comorbid diabetes and CKD. Intensive glycemic management has been reported to delay the onset and progression of increased urinary albumin excretion and decreased eGFR in diabetes patients. Uncontrolled blood glucose in patients with chronic diabetes escalates major pathological features, such as high blood pressure, progressive proteinuria, decreased GFR, and glomerulosclerosis, develop structural changes in the kidney (Wu, T. *et al.*, 2023). Kidneys play an important role in glucose regulation by reabsorbing filtered glucose and producing glucose via gluconeogenesis, contributing to about 20-25% of systemic glucose release and 40% of the body's gluconeogenesis (Sullivan, Mitchell A. and Forbes, 2019).

When blood glucose is increased, the glycolysis process is saturated. This means that the majority of glucose cannot complete the normal metabolism, which stimulates the collateral metabolism pathways such as polyol and sorbitol pathways. The excessive activity of collateral metabolism contributes to metabolic imbalance, causing biochemical disorders in key tissues, which result in irreversible changes in function and structure. Glycosylation occurs when reducing sugars, like glucose, react through a series of non-enzymatic processes with ketones or aldehydes, as well as proteins, lipids and nucleic acids, resulting in the formation of Schiff bases (Uceda *et al.*, 2024). Reversible Schiff base compounds convert into stable Amadori products, which then develop irreversible advanced glycation end products (AGEs) through the Maillard reaction. Amadori products generate α -dicarbonyl soroxo aldehydes through rearrangement which plays a vital role in worsening hyperglycaemia in diabetes. Thus, pentosidine, a byproduct of AGEs, is mainly filtered, reabsorbed, and modified by the kidneys; however, when renal tubular is damaged, it affects the clearance of the byproduct which leads to its accumulation in the body. Therefore, reduced renal clearance of AGE-free products is a key factor in this accumulation. Elevated AGEs are associated with the progression of DKD with ESRD patients presenting AGE levels twice as high as those in diabetic patients without renal complications (Cho *et al.*, 2007).

2.0.4.5 Hypertension and Renin-Angiotensin-Aldosterone System (RAAS)

CKD and hypertension are interconnected, such that renal failure is one of the most causes of secondary hypertension and hypertension is an important factor related to CKD progression. Renal artery stenosis, a key example, is identified by hypertension and the gradual decrease of kidney function. It played a significant role in identifying angiotensin-dependent hypertension and contributed to the development of the renin-angiotensin-aldosterone system (RAAS) (Basso and Terragno, 2001). RAAS is a critical regulator of blood volume, electrolyte balance, and systemic vascular resistance. It comprises three significant compounds: renin, angiotensin II, and aldosterone. These three compounds increase arterial pressure in response to decreased renal blood pressure, salt delivery to the distal convoluted tubule, and beta-agonism. Therefore, making RAAS an important mediator of cardiac, vascular, and renal physiology through regulating vascular tone and salt and water homeostasis (Fountain, Kaur and Lappin, 2025). Guidelines for management of hypertension in CKD aim to improve clinical practices and treatment outcomes. These recommendations suggest aiming systolic blood pressure of <120 mmHg, if tolerated, in patients with CKD and hypertension by using the standardized office blood pressure measurement (Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work

Group, 2024) Thus, National Institute for Health and Care Excellence (NICE) advice a blood pressure of <140 mmHg for individuals with CKD and ACR <70 mg/mmoL, and <130 mmHg for those with CKD and an ACR of 70 mg/mmoL or higher (Lee, J. Y. and Han, 2021).

2.0.4.6 Lipid Dysregulation

Hyperlipidemia is caused by an abnormal lipid intake and/or metabolism, which results in elevated levels of cholesterol, triglycerides, or both. When energy intake gradually exceeds the body's ability to store fat in adipose tissue, circulating lipids from various sources spill over into non-adipose tissue, such as muscle, liver, kidneys, and pancreas, which is known as "ectopic lipid accumulation" (Gai *et al.*, 2019). One of the mechanisms contributing to disease progression is lipid accumulation in the kidney tissue, which may trigger inflammation and fibrosis, similar observations reported in fatty liver diseases (Mitrofanova, Merscher and Fornoni, 2023). Lipid imbalances commonly occur in renal failure include elevated triglycerides (hypertriglyceridemia) and low levels of high-density lipoprotein cholesterol (HDL), both of which are significant risk factors for cardiovascular disease. Patients with CKD have a distinctive fatty acid profile with higher levels of serum monounsaturated fatty acids (MUFA) and lower levels of polyunsaturated fatty acids (PUFA). The decrease in PUFAs linked with CKD may further increase the risk of cardiovascular disease. Dyslipidemia typically occurs early in CKD and worsens as the disease progresses. Dialysis has limited impact on improving these lipid imbalances. Chronic hemodialysis may slightly lower triglyceride levels, peritoneal dialysis enhances hypertriglyceridemia due to glucose overload. The risk of cardiovascular complications decreases after kidney transplantation compared to dialysis, however fatty acid profile in transplant recipients remains altered (Mika *et al.*, 2018). Lipids represent more than 30% of the total energy intake in the Western diet. The main role of dietary fatty acids is to serve as a source of energy to the body; however, they also regulate metabolism (Kochan *et al.*, 2021). In the updated KDIGO renal guidelines to manage dyslipidemia is ω -3 PUFAs supplementation Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group (2024), whereas previous guidelines in 2013 recommended only pharmacological lipid-lowering treatment (Ferro *et al.*, 2018). Moreover, obesity is now considered an independent factor for the CKD development. Individuals with increased BMI have higher risk of CKD development compared to people with a BMI in the normal range (GBD 2013 Mortality and Causes of Death Collaborators, 2015).

2.0.4.7 Metabolic acidosis

As mentioned above, kidneys have a vital role in the maintenance of the acid-base balance, which makes metabolic acidosis a common complication of renal failure. It develops as CKD progresses, due to elevated acid-excretory capacity and increased daily endogenous and exogenous acid loads. When the nephron mass decreases in patients with kidney dysfunction, the remaining viable nephrons filter more blood per nephron, which therefore increasing the single nephron GFR (Nagami and Hamm, 2017). Serum bicarbonate levels are the most used to measure acid-base in renal failure, although other factors, such as net endogenous acid production, protein intake, and net renal acid excretion, also play a significant role (Chen, W., Levy and Abramowitz, 2019). Metabolic acidosis in CKD can impact several outcomes, such as disease progression, increased mortality risk, bone demineralization, and muscle breakdown. Persistent metabolic acidosis in renal failure can also result in renal interstitial fibrosis. Traditionally, metabolic acidosis in renal failure is diagnosed when decreased bicarbonate levels are presented due to H⁺ retention. Although, new guidelines suggest that H⁺ retention can occur even when bicarbonate levels are normal due to disease's progression. Current guidelines for management of metabolic acidosis in patients with CKD, recommend that the serum levels of total carbon dioxide (CO₂) should be maintained at ≥ 22 mEq/L, and if needed supplemental alkali salts should be given to achieve this goal (Andrassy, 2013). Dietary approaches to counteract metabolic acidosis in these patients include following a Mediterranean diet, due to its high contain in MUFAs and PUFAs while maintaining low intake of saturated fatty acids (SFAs), also following an Alkaline diet which consists of administration of sodium citrate or sodium bicarbonate to patients with serum bicarbonate levels below 22 mmol/L, a low-protein diet with a protein daily intake of 0.6 g/kg/day, or following a vegan low-protein diet with a protein daily intake of 0.6-0.7 g/kg/day with only plant-based foods (Noce *et al.*, 2021).

2.0.5. Risk Factors

Several factors contribute to the development and progression of CKD, with diabetes and hypertension being the most common. Other risk factors include obesity, family history, aging, and ethnicity. Chronic proteinuria is also a major risk factor for CKD progression and worsens kidney damage over time. Individuals with CKD often experience comorbid conditions that further complicate disease management. Several cohort studies have been examining CKD comorbidities and their prevalence rate. A recent cohort study by (Hawthorne *et al.*, 2023)

investigated the prevalence of multimorbidity and comorbidity patterns at all CKD stages. Multimorbidity is defined as two or more long-term conditions, and it was assessed by using a composite of self-report and clinical data, across four CKD groups. Results showed that out of 978 participants, 96% had multimorbidity of whom the mean number of comorbidities was 3.0 ± 1.7 . When stratified by CKD stage, the most prevalent comorbidities across all stages were hypertension and musculoskeletal disorders with $>55\%$ and $>40\%$ respectively. Another cross-sectional study investigated the prevalence of comorbidity, across 39 physical and mental health comorbidities in Scottish population with impaired kidney function. Higher levels of comorbidity were observed in patients with CKD compared to healthy individuals, with only 1.8% of patients with CKD reporting no comorbidities. Thus, concordant conditions with the strongest relations were hypertension, heart failure, and diabetes were significantly more common in patients with impaired kidney function, whereas discordant conditions with the strongest associations were rheumatological conditions, inflammatory bowel disease, and painful conditions. For mental health comorbidities, high prevalence of depression was around 17.7% in patients with CKD whereas 10.7% was observed in non-Individuals without CKD. Another important result was that people of low socioeconomic status are more likely to develop renal failure, and it is important given that individuals of lower socioeconomic status have greater mortality caused by comorbid factors which then predict mortality, including obesity and associated cardiovascular risk factors (MacRae *et al.*, 2021).

As mentioned above, the main factors that contribute to the development of CKD are diabetes, hypertension, and genetic predisposition, with many individuals being undiagnosed until CKD progresses to advanced stages (Lee, P. *et al.*, 2023). Studies reported that when modifiable factors such as diet, physical activity, smoking, and socioeconomic status are modified, the disease progression rate will decrease (Maringhini and Zoccali, 2024). Therefore, given the increased CKD burden, there is an essential need for early detection and intervention strategies that decrease the progression, which can lead to quality-of-life improvement for the patient (Tonelli and Dickinson, 2020). There are two types of factors affecting CKD; initiating factors are important in the start of the nephron loss cycle, which include age, gender, race, and chronic diseases; continuing factors are factors that continue the disease's progress, including proteinuria, obesity, smoking, and high protein intake (Taal and Brenner, 2006).

2.0.5.1 Metabolic Risk Factors and Albuminuria

The development of albuminuria and the risk of CKD are significantly associated by metabolic disorders such as hyperglycemia, dyslipidemia, obesity, and hyperuricemia. In a study of 225 adults with diabetes and/or hypertension, results showed 38.2% presented microalbuminuria, indicating a high burden of early kidney dysfunction. More specifically, the prevalence of microalbuminuria was higher in individuals with both diabetes and hypertension (48%), followed by those with diabetes alone and hypertension alone reaching 40.6% and 27.7%, respectively (Sivanantham *et al.*, 2024). Similar results were also found in a large survey study conducted in Turkey which showed that diabetes significantly increased the risk of albuminuria (OR 1.67). Furthermore, increased incidence of albuminuria was linked to poor glycemic control, underscoring the significance of efficient blood glucose control in lowering renal risk (Fici *et al.*, 2018). UACR was more closely linked to cardiovascular and all-cause mortality in individuals with coronary artery disease who had type 2 diabetes compared to individuals who did not. Glycemic status and UACR were found to interact, suggesting that even normal-range albuminuria levels may be linked with an increased risk of cardiovascular disease when metabolic abnormalities occur (Lin *et al.*, 2023). Moreover, albuminuria was substantially linked with lipid profiles; total cholesterol and triglycerides showed positive correlations with UACR, whereas HDL showed a negative correlation. As albuminuria severity increased, these associations were stronger and continued to be significant in multivariate analysis, indicating that lipid abnormalities are important causes of renal dysfunction (Hwang *et al.*, 2024). Similar results from a large cohort study showed that increased non-HDL to HDL cholesterol ratio (NHHR) was significantly linked to increased risk of microalbuminuria (OR 1.34). This association remained even after taking lipid-reducing medications into consideration and was more apparent in individuals with BMI more than 30 kg/m² (Huang, Dongli and He, 2025). Moreover, adiposity measurements such as BMI, waist circumference, and body fat content were shown to be substantially linked with albuminuria. Individuals in the highest quartile of these measures showed a significantly greater risk of increased albuminuria, even after adjusting for metabolic and lifestyle factors (Ren, M. *et al.*, 2016). Collectively, these findings highlight that the metabolic abnormalities not only contribute to the development and progression of albuminuria but also work together to accelerate renal impairment and raise cardiovascular risk.

2.0.5.2 Diabetes and Cardiovascular

Global reports indicated that CKD prevalence is threefold higher in patients with hypertension, diabetes, or cardiovascular diseases (CVD) compared to the general population. Moreover, CKD is also a developing factor for cardiovascular events to occur, such as stroke or death. The International Diabetes Federation (2021) reported that the number of new cases of CKD with diabetes increased by 74% from the years of 1990 to 2017, reporting also that 40% of diabetic patients will develop renal failure. Therefore, the causes of ESKD in individuals with diabetes and CKD were due to the presence of proteinuria with the reduction of eGFR (Gheith *et al.*, 2015). The presence of proteinuria and progressive loss of kidneys caused by diabetes due to microvascular complications to the organs is known as diabetic nephropathy. Although the diagnosis of DKD is not based on albuminuria or eGFR reduction renal markers, the diagnosis of diabetic renal disease should consider urinary albumin levels (Ioannou, 2017). The leading cause of ESKD is DKD due to the complexity of chronic elevated glucose levels, oxidative stress, and inflammation. In diabetic patients, kidney damage occurs from hemodynamic and metabolic imbalances such as hyperglycemia, formation of advanced glycation end products, proteinuria, and lipid overload (Chen, S. *et al.*, 2020). Moreover, the phenomenon, known as the “salt paradox,” is observed in diabetic patients with persistent elevated glucose levels because excessive filtration lowers the concentration of sodium chloride, therefore leading to heightened sensitivity to dietary sodium chloride. Therefore, when diabetic patients consume increased salt in their lives, which leads to GFR decline and increased blood pressure (Yang, Y. and Xu, 2022). Continuing high blood glucose in patients with T2DM has an important role in early CKD development due to moderate harm in the glomerular and tubular frames, which therefore have a negative impact on health outcomes (Siddiqui *et al.*, 2022). The prevalence of diagnosed diabetes in the Cypriot population was one of the highest in Europe, with a diagnosed-to-undiagnosed ratio of 2:1. A study by Loizou *et al.*, (2006) reported the importance of interventions that aim at modified glucose tolerance and metabolic syndrome based on the inclusion of 1,200 with elevated diabetic incidence and modifiable glucose tolerance. Moreover, the results of the study reported an increased prevalence rate of obesity and overweight children and adolescents, marking the importance of BMI and associated diabetes development. In addition, study that evaluated the prevalence Cypriot diabetic population, showed that prevalence of diabetes and pre-diabetes in Cyprus were medium-high with 9.2% and extremely high with 16.3% respectively. This suggests that

even though diabetes were relatively low, pre-diabetes rate was elevated showing a promising increase toward total rates of developing diabetes (Andreou *et al.*, 2017).

Hypertension (HTN) is a known risk factor for CVD; increased blood pressure damages the kidneys, and hypertensive nephrosclerosis is the strongest association to develop CKD. There is an association between the HTN incidence rate and renal dysfunction. Continuous high blood pressure increases CKD progression rate as well as the progressive decline in GFR, which can affect the achievement of blood pressure control (Georgianos and Agarwal, 2023). The 2010 annual report for renal data in the US, 23.3% of the population are diagnosed with hypertension without CKD, whereas data for patients with CKD shows 35.8%, 48.1%, 59.9%, 84.1% for stage 1, 2, 3, and 4-5, respectively. Thus, hypertension prevalence is different based on the cause of renal failure. For instance, renal artery stenosis, reported 93%, DKD was at 87%, and polycystic kidney disease was at 74% (Tedla *et al.*, 2011). In 2019, a total of 1.57 million new hypertension-related CKD was reported worldwide, which contributes to 161.97% increase from 1990 (Ren, Y. and Zhang, 2023). Early detection and the appropriate treatment to manage high blood pressure are needed to decrease the risk of developing renal failure and minimize any possible complications (Lee, H. *et al.*, 2022).

2.0.5.3 Age, Gender, and Racial Differences

Several studies have examined the link between aging and CKD progression, reporting that 60% of the population above 80 years have at least three chronic diseases. A population-based cohort study investigated the risks of renal failure and mortality in patients in stage 4 of CKD. Results mentioned that the incidence rate of patients of CKD at stage 4 was higher in older people, and the absolute risk of kidney failure was lower, especially in people with CVD above 75 years (Ravani *et al.*, 2020). Thus, the pathophysiology of renal dysfunction is different in both genders; while CKD is more common in females, the disease's progress is slower compared to males (Swartling *et al.*, 2021). Hormones are most likely to impact renal impairment due to estrogen and testosterone's positive and negative effects, respectively (Ahmed, Sofia B. and Ramesh, 2016). Moreover, the medical therapy of CKD and hypertension using inhibitors such as the renin-angiotensin system (RAS) is more complex in women's pregnancy, and therefore different treatments for CKD are based on gender. Research found that women are more likely to donate a kidney as living donors than undergo dialysis or transplant, which declines the use of kidney transplants in women (Hecking *et al.*, 2021). In the US, Black individuals have a higher prevalence of CKD, although there is limited research regarding the

CKD progression rate for racial differences. A longitudinal study evaluated the renal impairment progression in both Black and white Americans, with 2175 Black and 2207 white individuals, indicating that people of color have a higher CKD progression during the transition from young to middle-aged adulthood. This difference could be due to non-traditional and conventional risk factors such as obesity, hypertension, and forced vital capacity (interorgan crosstalk with renal to racial differences) (Choi *et al.*, 2023).

2.0.5.4 Obesity

Obesity is the excessive or abnormal production of fat or adipose tissue in the body that affects health. There is a positive association with several chronic diseases such as diabetes, CVD, hypertension, and hypercholesterolemia (Panuganti, Nguyen and Kshirsagar, 2025). Obesity resulted from the high energy consumption that exceeds the daily energy expenditure, which elevated triacylglycerols in fatty tissue. It can be considered a pandemic worldwide and in Europe due to up to 30% of the total adult population being in the obese category (Hojs *et al.*, 2023). The severity of the disease is highlighted based on Eurostat, reporting that in 2022, 43% of adults were overweight and 16% were obese. Emphasis is given in the percentage of overweight Cypriot individuals above 16 years being at 47.3% (Stival *et al.*, 2022). Thus, a recent cross-sectional study reported the highest overweight/obesity rates were shown in Greece at 37% and 17.8%, respectively, and Hungary with 35.4% and 19.7%, respectively (Diamantis *et al.*, 2022). Several developed countries have monitored the prevalence of obesity and mentioned that it has been elevated by a factor of two. There is a positive correlation between obesity with diabetes and hypertension, which then correlates with renal structure and histology impairment. However, a recent study by Kjaergaard *et al.*, (2022) investigated obesity and diabetes as contributing factors for renal failure. Increased BMI is correlated with CKD progression rate; results demonstrated that after adjusting for hypertension and/or diabetes, the correlation was still significant, suggesting that weight can be an independent factor for renal failure. Therefore, the relation between obesity and CKD is complex, with several contributing factors playing an important role in developing CKD in obese patients, such as insulin resistance, lipotoxicity, adipocytokine dysregulation, hypertension, and elevated glomerular blood pressure. Diagnosis of obesity-related renal failure is shown by proteinuria, glomerulomegaly, progressive glomerulosclerosis, and reduced kidney function (Jiang, Z. *et al.*, 2023). Obesity is self-diagnosed using BMI, as shown in Table 2.4, and it can be self-treated with some lifestyle changes. BMI categories are based on the impact excessive body fat has on

condition and mortality and are well linked to adiposity; as the BMI increases, the risk of diseases is higher.

Table 2.4: Self-evaluation of Obesity with BMI categories.

BMI (Weight (Kg) / Height (m²))	Nutritional Status
≤ 18.5	Underweight
18.5 – 24.9	Normal/Acceptable
25 – 29.9	Overweight
30 – 34.9	Obesity Class I (medically obese)
35.0 – 39.9	Obesity Class II (medically obese)
≥ 40.0	Obesity Class III (severe obese)

However, BMI does not distinguish between fat mass and lean mass, nor does it account for fat distribution, which leads to misclassification of individuals' metabolic risk. More recently, emphasis has shifted towards the assessment of adiposity as a more accurate indicator of health risk. Excess adipose tissue, especially visceral fat, is metabolically active and have a significant role in the development of insulin resistance, chronic low-inflammation, and metabolic dysfunction. Alternative measures like waist-to-hip ratio (WHR) and waist-to-height ratio (WHtR) complement BMI by better capturing central adiposity, which provides a more accurate assessment of metabolic risk (Carvalho *et al.*, 2023). Using multiple metrics allows for more personalized risk evaluation and targeted interventions. Additionally, genetic factors influence obesity risk, metabolism, and response to treatment; integrating genetic insights into assessment may improve precision and effectiveness of obesity management strategies (Chamarthi and Daley, 2026).

Physical fitness can significantly modify the relationship between BMI and health outcomes. Evidence shows that lean but unfit women had an increased risk for all-cause mortality than overweight but more fit women (Koolhaas *et al.*, 2017). This highlights that BMI alone is an incomplete predictor of health as it does not account for fitness levels or fat distribution, especially central adiposity, which is more strongly linked to mortality (Dong *et al.*, 2018). BMI

also has important limitations including misclassification of cardiometabolic risk, with large population studies, reporting millions of individuals incorrectly categorized as healthy or unhealthy. Its accuracy varies by age, sex, ethnicity, and genetic background, as body fat percentage differs across populations even at the same BMI (Yang, J. *et al.*, 2015). Moreover, genetic analyses show that fat distribution, rather than total fat alone, have a significant role in cardiometabolic health. More importantly, higher levels of gluteofemoral fat (GFAT) are linked with protective profile, including improved cholesterol levels, lower triglycerides, and reduced blood pressure, independent of BMI (Huang, Brian *et al.*, 2023). Therefore, lower GFAT is correlated to worse metabolic outcomes, suggesting that fat storage in the body is more important than how much, highlight the need for more precise obesity assessment beyond BMI.

The Edmonton Obesity Staging System (EOSS) is a validated clinical tool that classified obesity based on the presence and severity of weight-related health impairments. Instead of relying solely on anthropometric measures, it evaluated the impact of obesity on medical, physical, and psychological health, categorizing individuals into stages 0 to 4 according to the most severe obesity-related complications. Stage 0 indicated no apparent obesity-related risk factors, whereas stage 4 reflected advanced or end-stage disease (Kodsi *et al.*, 2022).

Body composition is a key component for maintain good general health and longevity, although it cannot be measured directly in vivo, therefore indirect models are used to assess nutritional status, defined by the balance between nutrient intake, absorption and utilization. The main approach used is the bicompartamental model, which divided the body into fat mass (FM) which includes the water-free body components and fat-free mass (FFM) including the remaining body components such as skeletal muscle, internal organs, and interstitial fat tissue. Gold standards methods to assess FM and FFM are densitometry (underwater weighting), hydrometry (deuterium dilution), Echo-MRI, and total body potassium (TBK) counting. These methods are highly accurate, although impractical in routine clinical use due to cost and complexity. In contrast, Bioelectrical impedance analysis (BIA) is widely used due to non-invasive, affordable, and practical method, although it has limitations related to variability in body water and composition (Marra *et al.*, 2019).

Therefore, to overcome these limitations, advanced methods such as Dual-energy X-ray absorptiometry (DEXA) and magnetic resonance imaging (MRI) provide more precise assessment of fat distribution and muscle mass. Thus, combining BMI with body composition,

fitness, and metabolic markers provide a more accurate, personalized evaluation of health risk and better-targeted interventions (Wu, Y., Li and Vermund, 2024).

Abdominal fat consists of subcutaneous (SAT) and visceral adipose tissue (VAT), which differ in both location and metabolic impact (Cesaro *et al.*, 2023). While most body fat is stored subcutaneously, visceral fat is more metabolically active and harmful, producing inflammatory cytokines and releasing fatty acids that impact liver metabolism and increase chronic disease risk. Based on these differences, VAT is higher associated with cardiometabolic risk, and the VAT/SAT ratio is considered a more accurate indicator of visceral obesity and overall health risk than measuring VAT alone (Chagas *et al.*, 2025). Beyond traditional classifications, distinct obesity phenotypes have been identified based on body composition. Sarcopenic obesity has emerged as a complex and underrecognized phenotype, involving the coexistence of excess adiposity with reduced skeletal muscle mass and function (Borba and Costa, 2025). The distribution of adipose tissue have a significant role in the pathophysiology of sarcopenic obesity. Elevated visceral fat accumulation promotes the release of pro-inflammatory cytokines and disrupts hormonal balance, leading to the development of the condition (Broskey *et al.*, 2018). Additionally, obesity aids the infiltration of fat into skeletal muscle, leading to worsening muscle deterioration. The accumulation of intramyocellular lipids leads to lipotoxic effects, which in turn drive mitochondrial dysfunction, insulin resistance, and chronic inflammation, thereby exacerbating sarcopenic obesity

Moreover, studies by Hayashi *et al.*, (2003); Tamba *et al.*, (2010) highlight the independent and critical role of visceral adiposity in cardiometabolic and renal risk, beyond traditional measures such as BMI. The first study, in Japanese men reported that increased visceral fat area was significantly associated with higher urinary albumin-creatinine ratio, indicating early kidney impairment and endothelial dysfunction, regardless of BMI. This suggests that visceral fat accumulation contributes directly to albuminuria and early CKD-related changes, especially in the presence of metabolic risk factors. Similarly, the second study in Japanese Americans reported that intra-abdominal fat was independently linked with a higher prevalence of hypertension, even after adjusting for total fat, subcutaneous fat, BMI, and insulin, suggesting that visceral fat remained the only adiposity measure consistently linked to hypertension. Thus, in obese-related kidney failure patients, at early stages, they are asymptomatic, with microproteinuria being the main diagnostic biomarker. Effective management of obesity requires reducing calorie intake, increasing physical activity, and adopting behavioral modifications (Andreou *et al.*, 2024).

2.0.5.5 High-protein diets

Increased prevalence of obesity in several countries: people have been interested in reducing their body weight rapidly by following low-carbohydrates high-protein, high-fat diets. These diets have been fueled by social media promotions for their rapid weight loss and managing glycemic control (Dyńska *et al.*, 2025). People with CKD or individuals with elevated development risk following persistent high-protein diets may lead to kidney dysfunction. The recommended daily protein intake is 0.83 g/kg/per day, which contributes to 20% of the total energy intake, whereas increased protein intake is 2-2.5 g/kg/day (Bilsborough and Mann, 2006). The recommended protein intakes are based on the minimum amount to maintain nitrogen balance, and they are optimized for physical activity level (PAL). For instance, people with low PAL have low levels of nitrogen retention, and in order to sustain muscle mass, higher protein requirements are required compared to those with high PAL (Lonnie *et al.*, 2018). Results from the National Health Nutrition Examination Survey (NHANES) show that the current average consumption of protein intake in the United States (US) is 1.2-1.4 g/kg per day, which is higher than the recommended allowance (Moore *et al.*, 2013). High-protein diets promote higher portions of protein while restricting carbohydrate intake based on the idea that carbohydrates are bad for the body, an accusation that has been refuted in the literature (Ko, Gang-Jee *et al.*, 2020). These diets recommend that protein intake should be 20-25% of the calories consumed, whereas carbohydrates should be lower than 45%. In extreme cases, such as a ketogenic diet, only <5-10% of total energy intake is from carbohydrates.

In short-term studies, patients with hypertension and T2DM have shown inconsistent effects of high protein intake on GFR and urinary albumin excretion. Although the largest short study, which included a total of 164 healthy people, showed that people who consumed a high-protein diet, comprised of 25% of the total energy intake increased eGFR by 3.8 mL/min/1.73m² compared to those who consumed 15% protein intake, after six weeks of intervention. However, in early stages, glomerular hyperfiltration occurs, proteinuria is observed, which is known as a contributing factor when followed for long periods of time (Juraschek *et al.*, 2013). Figure 2.4 demonstrates the consumption of a high-protein diet and the relation of increased GFR by the dilation towards arterioles, therefore leading to renal dysfunction, and over time damaging the kidney structure (Ko, Gang-Jee *et al.*, 2020). In the Prevention of Renal and Vascular End-stage Disease (PREVEND) study, there was no relation between baseline protein intake and rate of eGFR, although protein intake was significantly linked with cardiovascular events (Halbesma *et al.*, 2009). Thus, a population-based study evaluating renal individuals and

health people found an association between higher protein intake and decline of eGFR, which was significant after 12 years. It is suggested that 1 g per day of higher protein intake was linked to a reduction of 4.1 mL/min/1.73 m² more negative eGFR change and to a significantly increased risk of eGFR <60 mL/min/1.73m² incidence rate (Cirillo *et al.*, 2014).

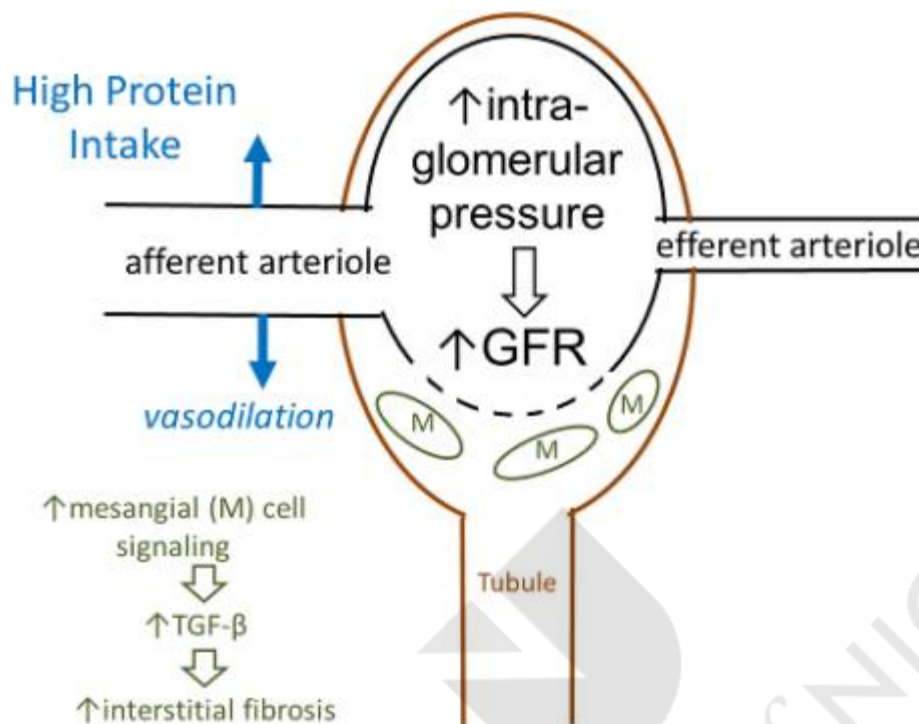


Figure 2.4: High protein and damage of kidney structure due to glomerular hyperfiltration.

Note: Diagram showing high protein intake and how it leads to dilation of the afferent arteriole and elevated GFR, causing kidney damage over time due to glomerular hyperfiltration. GFR: Glomerular Filtration Rate; TGF- β : Transforming growth factor beta. Modified by (Ko, Gang-Jee *et al.*, 2020).

Moreover, development of metabolic complications such as elevated levels of urea and nitrogenous waste products were observed with the increased protein consumption. In a crossover study, comparison of a high protein intake with 2.4 g/kg per day with a normal protein intake of 1.2 g/kg per day for a 7-day period for each meal plan in 24 healthy male individuals was assessed. Results showed that participants who consumed higher protein intake had higher blood urea nitrogen (BUN) than normal protein intake. Increased BUN concentration levels, caused by increased protein carbamylation and production of reactive oxygen species, may cause high oxidative stress, inflammation, endothelial dysfunction, and cardiovascular diseases (Frank *et al.*, 2009).

Identifying and addressing several contributing factors to renal failure is essential to prevent and treat CKD. Early detection and management of the disease can prevent or delay the disease

progression rate by half or may even reverse it. Risk factor-based screening can effectively identify a significant proportion of people with undiagnosed renal failure (Korsa *et al.*, 2025). Mortality risk in Individuals with CKD increases rapidly as kidney function worsens, due to the development of cardiovascular events, such as stroke. As reported, diabetes and hypertension are the leading causes of renal failure and are risk factors for the progression of both cardiovascular disease and CKD. Therefore, targeting risk factors that are modifiable can improve survival and quality of life by reducing cardiovascular complications in patients with CKD and CKD's progression to ESRD (Brück *et al.*, 2016).

2.0.6. Cardio-renal Metabolic Syndrome

2.0.6.1 Definition of CRMS

While the mechanisms of CKD progression have been described, these processes do not occur in isolation. Increasing evidence supports the concept of Cardiovascular-Kidney-Metabolic (CKM) or Cardio-Renal-Metabolic (CRM) syndrome, where renal dysfunction is closely interconnected with cardiovascular metabolic disturbances through shared pathophysiological pathways (Iacoviello *et al.*, 2025). More specifically, CRM is a combination of inflammatory, neurohormonal, and metabolic disorders causing damage to the kidneys and heart at the same time. Insulin resistance, visceral obesity, dyslipidemia, and low-grade inflammation are major contributors to endothelial dysfunction, maladaptive remodeling, and progressive organ damage (Singh, A. *et al.*, 2025). As illustrated in figure 2.4, CRM syndrome can be conceptualized as a three-system interaction consisting of renal, cardiovascular, and metabolic components, each influencing and exacerbating the others in bidirectional manner. Decreased eGFR, increasing proteinuria, and the accumulation of uremic toxins, all of which contribute to systemic complications, are indicators of the gradual decrease of kidney function, which is reflected in the renal axis. Renal impairment is directly linked with structural and functional cardiac dysfunctions such as hypertension, endothelial impairment, and myocardial alteration, which consist of the cardiovascular axis. Moreover, key characteristics of the metabolic axis include insulin resistance, central obesity, and dyslipidemia. These conditions cause oxidative stress and persistent low-grade inflammation, which are major causes of cardiovascular and renal conditions.

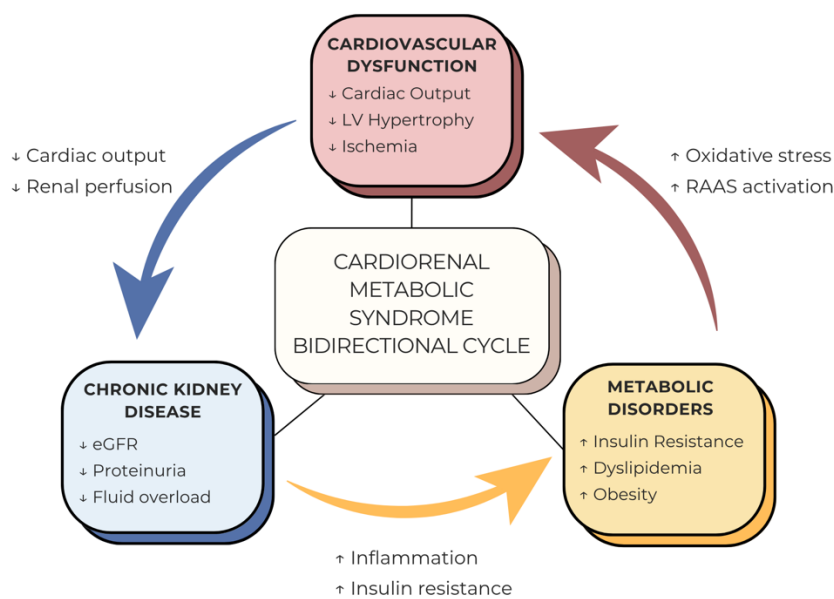


Figure 2.5: Bidirectional Interactions in Cardiorenal Metabolic Syndrome.

Source: Author's own conceptualization based on current literature.

Early stages of CKM syndrome are often asymptomatic, making early detection and intervention critical for better outcomes, therefore in order to guide prevention and management, CKM syndrome is distributed into stages 0 through 4. The inverted pyramid model presented in figure 2.6 demonstrated the progressive process of CKM syndrome, highlighting the transition from optimal health to advanced cardiovascular disease. At the widest level, representing the lowest risk, individuals report no CKM risk factors and maintain normal metabolic, renal, and cardiovascular function. As the pyramid narrows, excess and dysfunctional adiposity emerges, characterized by obesity, insulin resistance, and low-grade inflammation, marking the earliest stage of metabolic disturbance. Progression to stage 2 is defined by the development of metabolic risk factors, including hypertension, dyslipidemia, and type 2 diabetes, often accompanied by early CKD. These abnormalities further contribute to stage 3, where subclinical cardiovascular changes such as atherosclerosis and cardiac remodeling become evident, therefore indicating a significantly increased risk of adverse outcomes. At the narrowest and highest-risk level, stage 4 is characterized by overt clinical cardiovascular disease, including coronary heart disease, heart failure, stroke, and peripheral arterial disease.

Thus, the inverted structure of the pyramid reflects both the decreasing proportion of individuals and the increasing severity of disease across stages, while the vertical gradient emphasizes the increase of cardiovascular and renal risk. Importantly, the model highlights the critical role of early identification and intervention at the lower stages, where preventive strategies may reduce the progression to advanced CKM syndrome and its associated complications. Based on that, early-stage interventions targeting modifiable risk factors, especially dietary approaches such as plant-dominant low-protein diets, may have an important role in mitigating metabolic dysfunction and slowing CKM progression rate.

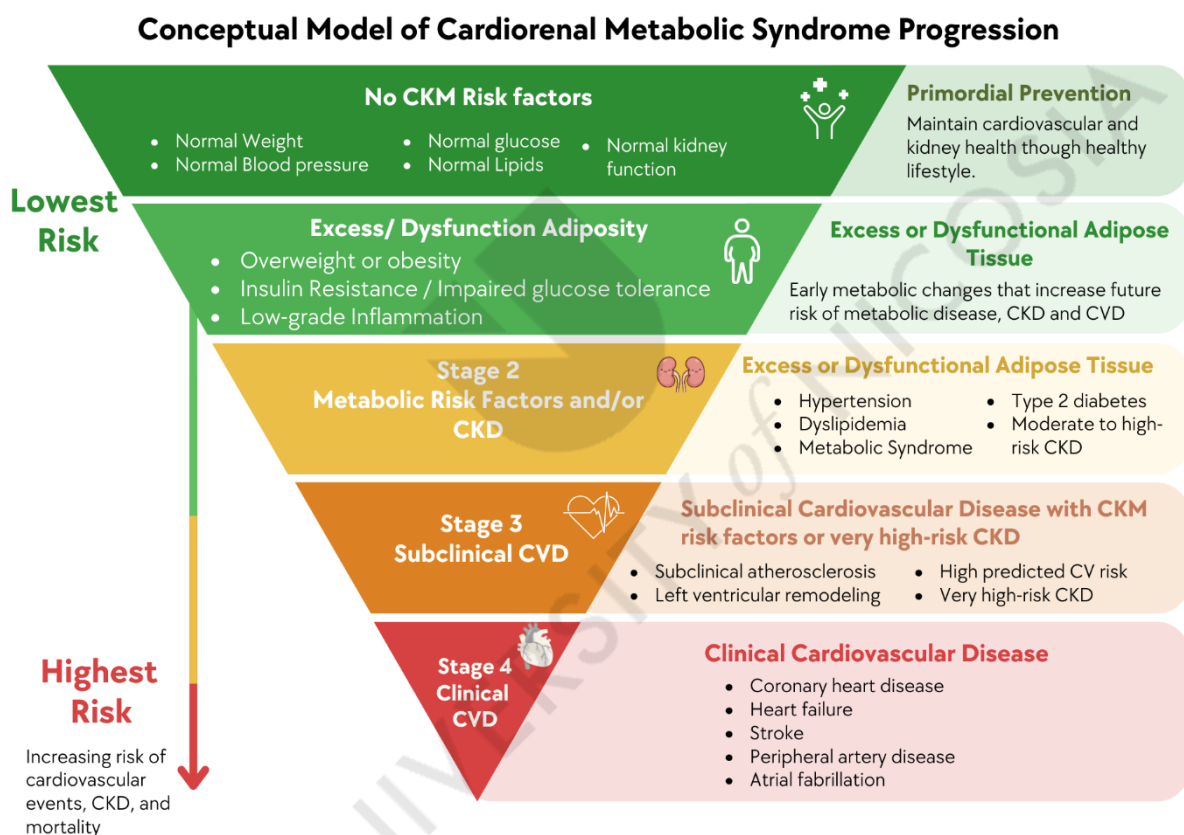


Figure 2.6: Cardiorenal Metabolic Syndrome: Risk Escalation Model.

Note: CKM, cardiovascular–kidney–metabolic; CKD, chronic kidney disease; CVD, cardiovascular disease.

Source: Author's own conceptualization based on current literature.

2.0.6.2 Epidemiology and Clinical Burden

Data from 2015 and 2010, demonstrated that more than one-third of US adults had at least one cardiorenal metabolic condition, while 9.5% had multiple conditions and 1.5% had all three diseases including CKD, diabetes, and CVD. The most common combination was CKD with

type 2 which reached 3.2%, followed by CKD with diabetes and CVD with CKD. Moreover, data showed that the burden of CRM was increased in adults above 65 years, male adults, with low income as well as low education level, and black non-Hispanic populations (Ostrominski *et al.*, 2023). Similar data were observed in a study by Aggarwal, Ostrominski and Vaduganathan (2024) where most American adults were classified in early to intermediate CKM stages 2, 1, and adults with ideal health reached 49%, 25.9%, and 10.6% respectively. Results of the study, demonstrated the burden of advanced CKM stages were strongly age-linked affecting more than half of adults above the age of 65, suggesting a high prevalence of early-stage disease and significant disparities in advanced CKM burden, especially by age, gender, and race. Another study included adults from Lithuania reported that 34.8% were classified with advanced stage 4 of CKM syndrome, while an additional 23.4% were in earlier stages stage 1 through 3, therefore indicated a high overall burden. The most common diseases who were linked with CKM were obesity and type 2 diabetes with 21.2% and 17.2% respectively. However, despite this high burden, key biomarkers were under-assessed in early-stage patients with lack of measurement of albuminuria reaching only 9% and N-terminal pro-B-type natriuretic peptide (NT-proBNP) reaching 4.9%. (Urbonas *et al.*, 2025).

2.0.6.3 Pathophysiology of CRM

These findings reflect underlying pathophysiological mechanisms including insulin resistance, chronic inflammation, endothelial dysfunction, as well as RAAS activation, which enhance the continuous development of metabolic, cardiovascular, and renal dysfunction. Main contributors of CRM are obesity and excess adiposity, which are influenced by both genetic and environmental factors which lead to impaired adipocyte function, resulting in adipocyte hypertrophy, tissue hypoxia, and the activation of oxidative stress and chronic low-grade inflammation (Turner *et al.*, 2025). More specifically, visceral and ectopic fat production promotes metabolic disturbances through elevated lipid storage, reduced insulin sensitivity, and the secretion of pro-inflammatory atherogenic, and diabetogenic adipokines. Furthermore, CRM is often linked with subclinical atherosclerosis, arterial stiffness, and early cardiac impairment, which increases the risk of adverse cardiovascular outcomes. Clinically, CRM may present across a spectrum ranging from asymptomatic disease to overt cardiovascular and renal complications, therefore, early identification and management of excess adiposity are crucial to mitigate the progression of metabolic and renal dysfunction (Kyaw, 2025).

2.0.6.4 Role of CKD in CRM

The pathophysiological mechanisms underlying CRM contribute significantly to the development and progression of CKD. These consistent processes promote structural and functional impairments in the kidney, leading to reduced GFR and albuminuria. Crucially, CKD acts as a major facilitator of cardiorenal metabolic dysfunction in addition to being a result of these disruptions. The development of uremic toxins, chronic inflammation, as well as fluid and electrolyte imbalances worsen cardiovascular and metabolic complications as kidney function declines (Säemann *et al.*, 2025). Therefore, CKD plays a crucial role in CRM, acting as both as an organ of interest and as an agent for the disease progression rate.

2.0.6.5 Management of CKM Syndrome

Management of CKM syndrome focuses on a multifactorial approach targeting both cardiovascular and renal risk factors with key strategies including lifestyle modifications, glycemic control, blood pressure management, lipid management, kidney protection, and comprehensive care. It should be tailored based to disease stage, with intervention intensifying as risk increases. In the early stages, emphasis is placed on prevention, while advanced stages require comprehensive medical management (Shahid *et al.*, 2025).

More specifically, at stage 0, management focuses on maintaining optimal health through lifestyle modification, including a balanced diet, regular physical activity, weight control, and avoidance of smoking. The primary aim is to preserve cardiovascular and renal health and prevent the development of metabolic risk factors (Lloyd-Jones *et al.*, 2022). At stage 1, interventions target excess and dysfunctional adiposity. These strategies include weight reduction, improvement of insulin sensitivity, and early dietary modifications. Several randomized controlled trials have evaluated the effects of dietary composition and lifestyle intervention on weight loss and cardiometabolic risk factors. In a large trial by Sacks *et al.*, (2009), involving 811 overweight adults, weight loss at two years was modest and similar across diets with varying macronutrient compositions, suggesting that overall caloric reduction, rather than macronutrient distribution, plays a significant role in long-term weight management. Similarly, the CALERIE study demonstrated no significant differences in weight loss between high and low glycemic load diets after 12 months of caloric restriction (Das *et al.*, 2007). However, in a study by Foster *et al.*, (2003) reported that a low-carbohydrate, high-protein diet resulted in greater short-term weight loss and improvements in triglycerides and

HDL-cholesterol compared to a conventional low-fat diet; although, these differences were not sustained at 12 months.

Beyond dietary composition, lifestyle interventions have shown substantial benefits in metabolic risk reduction. The Diabetes Prevention Program demonstrated that intensive lifestyle modification, including weight loss and increased physical activity, reduced the incidence of type 2 diabetes by 58%, outperforming pharmacological intervention with metformin (Tuomilehto *et al.*, 2001). Similarly, the Trials of Hypertension Prevention (TOHP) study showed that weight loss and dietary sodium reduction significantly reduced blood pressure and lowered the incidence of hypertension over time (Effects of weight loss and sodium reduction intervention on blood pressure and hypertension incidence in overweight people with high-normal blood pressure. The Trials of Hypertension Prevention, phase II. The Trials of Hypertension Prevention Collaborative Research Group 1997). These findings are particularly relevant to stage 2 of CKM syndrome, which is characterized by the presence of cardiometabolic abnormalities. At this stage, dietary approaches such as the Dietary Approaches to Stop Hypertension (DASH) diet and the sodium restriction have been shown to effectively lower blood pressure, while weight loss, increased physical activity, and reduced alcohol intake further contribute to cardiovascular risk reduction (Appel, L. J. *et al.*, 1997; Sacks, F. M. *et al.*, 2001). Behavioral intervention trials by Miller *et al.*, (2002); Appel *et al.*, (2003) including PREMIER and DEW-IT, respectively, support the effectiveness of structured lifestyle interventions in improving blood pressure control, even among individuals receiving pharmacological treatment. Moreover, while the DASH diet has been shown to reduce blood pressure and LDL cholesterol, its effects on HDL and triglycerides are less favorable. Evidence from the OmniHeart trial suggests that modifying the DASH approach by replacing carbohydrates with protein or unsaturated fats results in greater improvements in both blood pressure and lipid profiles (Appel, Lawrence J. *et al.*, 2005). As CKM progresses to stage 3, the presence of subclinical cardiovascular disease reflects a transition from risk factor accumulation to early structural and functional cardiovascular changes. Subclinical atherosclerosis and cardiac dysfunction can be identified through imaging and biomarkers, indicating a substantially increased risk of overt cardiovascular disease. At this stage, targeted lifestyle intervention remains crucial. Evidence from the DISCO-CT trial demonstrated that individualized dietary counseling and lifestyle medication can reduce high-risk atherosclerotic plaque characteristics. In addition, exercise intervention continues to provide cardiovascular benefits, with high-intensity training shown to improve cardiorespiratory fitness to reduce

myocardial stiffness, which is a key factor in the development of heart failure (Henzel *et al.*, 2021). In stage 4, CKM syndrome is characterized by established clinical cardiovascular disease, such as coronary heart disease, stroke, peripheral artery disease, heart failure, and atrial fibrillation. At this stage, evidence shifts from surrogate outcomes to hard cardiovascular endpoints. Dietary intervention, especially Mediterranean style diets, have demonstrated significant reductions in cardiovascular events, as shown in trials such as the Lyon Heart study conducted by de Lorgeril *et al.*, (1994) and CORDIOPREV conducted by Delgado-Lista *et al.*, (2022). Sodium reduction strategies, including the use of potassium-enriched salt substitutes, have also been linked with reduced stroke risk. In addition, comprehensive lifestyle intervention, such as structured exercise programs, cardiac rehabilitation, and weight management, have been shown to improve clinical outcomes, functional capacity, and quality of life across several cardiovascular conditions.

Collectively, these findings highlight that while specific dietary compositions may influence short-term outcomes, sustained weight loss and improvements in cardiometabolic health are primarily drive by long-term adherence to lifestyle interventions, such as dietary modification and physical activity.

2.0.7. CKD's Impact on Health and Healthcare

CKD is a major global health issue, and it ranked 16th among the leading causes of death in 2016 and is expected to rise to 5th position by 2040. It is a continuous health issue affecting 13% of the total population, with increasing impact on the economy and environment (Lv and Zhang, 2019). Thus, it represents a multifaceted burden, which is further worsened by comorbidities and an aging population. It is a leading cause of mortality and morbidity and is more frequent in individuals with comorbidities, leading to worse clinical outcomes (Rao *et al.*, 2025). Several complications that have a great impact on the human body occur in renal failure, and when comparing population with impaired kidney function with the general population, patients with CKD report a lower health-related quality of life (Sullivan, Michael K. *et al.*, 2020). Studies have shown that both CKD with concordant comorbidities (diseases that share pathophysiology and/or pharmacological treatments) and non-concordant conditions (diseases where pathophysiology is unrelated and/or where treatments of different conditions are complicating or contradictory) are associated with increased healthcare utilization, length of inpatient hospital stay, and mortality (Levin *et al.*, 2017).

Considering the health system perspective, CKD progression rate from stages 1-3b was linked to a 1.1 to 1.7-fold increase in per patient mean annual health care cost. In more advanced CKD stages progression rate was seen from 1.3 to 4.2-fold increase in costs, with the highest costs related to ESKD, reporting \$20,110 to \$100,593 per patient (Elshahat *et al.*, 2020). The economic burden of CKD is significant on a global scale. An analysis across 31 countries reported that between the years 2022 and 2027, the annual direct healthcare costs of renal failure, pre-kidney replacement therapy, will increase by 8.7%, from approximately 202 billion to 220 billion dollars (Chadban *et al.*, 2024).

As previously mentioned, most patients with impaired kidney dysfunction who are at early stages of CKD are often asymptomatic, and studies have reported that up to 93% of patients with CKD stage 3 are unaware of their clinical status (Sultan *et al.*, 2021). Existing evidence has found a correlation between advanced stage of renal disease and increased utility of health care. More specifically, a recent cohort study by Sakoi *et al.*, (2024) investigated the utilization of excess health care, including health care cost, duration of outpatient treatment, and hospitalizations, with proteinuria and eGFR in patients with CKD at early stages of the disease. Results showed that a significant number of participants, 5.3%, had early-stage renal failure detection based on screening results in the general population. Thus, over the five-year period, observations based on the use of excess health care for proteinuria and mild reduction of eGFR were consistent. This leads to the significance of the CKD and health care utilization association. Medication treatment such as angiotensin receptor blockers (ARBs) and SGLT2 inhibitors may increase the health care costs, although they can decrease long-term care utilization due to their effectiveness to lower CKD progression. Therefore, the importance of designing preventive strategies for CKD development and progression as well as reducing health care burden is associated with a more sustainable health care system.

2.0.8. Prevention of CKD

CKD is a progressive condition that typically follows a continuing decrease in kidney function over time. As kidney function decreases, patients move through different stages, and the risk of complications such as CVD, anemia, and bone mineral disorders increases. Understanding the progression of CKD is essential for implementing appropriate interventions to decrease its progression rate before it leads to ESRD.

CKD is often considered a condition that tends to progress over time. With population aging, the burden of the most age-related conditions, including renal failure, is expected to increase.

Referral to a nephrologist is advised for progressive CKD or for eGFR of less than 30 mL/min/1.73 m², patients with less severe CKD are increasingly referred to a specialist nephrology care, perhaps in anticipation that such care will eventually be required (Levin *et al.*, 2013). Thus, understanding how over CKD regression occurs and its outcomes and whether CKD regression varies by age may inform clinical decision-making and health policy, including referral recommendations.

Increased emphasis is being placed on early detection and intervention in renal failure. CKD is managed by using a multifaceted approach that includes lifestyle modifications, blood pressure control, lipid management, glycemic control in diabetic patients, and, more recently, use of new medications with cardiovascular and kidney benefits, such as SGLT-2 inhibitors (Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group, 2024). In addition, despite efforts to improve healthcare practitioner awareness of CKD, as well as clear guidelines promoting early detection and intervention, diagnosis of stage 1-3 CKD remained low (Schneider *et al.*, 2022).

There has been remarkable progress regarding treatments to improve outcomes for patients with CKD in the last five years. In addition, renal failure is also in the high rank scale of public health concern due to the number of people affected and the expensive care, when prevention strategies are not implemented sufficiently. The main key strategies for primary prevention of renal failure include early diagnosis and treatment of CKD risk factors (e.g. diabetes, CVD, obesity etc.). Therefore, public health strategies to prevent these contributing factors are essential (Luyckx, Cherney and Bello, 2019). A recent study conducted in Italy, aimed to improve awareness of CKD and the impact in primary care of targeted training and networking with nephrologists. Results showed a corresponding increase in the prevalence of CKD, especially in people with contributing factors; CKD prevalence in diabetic patients was 6.3% to 12.7%, patients with hypertension were 5.6% increased up to 9.9%, and people with heart failure CKD prevalence was 10.8% and increased to 23.7%, and the proportion of patients living with CKD increased from 2.2 to 3.8%. This suggests that training and networking to general practitioners by nephrologists improved CKD awareness and the identification of renal failure increased (Pesce *et al.*, 2022). Thus, while addressing the lack of awareness in healthcare practitioners is important, awareness and encouraged to seek medical advice to the public is also crucial. This led to the European Kidney Health Alliance and the European Kidney Patients Federation, to develop a campaign to encourage communities and individuals to remind their healthcare practitioners to assess their risk of kidney failure. The campaign is known as the ABCDE

campaign which is based on five simple questions regarding health status that only the healthcare system can provide. The infographic of the campaign is shown in figure 2.5, which helps individuals to establish whether their kidneys are healthy or whether they are at risk of developing renal failure. It is based on the risk factors information: (A) What is my albuminuria? (B) What is my blood pressure? (C) What is my cholesterol? (D) Am I diabetic? (E) What is my kidney function, based on eGFR).

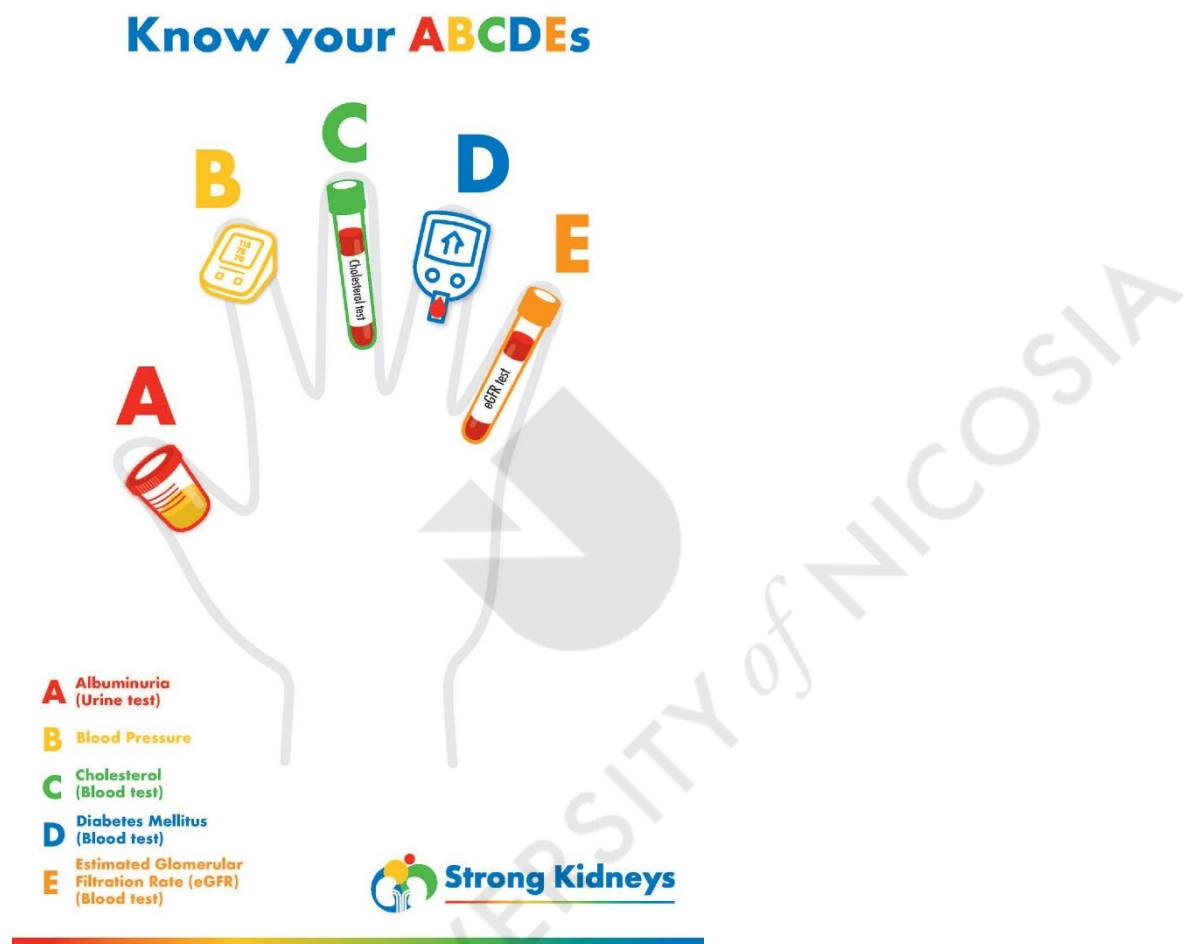


Figure 2.7: Infographic for the Strong Kidneys ABCDE campaign (Ferro *et al.*, 2025).

Prevention is more effective than cure; however, there is a lack of evidence-based lifestyle recommendations for the primary prevention of renal failure. A recent meta-analysis by Kelly *et al.*, (2021) evaluated evidence regarding modifiable lifestyle factors and CKD incidence. Results showed that higher vegetable intake and higher potassium intake had a significant correlation with decreased odds of renal failure, whereas evaluation of the consumption of carbohydrate intake, fish, fruits, phosphorus, protein, and sugar-sweetened beverages did not show any clear relation. Thus, another correlation was reported with higher sodium-potassium

ratio and processed meat consumption. The association between different activity levels and incidence rate showed that people who were more active had lower odds of renal incidence rate compared to those who were less active.

2.0.9. Nutritional Management of CKD

As previously mentioned, kidneys are responsible for filtering metabolic waste products from the blood, regulating fluid and electrolyte levels, and maintaining acid-base homeostasis (Gantsova *et al.*, 2024). As kidney function decreases, these regulatory processes become altered, leading to the formulation of waste products such as urea, creatinine, and phosphorus, which contribute to uremic toxicity and further kidney damage (Lim, Y. J. *et al.*, 2021). The importance of nutrition in renal failure management is crucial, as it can impact the disease's progression rate, and the patient's clinical outcomes. A well-balanced dietary plan tailored to patients with CKD can help decrease the burden on the kidneys, delay the need for dialysis, and improve the patient's quality of life.

2.0.9.1 Protein Requirements and Protein Restriction in CKD

Current CKD care guidelines recommend medical nutrition therapy (MNT), a personalized, evidence-based application of the Nutrition Care Process (assessment, intervention, diagnosis, monitoring, and evaluation) provided by registered dietitian nutritionists (RDNs) to help reduce CKD progression, improve quality of life, and delay kidney failure (Lee, P. *et al.*, 2023). This approach includes careful monitoring of dietary intake, especially those with protein restriction in advanced CKD stages, calcium, phosphorus, potassium, and sodium. Optimizing these nutritional needs, MNT can reduce symptoms associated with renal failure while ensuring that the nutrient composition of the meal plan meets the patient's nutritional status, therefore reducing the risk of malnutrition (Beto, Ramirez and Bansal, 2014).

Considering renal failure as a chronic inflammatory disease, elevated insulin resistance in patients with CKD can induce protein catabolism, which can significantly impair the patient's nutritional status (Kalantar-Zadeh and Fouque, 2017). Thus, dietary modifications can reduce the accumulation of waste products, which may reduce uremic symptoms and delay the initiation of dialysis. Nutritional management should be provided to the patients at all stages of renal failure, and all healthcare professionals should be aware of the dietary and nutritional requirements of these patients. Renal diets typically focus on limiting protein intake,

controlling phosphorus and sodium levels, and managing potassium intake based on the patient's needs and wants (Hsu, H. *et al.*, 2021; Dumler, 2011).

Protein restriction is the primary nutritional guideline due to excessive protein intake increasing kidney blood flow and increasing intraglomerular pressure, leading to higher GFR and more efficient excretion of protein-derived nitrogen products. The lowest acceptable protein intake for the general population is 0.8 grams per kilo of body weight per day; this amount of protein also represents the initial dietary protein level at the early CKD stages. However, patients with CKD or at risk of CKD consuming increased dietary protein, mainly from animal-based products, led to dramatic effects on kidney function and long-term kidney health. The definition of high protein consumption is between 1.2 and 2.0 g/kg/per day (Joint WHO/FAO/UNU Expert Consultation, 2007). Conversely, a low-protein diet (LPD) has been shown to reduce the production of toxic metabolic byproducts, alleviate uremic symptoms, and delay the need for dialysis (Bellizzi *et al.*, 2018). Moreover, there have been several protein-restricted dietary regimens suggested for moderate to advanced CKD; a typical LPD provides around 0.6-0.7 grams of protein per kilogram per day; a very low-protein diet (VLPD) provides around 0.3-0.4 grams of protein per kilogram per day, which is a vegetarian diet supplemented with essential amino acids to satisfy the body's nitrogen needs and with nitrogen-free ketoanalogues to recirculate the endogenous urea (Bellizzi *et al.*, 2016). Furthermore, limiting protein intake improved metabolic dysfunction in individuals with CKD, which leads to enhanced protein metabolism, decreased muscle catabolism, and decreased uremic symptoms (Goraya and Wesson, 2015). Reducing protein intake, especially animal-based products, dietary modification focuses on managing hyperphosphatemia, which might occur in patients with impaired kidney function due to mainly consuming animal protein (Ko, Gang Jee *et al.*, 2017).

(Hsu, H. *et al.*, 2021)(Dumler, 2011)Another nutritional guideline is sodium restriction due to dietary sodium being associated with fluid retention, elevated blood pressure, and increased CVD risk in patients with CKD. Studies showed that decreasing salt intake increased the beneficial properties of LPD by reducing intraglomerular pressure, suggesting a decrease in proteinuria, therefore reducing CKD progression (Kalantar-Zadeh and Fouque, 2017). Considering the risk of hyponatremia and adverse outcomes, dietary sodium intake lower than 1.5 g/day is not recommended for advanced stage renal disease or patients on dialysis, with the recommended sodium intake being from 2 to 2.3 g/day (Kim, S. M. and Jung, 2020).

Moreover, potassium management is also essential when considering nutritional intervention in People diagnosed with CKD. Low potassium levels are linked with muscle weakness and hypertension, whereas hyperkalemia leads to ventricular arrhythmia and death, suggesting the importance of regulating serum potassium. KDOQI guidelines regarding potassium intake of 2 to 4 g/day for patients with advanced renal failure; however, individuals diagnosed with CKD at early stages have no restrictions recommended (Ikizler, Talat Alp and Cuppari, 2021). A recent study assessed dietary potassium intake with the development of renal failure and renal function in kidney patients at early stages. Results reported that the reduction in eGFR was lower in patients with increased potassium intake, and in hypertensive patients, there was a decrease in high diastolic blood pressure development (Mun *et al.*, 2019). Moreover, while limiting animal-based products due to their higher acidic load, plant-based foods are the main source of protein. However, plant-based foods are high in potassium content, especially fruits and vegetables, leading to the concern that plant-based foods may cause hyperkalemia. On the contrary, vegetarian foods have specific qualities, including blunt potassium retention, including their alkalinizing effects, the lack of bioavailable potassium, and the impact of dietary fiber (Babich *et al.*, 2023).

Another essential nutrient that requires control and nutritional management is phosphorus, which is required to maintain homeostasis. It is essential for bone growth and mineralization, as well as energy regulation and acid-base homeostasis. Hyperphosphatemia is associated with increased cardiovascular risk in patients with CKD as well as the healthy population. Renal guidelines suggest maintaining phosphorus intake of 800 to 1000 mg/day in advanced stages of kidney failure and for dialysis patients. Shifting from animal-based products to more plant-based due to phosphorus bioavailability in plant-based products being lower, 20% to 50%, compared to animal-based products being 40% to 60%. Thus, food additives in processed and fast foods contain inorganic phosphorus, which reports almost a 100% intestinal absorption; therefore, patients with impaired kidney function should not consume them (Kalantar-Zadeh *et al.*, 2010).

Moreover, calcium and vitamin D have an essential role in body functions. Calcium is essential for muscles to function properly as well as the circulatory and digestive systems and is important for bone accumulation and blood cell synthesis. Given the important role of the kidneys to maintain normal calcium levels, when low levels of calcium in the body present it can lead to secondary hyperparathyroidism and therefore leading to increase CKD progression rate (Janmaat *et al.*, 2018). Recommended calcium intake is around 800 to 1000 mg/day in order

to maintain the required calcium intake in patients with advanced stage of CKD. Lastly, vitamin D should be considered due to the prevalence of vitamin D deficiency being elevated in patients with advanced CKD stage compared to healthy individuals (Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group, 2024).

2.0.9.2 Nutritional Challenges in CKD

Adherence and the risk of protein-energy wasting (PEW) are two of the main concerns regarding protein restriction in patients with CKD, even though several studies assessing the effectiveness and safety of these diets found them safe with no serious complications, with low rates of PEW and malnutrition. A recent cross-sectional study that included patients with CKD stages 3 to 5 assessed the association between LPD with body composition, muscle function, inflammation, and amino acid-based metabolic profile. Only 15% of the participants met the recommended daily calorie intake at 30-35 kcal/kg/day, with the rest achieving only 23±6 kcal/kg/day. The mean protein intake was around 0.9±0.3 g/kg/day, and only 34% of the patients met the recommended goal of daily protein intake lower than 0.8 g/kg/day. Results showed that patients following LPD reported significantly lower hemoglobin and albumin levels and lower leucine levels compared to patients with CKD who did not follow an LPD. The study suggests that protein restriction as well as inadequate energy intake could lead to malnutrition (Hsu, H. *et al.*, 2021). In contrast, another study examining the effect of protein-restricting diets reported that VLPDs can maintain mean lean and body cell mass for a prolonged period of time in patients with CKD at stages 3 to 5. Thus, it highlights the importance of adequate calorie intake as well as protein to reduce the risk of malnutrition. Thus, it states that these diets require regular clinical monitoring by nephrologists and renal dietitians, with a focus on nutritional monitoring, dietary protein and energy intake, and body composition changes (Dumler, 2011).

2.0.9.3 Body Composition Alternations in CKD

Assessment of body composition is increasingly recognized as an important component of nutritional evaluation in patients with CKD. Changes in muscle mass, fat mass, lean tissue index, hydration status are commonly observed in individuals with CKD and are linked with disease progression, PEW, reduced functional status, and increased mortality risk (Pérez-Torres *et al.*, 2018). Thus, body composition monitoring has become an important tool in evaluating the nutritional impact and safety of medical nutrition therapy in patients.

Bioelectrical impedance analysis is widely used in CKD populations as a non-invasive method for assessing body composition parameters, including muscle mass, fat-free mass, phase angle, and muscle quality (Ward, 2021). Moreover, phase angle has been linked with cellular integrity, nutritional status, inflammation, and kidney function decline in adults with CKD.

Alterations in body composition are common in patients with CKD and become progressively more pronounced with declining renal function. CKD is linked with significant metabolic and nutritional disturbances that may contribute to reductions in muscle mass, changes in fat distribution, fluid imbalance, and increased risk of PEW, malnutrition, and sarcopenia (Guo, Y. *et al.*, 2023).

Patients at advanced CKD stage showed lower percentage of muscle mass compared to healthy individuals. More specifically, individuals with CKD stage 3, muscle mass decreased by 0.59 kg for every 10 mL/min/1.73 m² (Kittikulnam *et al.*, 2021). Moreover, skeletal muscle mass index (SMI) has been shown to decrease significantly as CKD progresses, with CKD stage 5 reporting lower SMI values compared with patients in earlier CKD stages (Liu, L. *et al.*, 2022). Moreover, SMI generated from BIA has also been studied as a predictive indicator in CKD populations. After multivariate correction, sarcopenia detected by SMI measures continued to be independently linked with mortality when compared to anthropometric measurements and subjective global assessment (Pereira, R. A. *et al.*, 2015). Based on these results, body composition evaluation may offer therapeutically useful information regarding the prognosis, disease progression rate, and nutrition status among individuals diagnosed with CKD.

Assessments of body composition have also shown significant connections between physical function and lean tissue. Grip strength has been positively correlated with fat-free mass (FFM) as determined by BIA; however muscular function has been negatively related with increasing fat mass (Jiang, K. *et al.*, 2021). Additionally, it has been demonstrated that adults who are not on dialysis and have greater lean tissue index reported improved quality of life outcomes, suggesting that maintaining lean tissue may be important for preserving patients' functional status and physical well-being (Yongsiri *et al.*, 2014).

Another measurement derived from BIA, is phase angle, which has emerged as an important marker of nutritional and functional status in patients with CKD. Reduced phase angle values have consistently been reported in patients in advanced pre-dialysis CKD when compared with healthy individuals, suggesting impaired cellular integrity and altered body composition among these population (Bellizzi *et al.*, 2006). Moreover, studies reported that patients with diabetes

and stage 5 of CKD had lower phase angle than patients with CKD without diabetes, suggesting a higher level of nutritional and metabolic impairment. Thus, phase angle has been found to be negatively correlated with inflammatory indicators such as CRP and positively correlated with lean tissue index, muscle mass percentage, body cell mass percentage, albumin, and hemoglobin levels (Han *et al.*, 2019). Additionally, lower dietary protein consumption has also been linked to reduced phase angle values, indicating that poor nutritional intake may be a factor in patients' compromised cellular health and muscle maintenance (Seo *et al.*, 2020)

2.0.9.4 Dietary Patterns in CKD Nutritional Management

Several studies have been examining the impact of dietary patterns and CKD incidence. The Dietary Approaches to Stop Hypertension (DASH) diet was designed for hypertensive patients, and it has proven to have beneficial effects on stroke, cardiovascular disease, and metabolic syndrome. The DASH diet consists of the consumption of fruits, vegetables, lean meat and dairy products, while also reducing sodium intake to 1500 mg/day, which is lower than the daily recommended for healthy adults which is around 2300 mg/day (Filippou *et al.*, 2020). Based on that, the relation of DASH diet and CKD incidence were evaluated in a study by Asghari *et al.*, (2017) reported that people who consumed the top quintile of the DASH diet showed a 30% incidence of renal failure, which was 18% lower compared to those who consumed the lowest quintile of the dietary pattern. Adherence to the diet was significantly linked to a lower risk of incident in patients with CKD.

Another dietary pattern is the Mediterranean pattern, which is characterized by increased consumption of fruits, vegetables, whole grains, nuts, beans and legumes, and olive oil, while limiting the consumption of red or processed meat. It has proven effective on several chronic conditions such as obesity and CVD, as well as cancers (Rosato *et al.*, 2019). Recent randomized controlled trial (RCT) conducted in Spain evaluated the 1-year efficacy of an intensive weight-loss intervention with an energy-reduced Mediterranean diet with increased physical activity on renal function. Results showed that after one year, eGFR reduced by 0.66 mL/min/1.73m² in the Mediterranean group with energy restriction compared to the control group without energy restriction, reporting eGFR reduction by 1.25 mL/min/1.73m². Thus, based on the outcomes, altering lifestyle patterns, such as following a Mediterranean dietary pattern, increasing physical activity, and weight loss, showed a promising intervention approach that can preserve renal function and delay CKD progression in overweight/obese adults. Therefore, KDIGO guidelines in 2020 proposed the Mediterranean dietary pattern as the preferred diet for

individuals living with CKD, regardless of the disease stage, due to its beneficial properties on body weight, lipid profile, blood pressure, and net acid production (Ikizler, Talat Alp and Cuppari, 2021). One of the main concerns of following this dietary pattern is potassium consumption, which patients living with CKD should carefully monitor in order to avoid elevated potassium levels to occur. However, recent evidence suggests that the high potassium content in the Mediterranean diet is not correlated with increased potassium levels or facing a negative impact on kidney health in patients with kidney impairment (Caldiroli *et al.*, 2022).

2.0.9.5 Adherence to Renal Diet

However, due to nutritional therapy in renal failure being so restrictive, adherence to the diet is low. Studies showed that more than half of adult patients with renal failure did not adhere to their diet meal plans due to dietary restrictions being challenging. Patients with CKD, across all stages including kidney transplant, face several challenges that leads to decrease self-care and adherence to a specific lifestyle, which can be related to social, personal, environmental or psychological aspects. The main challenge is the adaptation of several major lifestyle changes. Based on evidence, lack of time, work, economy, food preference and cravings were the main contributing factors to lead to lower adherence levels in patients with CKD from stages 3 to 5 and those who performed transplant, whereas low willingness to eat healthier and dietary restrictions were the main challenges in dialysis patients (Trigueros-Flores, Xochitl B. *et al.*, 2025). Therefore, based on diets being complicated, specific strategies to improve willingness to eat healthier, counseling regarding food variety and preparation, some liberalization of dietary restriction, as well as considering family support can aid patients with CKD to improve their adherence to this restrictive diet.

Recently, there has been an increased interest in plant-dominant dietary approaches for renal management. Vegetarian proteins have been shown to exert less renal stress, reduce acid load, and improve gut microbiota composition, promising a decrease in CKD progression rate (Valim, Carpes and Nicoletto, 2022). The plant-dominant low-protein diet (PLADO) is an emerging dietary approach that focuses on the consumption of plant-based sources while following protein restriction, therefore suggesting its kidney and health benefits. However, despite promising research on PLADO, studies evaluating its feasibility, effectiveness, and adherence among different cultural populations remain limited.

2.1 RELEVANCE OF PLANT-DOMINANT DIET IN RENAL NUTRITION

2.1.1. Concept of Plant-Dominant Low-Protein Diet (PLADO)

The term “plant-based diets” has been used for more than 20 years, with discussion of potential benefits and risks. They have been identified as a fundamental dietary component for health among a wide range of eating patterns. Plant-based foods include all food products derived from plant sources such as fruits, vegetables, grains, legumes, herbs and spices, nuts and seeds, plant-based fats and oils (e.g. olive oil) and plant-based beverages (e.g. tea and coffee) (Creedon *et al.*, 2025). Regarding dietary patterns, plant-based diets are an umbrella term used to describe eating patterns that include a large proportion of plant-dominant foods, such as flexitarian, vegetarian, Mediterranean, and vegan diets, as shown in the figure bellow (Joshi, McMacken and Kalantar-Zadeh, 2021). Consuming more plant-based products has been adapted since the 1800s with the Greek philosopher Pythagoras, who praised vegetarian diets for their health properties. Many religions have adapted to consuming more vegetables, including Buddhism and Jainism. Nowadays, plant-based diets have gained popularity, with the number of Americans following vegan diets increasing by 600% from 2014 to 2018. Factors leading to higher adherence to plant-based diets are health impact, concern for animal welfare, and reducing environmental impacts. Thus, as more people consumed more plant-based products, the market needed to implement plant-based alternatives, leading to plant-based food markets increasing by 29% in the US from 2017 to 2019 (Clem and Barthel, 2021). The main types of plant-based diets are; semi-vegetarian, which are pescatarians and pollo vegetarians, that includes plant-based food as well as dairy, eggs, and seafood; vegetarian, including lacto-vegetarian and ovo-lactovegetarian, ovo-vegetarian that is the consumption of plant-based as well as allowing eggs and dairy products; flexitarian, is mainly based on plant origin foods, but also includes small amounts of animal products such as meat and fish; vegan diet, there is no animal products excluding meat, dairy, eggs, and sometimes honey, mainly for ethical and environmental reasons; whole-foods vegan diet, is similar to vegan diet, that focuses on health aspect instead of ethical reasons (Michail and Andreou, 2025). Thus, plant-based dietary patterns include the Mediterranean diet, the DASH diet, and Blue Zone diets. Blue Zone dietary patterns are mainly in world areas characterized by exceptionally long-lived populations, and they are “models in progress” developed by several historical traditions and societal evolution (Pes *et al.*, 2022).

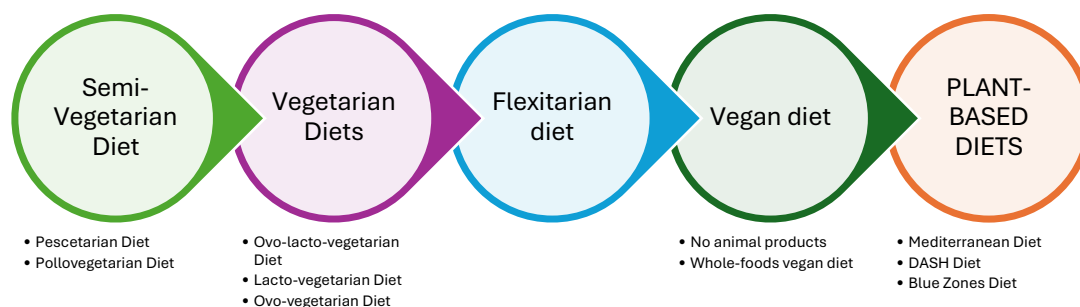


Figure 2.8. Showing all different types of plant-based diets.

Thus, the consumption of whole plant-based foods has been reported to prevent and treat many lifestyle-related diseases such as obesity, type II diabetes, hypertension, and hyperlipidemia (Joshi, Ettinger and Liebman, 2020). Recently, the adaptation of a plant-based diet for CKD has become increasingly apparent. PLADO is a dietary approach designed specifically for individuals with kidney impairment, which is a low-protein diet, 0.6-0.8 g/kg/day, with at least 50% plant-based sources to meet the targeted dietary protein requirements, and which should be whole, unrefined, and unprocessed foods (Kalantar-Zadeh *et al.*, 2020). PLADO is based on the principle that plant-based sources have a lower acid load, lower bioavailable phosphorus, and a higher fiber content, which may positively impact kidney function and gut microbiota (Zarantonello and Brunori, 2023).

The adaptation of PLADO represents a good approach in renal nutrition, moving away from animal-based dietary patterns towards a more sustainable and physiologically beneficial plant-based approach. However, clinical trials evaluating the long-term efficacy and adherence of PLADO remain limited, highlighting the need for further research in different populations, including Cypriot individuals with CKD.

2.1.2. Benefits of Plant-Based Protein in Patients with CKD

There are two main roles of plant-based diets in CKD: one role is the decrease of CKD progression rate, and the other role is preventing the risk of development (Chauveau *et al.*, 2019). Metabolic and physiological benefits of a plant-based protein diet are shown in figure 1.7, suggesting the promising role of PLADO in patients with CKD. Studies by Blaha and DeFilippis (2021) and Azizi (2018) are the two main cross-sectional studies that investigated the incidence of CKD and the relation with protein type consumed. The Tehran Lipid and Glucose Study (TLGS) reported that individuals who consumed higher vegetarian protein sources had a 30% lower risk of CKD incidence out of 5000 participants who consumed fewer plant-based sources (Azizi, 2018). Thus, based on the Multi-Ethnic Study of Atherosclerosis (MESA), results showed that people who consumed more whole grains, fruits, vegetables, and low-fat dairy products had lower urinary ACR levels (Blaha and DeFilippis, 2021). Thus, the consumption of plant-based sources has a lower impact on kidney hemodynamics compared to animal-based sources by decreasing the renal load and hyperfiltration. Although, this could be due to the combination of the diet with pharmacological effects of renin-angiotensin-aldosterone system (RAAS) inhibitors (Cupisti, Giannese *et al.*, 2020). Moreover, following PLADO reduces the onset of metabolic acidosis due to vegetarian proteins having a lower acidic load compared to animal products. An RCT by Goraya *et al.*, (2019) conducted in patients with CKD with metabolic acidosis reported that when they consumed base-produced fruits and vegetables instead of oral sodium bicarbonate recorded an improved CVD. This is also mentioned in a study reporting that vegetarian foods have a more effective lipid composition due to lower contents of saturated fatty acids and dietary cholesterol, therefore leading to better lipid profile control (Di Micco *et al.*, 2019). Moreover, a previous study assessed phosphorus levels and the implementation of a plant-based diet in patients with CKD. Results indicated that patients who shifted from an omnivorous protein restriction diet to a plant-based low-protein diet had lower phosphorus levels even just after one week of intervention (Moe *et al.*, 2011). Vegetarian foods are high in fiber and vitamin K1, which has been proven to lower phosphorus levels as well as the risk of developing metabolic acidosis, therefore suggesting the beneficial effect of plant-based products on vascular calcification and bone health (Di Micco *et al.*, 2019). Thus, plant-based products are rich in magnesium, which is also beneficial in vascular calcification, which was reported in an RCT with participants with CKD at stages 3 and 4 of CKD who were supplemented with oral magnesium and reported a significantly lower coronary artery calcification progression rate (Sakaguchi, Kaimori and Isaka, 2023).

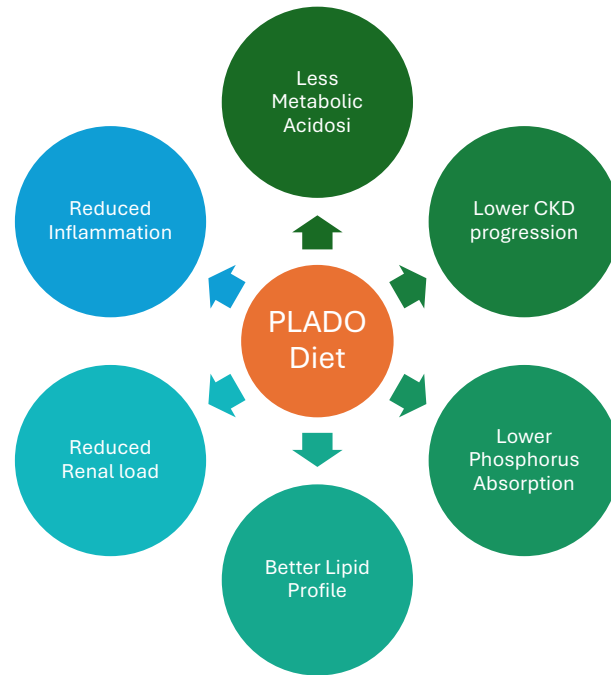


Figure 2.9: Benefits of PLADO for clinical improvements for individuals with CKD.

2.1.3. Current Challenges in Implementing Plant-Based Diets in CKD

Despite the clear benefits of following the PLADO diet, there are several barriers, shown in table 2.5, that limit their widespread adoption among people diagnosed with CKD. Many patients and healthcare professionals question whether plant-based diets provide sufficient essential amino acids. Vegetarian diets usually contain less protein than omnivorous diets, however, they are not low in protein. EPIC-Oxford study investigated the differences in dietary intakes between meat eaters, fish eaters, vegetarians, and vegans. Results indicated that the percentage of energy intake from protein was 17.5% and 13% for meat-eaters and vegans respectively (Sobiecki et al., 2016). Guidelines from British and Americans reported that the minimum percentage for energy derived from protein is 9% and 10%, therefore the result from the previous study is that vegans do get the essential amino acids.

Moreover, another challenge that PLADO might be facing is the lack of products or the assumption of limited choices.

Table 2.5: Possible concerns of PLADO diet, causes, and possible solutions.

Concern	Cause	Possible Solution

Amino Acid Deficiency	Lower lysine in grains; lower methionine and cysteine in legumes	Combine plant proteins (Complementation protein); supplement with essential amino acids and keto acids (EAA and KA)
Hyperkalemia	High potassium in plant foods; impaired kidney excretion	Monitor potassium levels; prioritize low-potassium plant foods; use potassium binders if needed; leeching vegetables to reduce potassium content
Vitamin B12 Deficiency	B12 is found primarily in animal products	Supplement with methylcobalamin or hydroxycobalamin
Iron Deficiency	Lower bioavailability of non-heme iron in plant foods	Consume iron-rich plant foods with vitamin C; monitor ferritin and hemoglobin

2.2 FOCUSING ON CYPRIOT POPULATION

2.2.1. Overview of the Cypriot Diet and Nutritional Trends

Eating habits are seen in geographical territories surrounding the Mediterranean Sea, although there are changes based on some food choices and cooking practices specific to each country and culture. The traditional Mediterranean diet is deeply rooted in the Cypriot population. This diet is characterized by high consumption of fruits, vegetables, legumes, whole grains, and olive oil, moderate intake of fish and poultry, and limited consumption of red meat and processed foods (Davis *et al.*, 2015). An updated mediterranean diet pyramid is shown in figure 2.8 (Serra-Majem, Llu *et al.*, 2020) where it demonstrates a pyramid framework for healthy adult population and should be altered in order to meet specific nutritional needs and diets of

children, pregnant women, elderly, and individuals with health problems such as cardiovascular diseases.

In Cyprus, where the traditional Mediterranean diet is characterized by a moderate intake of plant-based foods along with animal-protein sources, there is an opportunity to assess how modified plant-dominant diets can be adapted for CKD Cypriot patients. Existing research on dietary patterns among Cypriot individuals with CKD is sparse, and there is a lack of studies investigating whether plant-based approaches can be effectively integrated into local dietary habits. This study seeks to address this gap by evaluating the effects of PLADO among Cypriot individuals with CKD, assessing its impact on renal function, metabolic parameters, and dietary adherence. Therefore, the research aims to provide evidence-based recommendations for culturally appropriate renal nutrition strategies in the Cypriot population.

Cypriot traditional foods such as “haloumi” cheese, smoked pork tenderloin “lountza” and fish by-products (e.g. fish roe salad “taramosalata”). Seasonal ingredients are often adopted into enhance local dishes, including taro root (“kolokasi”), sautéed pork (“afelia”), stuffed vine leaves (“koupepia”), and “trahana” soup which is made of fermented goat’s milk and cracked wheat flour. There are notable differences that exist among Mediterranean countries based on cooking techniques and meal preparations. For instance, Cypriot and Greek cuisines that feature extensive assortments of appetizers, called “mezes” which are less common in other Mediterranean regions. Additionally, religious traditions, especially those tied to the Greek Orthodox faith, significantly influence dietary habits in Cyprus and Greece, where fasting practices can involve vegan diets for approximately 180-220 days annually (Philippou *et al.*, 2023).



Figure 2.10: Updated Mediterranean diet pyramid (Serra-Majem, Lluís *et al.*, 2020).

However, in recent decades, Cyprus has witnessed significant dietary shifts influenced by globalization, urbanization, and lifestyle changes. During the lockdown of COVID-19 the eating behaviors, food purchasing habits, and lifestyle of Cypriots and Greeks had been affected. A study conducted by (Andreou *et al.*, 2025) showed that lockdown had significantly affect individuals by increasing body weight by 0.5 kg per participant ($p < 0.01$). Thus, respondents increased their intake of sweets, snacks, fruits, vegetables, legumes, pasta, soft drinks, and meat consumption, however alcohol consumption was decreased. The traditional Mediterranean dietary pattern has gradually been replaced by more Westernized eating habits which can be led to a rise in non-communicable diseases (NCDs), including obesity, diabetes, hypertension, which are key risk factors for developing CKD (Kyprianidou *et al.*, 2023).

2.2.2. CKD prevalence and risk factors in Cyprus

Renal failure poses a significant public health challenge in Cyprus. Although comprehensive national prevalence data are limited, available studies indicate an increase trend in CKD cases, paralleling the global epidemiological shift. In February of 2022 there has been reported that 933 people were on dialysis which is estimated to have a 70% increase between 2014 to 2021 (*Chronic Kidney Disease (CKD) 2022*).

Table 2.6 demonstrates the number of Cypriot beneficiaries by diagnostic code from January 2022 to June 2025. Individuals with CKD in stages 2 and 3 (N18.2-N18.3), were the largest categories, with 12,046 and 15,783, respectively, followed by nephrolithiasis (N20.0), reaching

16,298 people. In contrast, fewer patients, almost 800 people, were listed under kidney transplant (Z94.0). These data highlight the significant burden of kidney failure within the Cypriot healthcare system. However, the table reports only patient number, without mortality, comorbidity, or risk factors, which serves as a descriptive baseline rather than a comprehensive epidemiological measure.

Table 2.6: Distribution of Renal Cypriot Patients by Diagnosis (Aggregated GeSY Data, 2022 - 2025).

CKD Diagnosis (GeSY ID)	No. of Beneficiaries
Chronic Kidney Disease, stage 1 (N18.1)	8582
Chronic Kidney Disease, stage 2 (N18.2)	12,046
Chronic Kidney Disease, stage 3 (N18.3)	15,783
Chronic Kidney Disease, stage 4 (N18.4)	4533
Chronic Kidney Disease, stage 5 (N18.5)	2855
Kidney Stone (N20.0)	16,298
Dialysis (Y84.1)	1913
Kidney Transplant (Z94.0)	797

Note: CKD = Chronic Kidney Disease. Data source: Aggregated GeSY (General Healthcare System of Cyprus) data, 2022–2025.

Primary risk factors for renal failure in Cyprus, include high rates of diabetes mellitus, hypertension, and obesity, all of which are closely related to dietary habits. Table 2.7 represents the prevalence (%) for the risk factors for Cyprus population. The data are based on a recent study that assessed the prevalence and sociodemographic determinants of selected NCDs among the Cypriot population (Kyprianidou *et al.*, 2023).

Table 2.7: Cyprus prevalence of risk factors

Risk factor	Prevalence in Cyprus (%)
Diabetes Mellitus	2.2
Hypertension	12.9

Adult obesity	22.9
Hyperlipidemia	17.4

The importance of these risk factors marks the urgent need for effective dietary interventions tailored to the Cypriot context to mitigate the progression of CKD and its associated complications.

Clinical dietitians have a significant role in the multidisciplinary management of CKD. In Cyprus, data from the General Healthcare System of Cyprus (GeSY) indicate that a substantial number of beneficiaries are diagnosed with several renal conditions, including different stages of CKD, kidney stones, dialysis, and kidney transplantation. However, access to specialized nutrition care depends largely on referrals to clinical dietitian services. Table 2.8 presents the distribution of Cypriot individuals with CKD by diagnosis and the proportion of beneficiaries who visited a clinical dietitian according to GeSY aggregated data for the period of 2022 through 2025.

Table 2.8: Distribution of Individuals with CKD and Utilization of Clinical Dietitian Services by Diagnosis (GeSY Data, 2022–2025).

Diagnosis	Number of Beneficiaries	Visited a Clinical Dietitian	Percentage
CKD Stage 1	8,582	2,137	24.90%
CKD Stage 2	12,046	2,908	24.14%
CKD Stage 3	15,783	3,593	22.77%
CKD Stage 4	4,533	1,441	31.79%
CKD Stage 5	2,855	1,259	44.10%
Kidney Stones	16,298	2,562	15.72%
Dialysis	1,913	972	50.81%
Kidney Transplant	797	305	38.27%

Note: CKD = Chronic Kidney Disease. Data source: Aggregated GeSY (General Healthcare System of Cyprus) data, 2022–2025. Percentages represent the proportion of beneficiaries referred to a clinical dietitian.

2.2.3. Barriers and Cultural considerations in Adopting Plant-Based Diets

Despite the historical alignment of the traditional Cypriot diet with plant-based principles, several barriers delay the adoption of contemporary plant-dominant diets among Participants with CKD. Commonly known barriers towards plant-based diet are lack of skills, cognitions about balanced eating, perceived hardships such as access and availability, finding recipes as well as perceptions of inadequacy and tastelessness of diet without animal-based meals. Thus, socio-demographics matter, women in general are likely to adopt a plant-based diet whereas men believe that meat consumption is a masculine feature (Perez-Cueto *et al.*, 2022). Cultural preferences for meat-focused meals, social norms surrounding food consumption, and misconceptions about protein adequacy in plant-based diets contribute to resistance. Limited awareness about the health impacts of plant-based diets, mixed with the inadequate nutritional education among healthcare providers, increases the challenge (Rickerby and Green, 2024).

2.2.4. Need for a Localized Dietary Approach

Given the unique cultural, social, and economic landscape of Cyprus, there is a critical need for a localized dietary approach to CKD management. PLADO offers a promising framework, emphasizing plant-based protein sources while maintaining protein restriction which is essential for individuals diagnosed with CKD. Adapting PLADO to align with Cypriot food traditions can enhance acceptability and adherence, ultimately improving clinical outcomes.

2.2.5. Treatment and Management of CKD

Management of CKD is multifaceted, involving pharmacological treatment, lifestyle modifications, and dietary interventions aiming to slow disease progression, improving patient's quality of life, and delaying or preventing the need for dialysis or kidney transplant. The primary focus of treatment in the early and moderate stages (pre-dialysis) is to slow the progression of CKD before dialysis becomes necessary. This approach has been shown to improve long-term patient outcomes, minimizing complications, and significantly reduce healthcare costs. Latest guidelines for managing CKD are provided by the KDIGO organization, and they were last updated in 2020 (Kidney Disease: Improving Global Outcomes

(KDIGO) Diabetes Work Group, 2020). Pharmacological management for renal failure such as ACE inhibitors, angiotensin receptor blockers (ARBs), diuretics, and statins are the most common (Chen, W., Levy and Abramowitz, 2019). Hypertension is both a cause and a consequence of renal failure. Recent meta-analysis assessed renal outcomes in hypertensive patients treated with either ACE inhibitors or ARBs. Based on 17 randomized controlled trials, results showed that ACE inhibitors and ARBs can reduce urine protein levels, improve blood pressure, and were similarly effective in reducing urinary protein excretion (Xu *et al.*, 2015). These medications help to protect the kidneys by reducing glomerular hypertension and inflammation, slowing the progression to ESRD. In diabetic patients, controlling blood glucose levels is essential. Chronic hyperglycemia induces pathological microvascular and macrovascular changes in the form of myocardial infarction, stroke and diabetic kidney disease (Jiang, G. and Zhang, 2003). Medications such as SGLT2 inhibitors have shown to have beneficial effects on cardiovascular and kidney-related effects. SGLT2 inhibitors are a new class of diabetic medications that reduce the absorption of glucose in the kidney, decrease proteinuria, control blood pressure, and are linked with weight loss. Thus, SGLT2 inhibitors improve fasting plasma glucose and can reduce absolute glycated hemoglobin A1c (Vasquez-Rios and Nadkarni, 2020). Another medication to control glucose in type 2 diabetes patients is metformin which is considered effective, safe, inexpensive, and widely available, reduce cardiovascular events and mortality. However, metformin is filtered by the kidneys, and it has been proven that can contraindicate in patients with CKD due to concerns of lactic acidosis with drug accumulation (Shin, Créon and Carrero, 2025). The use of statins in managing dyslipidemia in patients with CKD has been extensively monitored and investigated. It is important to note that specific statin dosage adjustments might be required for these patients due to altered drug metabolism and potential drug-drug interactions (Mehta, 2024). Administration of statins (20 mg of simvastatin) has been shown to reduce cardiovascular disease and all-cause mortality and prevent major cardiovascular events in patients with CKD stages 1 to 4. More specifically, based on Study of Heart and Renal Protection (SHARP), a total of 9270 patients with CKD from stages 3 to 5 of which 1533 were dialysis patients, randomly assigned to either simvastatin plus ezetimibe or a placebo, showed that lipid-lowering treatment reduced the risk of a combined endpoint. This endpoint included non-fatal myocardial infarction, coronary death, non-hemorrhagic stroke, or any arterial revascularization procedure, by 17% (Baigent *et al.*, 2011). Another complication that needs intervention is the reduction of erythropoietin production which leads to anemia in patients with kidney dysfunction. The most commonly used medications to treat anemia in CKD are

erythropoiesis-stimulating agents (ESAs) such as epoetin alfa and darbepoetin alfa and are used to stimulate red blood cell production. Based on KDIGO guidelines ESAs are typically considered in patients with CKD when hemoglobin levels are below 10 g/dL. Although ESA treatment is individualized based on anemia symptoms, transfusion requirements, the reduction rate of hemoglobin, and response to iron therapy (Macdougall, 2024). Moreover, renal failure patients are at higher risk of iron deficiency due to factors such as impaired dietary iron absorption, chronic bleeding from platelet dysfunction caused by uremia, frequent phlebotomy, and blood trapped in the dialysis apparatus. In addition, to the depletion of circulating iron from erythropoiesis stimulated by ESAs, this deficiency requires iron supplementation to manage anemia in CKD, due to elevated hepcidin levels, oral iron supplementation is generally ineffective, making intravenous iron the preferred treatment for hemodialysis patients and those with advanced CKD (Hashmi *et al.*, 2025). Hyperphosphatemia indicated “A silent killer of patients with CKD”. One in two individuals diagnosed with CKD and elevated phosphorus levels at the upper limit do not survive after four years. Ideal phosphate binder should not only bind phosphate adequately but also protect people with CKD from accumulation of various metals such as aluminum or calcium. Phosphate binders, like sevelamer or lanthanum carbonate, are mostly used to reduce phosphate levels and prevent vascular calcification. Studies have shown that sevelamer sequesters phosphate within the gastrointestinal tract, therefore prevents its absorption and enhances its fecal excretion. It has also been accompanied by lower incidence of hypercalcemia, decreased incidence of low PTH levels, a 15-31% decrease in LDL-cholesterol in both predialysis and dialysis patients, decrease of uremic toxins, therefore, suggesting an overall anti-inflammatory effect (Spaia, 2011). Regarding elevated levels of PTH, studies suggest that active vitamin D analogs and calcimimetic agents are primary medications. However, a recent meta-analysis by (Liu, X. *et al.*, 2024) included 21 randomized controlled trials found no statistical difference between two active vitamin D analogs and three calcimimetic agents in the PTH, and phosphorus levels altered in dialysis patients with secondary hyperparathyroidism.

Patients with CKD may develop elevated potassium and phosphorus levels, anorexia, as well as muscle and fat wasting. Protein-energy wasting (PEW) is a condition characterized by the depletion of both protein and energy stores in patients with CKD without undergoing dialysis. PEW affects 20% to 25% of those with early to moderate renal failure, and this percentage rises to 75% in renal failure. Contributing factors include malnutrition, low physical activity, hyper catabolism caused by uremia, acidosis, and ongoing inflammation, all of which increase

the risk of hospitalization and mortality (Hanna *et al.*, 2020). Diet has an important role in renal failure, due to dietary modifications can reduce the production of waste products, therefore decreasing uremic symptoms, delay the initiation of dialysis. Key components of dietary management include protein restriction, one of the primary strategies in CKD management, which helps to reduce the burden on the kidneys and decreases the production of nitrogenous waste products. A high-protein diet is defined as intake of more than 1.2 g protein per kilogram of body weight per day (g/kg/day) has shown a significant deterioration in kidney function. Thus, a high-protein diet increases kidney blood flow and increases intraglomerular pressure, therefore higher GFR and more efficient excretion of protein-derived nitrogen products. A recent cohort study showed that high-protein diet induced glomerular hyperfiltration and a rapid decline in renal function in the general population (Jhee *et al.*, 2020). Another dietary modification is sodium and fluid management especially when edema or hypertension is presented. High sodium intake has serious effects on cardiovascular health, kidney function, and CKD progression. In patients with CKD, sodium restriction is recommended to control fluid retention, decrease blood pressure, and reduction cardiovascular risk. Guidelines recommend reducing sodium intake to 2 to 2.3 g/day in adults, however risk of hyponatremia and severe outcomes, dietary sodium intake lower than 1.5 g/day is not recommended for patients with advanced CKD as well as dialysis patients (Ikizler, Talat Alp and Cuppari, 2021). Another factor to consider for dietary management, is dietary potassium, hypokalemia is linked with muscle weakness and hypertension, whereas hyperkalemia can result in ventricular arrhythmia and death. Guidelines suggest a potassium intake of 2 to 4 g/day (51 to 102 mmol/day) for kidney patients from stages 3 and 4, although no restrictions for those with earlier renal failure. General guidelines for phosphorus and calcium intake should be from 800 to 1,000 mg/day in kidney patients from stages 3 to 5 and on dialysis patients. Moreover, there are no specific guidelines that specify a safe dose of vitamin D supplementation in order to prevent side effects in kidney patients; therefore, individualized vitamin D supplement regimens are needed (Kim, S. M. and Jung, 2020).

2.2.6. Prevention of CKD progression

Regardless of the underlying cause of CKD is a slowly progressive disease and leads to irreversible loss of nephrons. Adopting measures to help prevent this process may decrease the disease's evolution and even preserve long-term renal function. Current management of CKD is medication, such as ACE, ARBs, and SGLT2 inhibitors. In addition to medication treatment, dietary management is also essential. Low-protein diet plays a major role in renal failure

therapy at pre-dialysis stages, and it has been proven effective in delaying ESRD and improving metabolic control and quality of life (Simonini and Vezzoli, 2022). Preventing CKD progression is a high priority for patients and healthcare professionals in order to reduce the requirement of dialysis. Addressing behavior changes such as poor adherence to diet, medication and other treatments, in renal failure as a lifestyle modification can be challenging. Barriers to alter lifestyle include low health literacy, conflicts with cultural norms, complicated nutritional requirements, and safety concerns (Clarke *et al.*, 2015). A recent systemic review examined studies that had interventions such as diet, physical activity, education, social support, behavioral demonstration etc. Results showed that the most used intervention function was education, followed by enablement and training which shows that patients with impaired kidney function lack awareness about lifestyle risk factors and have low health literacy. Thus, results showed that these individuals were overwhelmed by dietary information which can be difficult to understand, restrictive, and insensitive to culture. Educational materials, for example cooking and educational sessions for both patients and family members led to a decrease in salt intake (Evangelidis *et al.*, 2019).

2.3 DIETARY INTERVENTIONS IN CKD

2.3.1. Role of diet in CKD management

Medical nutrition therapy provided by a registered dietitian is recommended for all individuals with renal failure. It includes complete nutrition assessment, nutrition diagnosis, anthropometric assessment, individualized intervention, monitoring and evaluation to promote lifestyle modifications that will slow or prevent CKD progression (de Waal, Heaslip and Callas, 2016). Moreover, medical nutrition therapy can mitigate the impact of associated comorbid conditions, including diabetes, obesity, hypertension, and hyperlipidemia. Nutrition therapy aims to control metabolic abnormalities, improve nutritional status, and reduce renal workload (Jimenez *et al.*, 2020).

Key components of medical nutrition therapy for patients with CKD include:

- **Protein Restriction:** Limiting protein intake reduces the kidneys' filtration load, thus slowing the progression of kidney damage. Optimal amount of protein intake is individualized based on the patient's stage of renal failure and comorbid conditions. Low-protein diets are recommended to reduce the production of nitrogenous waste products, especially in advanced stages of CKD.

- **Sodium Management:** Reducing sodium intake helps to control hypertension, manage fluid balance, and prevent edema. Sodium restriction is crucial in kidney failure patients to manage blood pressure and reduce the strain on the kidneys.
- **Potassium and Phosphorus Management:** Patients with CKD are often at risk of elevated levels of potassium and phosphorus. Dietary restrictions of potassium and phosphorus can help to avoid complications such as cardiac arrhythmias and vascular calcification.
- **Micronutrient Monitoring:** The loss of kidney function can interfere with the body's ability to manage certain vitamins and minerals, such as calcium, vitamin D, and iron. Following a well-balanced diet that includes the right amount of these nutrients is critical for bone health and preventing anemia.

While dietary management plays an important role in CKD, patient adherence to these dietary guidelines is often a challenge. Studies have shown that dietary restriction, particularly protein, sodium, potassium, and phosphorus, can be difficult for patients to sustain, which may reduce the long-term effectiveness of these strategies in slowing disease progression.

2.3.2. Current Dietary Strategies: Low-Protein Diets, Managing Sodium, Potassium, and Phosphorus

2.3.2.1 Protein Restriction

The combination of studies between rats and humans were a good beginning for major organizations such as the Kidney Disease Improving Global Outcomes and the Kidney Disease Outcomes Quality Initiative to develop guidelines for ongoing debates and new evidence in nephrology. Over the years, despite little additional data, these guidelines have continued to evolve. KDOQI guidelines in 2020 stated protein restriction for renal non-dialysis and non-diabetic patients. Thus, individuals with CKD at stages 3 to 5 who are metabolically stable, close supervision is recommended, protein restriction with or without keto acid analogues, to reduce risk for ESRD or mortality, as well as improving quality of life (Ikizler, Talat Alp and Cuppari, 2021). European Society for Clinical Nutrition and Metabolism (ESPEN) also agrees with protein restriction of 0.7 g/kg/day (Fiaccadori *et al.*, 2021).

Historical Context of Protein Restriction in CKD

Protein restriction as a therapeutic strategy in CKD is one of the earliest interventions in the management of renal failure and is still followed by physicians, nutritionists, and patients

around the world. The use of LPD in renal failure was first suggested by Baicale in 1869 (Beale, 1869), however only in 1926 researchers try to experimentally evaluate LPD in humans, using a case study approach. As early as the 1930s, a study by (CHANUTIN, 1934), showed that restricting dietary protein helped decrease kidney damage, lower blood pressure, and improve survival in CKD rats. Similar results were shown in later animal experiments, where rats with one or more kidneys removed had increased proteinuria and glomerulosclerosis when fed a high-protein diet (Hostetter *et al.*, 1986). A high-calorie, low-protein diet significantly reduced urea excretion, and anuric patients with acute kidney failure were able to survive for over three weeks without dialysis before their kidney function recovered (KOLFF, 1951). In 1962, the first human study was conducted with eight uremic patients that follow a low-protein diet showed uremic symptoms improvement as well as biochemical markers. Although the risk of protein depletion was significant, especially in long-term treatment for patients with CKD without undergoing dialysis. Thus, the first human study on severe protein restriction was conducted in 1926, it was a case-report study including a 28-year health study. The results showed that after three weeks of intervention, the participant's creatinine levels decreased significantly from 0.74 mg/dL to 0.41 mg/dL, indicating a reduction in muscle mass and/or an increase in kidney function. However, adherence to the diet in the beginning of the study was good, due to excitement of following a new diet, however he abandoned the diet on the 25th day (Smith, 1926).

These findings led to the formation of low-protein diets (LPDs) as a means of reducing the workload on the kidneys, with the idea that protein restriction would decrease the production of nitrogenous waste products like urea and creatinine, which increases as kidney function declines. Early recommendations for protein restriction assumed that proteinuria was directly related to kidney dysfunction. Thus, decreasing protein intake was thought to reduce proteinuria, slow disease progression, therefore delay the need for dialysis or kidney transplant.

Clinical Rationale for Protein Restriction in CKD

Clinical rationale for protein restriction in renal failure focuses on reducing the workload on the kidneys and managing toxic byproducts of protein metabolism. Normal kidney function efficiently filters proteins through the glomeruli and reabsorb them in the renal tubules. However, as kidney function decreases, the kidneys become less effective in handling the metabolic waste products generated from the breakdown of proteins. A protein restricted diet providing adequate amounts of amino acids and energy stores was the only known therapy to

decrease the uremic symptoms and to prolong survival. Dialysis techniques and facilities, as well as kidney transplant, rapidly increased. As these therapies came to represent milestones in the history of modern medicine, at the same time an interest reduction in the low-protein diet as a treatment for advanced CKD was observed. It is important to say that renal diet is not only a matter of restriction, although is also essential to ensure that full energy requirements is met in patients with CKD to prevent protein catabolism, maintain neutral nitrogen balance, and to maintain adequate nutritional status and body composition (Bellizzi *et al.*, 2016). Moreover, controlling uremic symptoms and reducing the disease's progression towards ESRD, each dietary component, protein waste products, phosphate, sodium, and acid load should be considered separately. Uremic syndrome is caused by a progressive reduction in renal function, which therefore kidney dysfunction reduces the excretion of many compounds developed in extra- and intracellular compartments which contribute to the development of uremic syndrome. These uremic toxins include protein-bound substances and free water-soluble molecules of low to medium molecular weight, most of which obtain from protein breakdown (Nigam and Bush, 2019). Following a low-protein diet can reduce either the production of these toxins or the onset or severity of uremic symptoms (such as nausea, vomiting, fatigue, and itching) and complications (Black *et al.*, 2018).

Phosphate and sodium are mainly found in foods with high protein content, such as meat and cheese. Kidneys regulate serum phosphate concentration by modulating its urinary excretion and balancing the net phosphate absorption from the gastrointestinal tract. As kidney dysfunction occurs the body total sodium increases and causes hypertension and edema. High salt intake increases the amount of urinary protein excretion, a major risk factor for the onset and progression of both kidney and cardiovascular disease (Gutiérrez, 2013). As previously mentioned, metabolic acidosis is caused by the decrease of both acid excretion and the regeneration of bicarbonate therefore decreasing renal function. Metabolic acidosis has several negative complications such as bone mineral loss, muscle wasting, decreased protein anabolism and increased protein catabolism, therefore leading to protein malnutrition and progressive impairment of nutritional status. Another significant effect of metabolic acidosis is the change of potassium from the intracellular to the interstitial fluid, caused high potassium and phosphorus levels in the blood (Mathur *et al.*, 2022).

One of the earliest outcomes to kidney damage in CKD is glomerular hyperfiltration, where the remaining healthy nephrons attempt to compensate for the lost nephrons by increasing their filtration capacity (Fattah, Layton and Vallon, 2019). About 90% of the protein metabolic waste

are excreted by the kidneys. This results in increased glomerular pressure and an elevated filtration load on the nephrons. At first, this adaptation might maintain kidney function in the short term, however long-term it causes glomerular damage and worsens the progression of CKD (Cheng *et al.*, 2024).

In the past 20 years, dietary protein intake has increased to above the recommended level in the general population. According to the Korea National Health and Nutrition Examination Survey in 2017, the mean dietary protein intake was 153% and 128% of the recommended intake in men and women, respectively. Major food sources of protein were cereals, which was 12.7% of the total dietary protein intake, pork at 11.3%, and chicken at 8.3% (Ministry of Health and Welfare, 2013). High-protein diets, especially those high in animal proteins, increases this process. In 1928, a frog model reported that amino acids and peptides could increase blood flow to the kidneys (Watzadse, 1928). The largest short-term human trial showed that high-protein diet, 25% of the total calorie intake, increased eGFR by 3.8 mL/min/1.73m² after six weeks compared to a diet of which 15% of the total calorie intake was protein (Juraschek *et al.*, 2013). Thus, observation studies reported that every 10 g increase in protein intake was significantly associated with a change in eGFR of -1.69 mL/min/1.73m² (Knight *et al.*, 2003). A meta-analysis investigated the effects of high protein against normal/low protein diet on kidney function in general population. Results of 30 studies showed that high protein regimens increased eGFR, serum urea, urinary calcium excretion significantly when compared to the normal/low protein regimens (Schwingshackl and Hoffmann, 2014). Although, a recent study hypothesized whether higher protein intake was linked with higher risk of CKD in Japanese general population. In the 8-year follow-up a total of 300 CKD cases were reported, and showed that higher total, animal protein and seafood intake were associated with a lower risk of incident CKD (Kubo *et al.*, 2023). These data, agrees with another cohort study conducted in Korea, and found that protein intake, especially from plant proteins, was negatively associated with the incidence of new-diagnosed renal failure. The incidence of CKD among low-protein diet and high-protein diet compared to normal protein diet group were 1.49 and 0.63, respectively. Highest tertile group of plant-protein intake in relation to incident CKD was 0.72, compared to the lowest tertile group (Kwon, Park and Lee, 2022). However, a prospective cohort study sued the UK Biobank study showed that second, third, and highest quartiles of plant protein intake were 0.90, 0.83, and 0.82, respectively when compared to the lower quartiles. As a continuous variable, the adjusted hazard ratio for every 0.1 g/kg/day increase in plant protein intake was 0.96. Thus, increased dietary plant protein intake was associated with a

lower risk of CKD incident (Heo, Ga Young *et al.*, 2023). Moreover, a recent 33-year-long, single-patient, observational study explored the effectiveness and safety of LPDs. 11-year-old patient with nephronophthisis had impaired renal function. Over the first 8 years (stages 2 and 3a) the patient was following a protein intake of 1.0-1.26 g/kg/day. For next 27 years the patient was following a protein intake of 0.8 g/kg/day, 0.6 g/kg/day, and 0.3 g/kg/day vegan protein supplemented with keto-analogues for stages 3a/b, 3b-4, 4-5 respectively. Results showed that with personalized LPDs and patient concordance, it is possible to maintain high, long-lasting adherence to several protein intake, which slows the disease's progression, improved metabolic control and metabolic status (Bellizzi and Fouque, 2024). Another study conducted in 2024, included data from 3 cohorts' data to estimate the associations of total, animal, and plant protein intake with all-cause mortality in patients with CKD and compare to individuals without CKD. Results showed that higher total protein intake was linked to lower mortality in patients with CKD. Protein intake of 1.00 vs 0.8 g/kg/day, 1.20 vs 0.8 g/kg/day, and 1.40 vs 0.8 g/kg/day, a 12%, 21%, and 27% reduction of mortality risk was observed for those with higher protein intake. Moreover, for each 0.20 g/kg/day increase in protein intake a reduction of 20% for plant protein and 12% for animal protein was observed. In patients without CKD, hazard ratio for protein intake was lower, indicating a lower risk of mortality for the same increase in protein intake, compared to individuals with impaired kidney function (Carballo-Casla *et al.*, 2024). Thus, a recent randomized controlled study reported that individuals with CKD following a low-fat diet or a Mediterranean diet, even though eGFR was declined, participants following a Mediterranean diet produced a lower decline in eGFR, due to clinical benefits linked with cardiovascular disease prevention (Podadera-Herreros *et al.*, 2022).

Understanding the mechanisms of how renal dysfunction affects the body's ability to respond to changes in nutrient intake is important since low-protein, high-calorie diets are commonly used as a CKD treatment. The human body can maintain lean body mass and body protein balance over several range of dietary protein intakes. Research has demonstrated that when protein intake is decreased, the body adapts through several metabolic changes, including a decrease in amino acid oxidation, improved utilization of amino acids from protein breakdown, reduced protein degradation, and at last, a reduction in overall protein synthesis throughout the body. In patients with kidney dysfunction, the ability to activate these mechanisms is altered when nutrient/protein intake is reduced. Factors that cause loss of muscle protein are complex and not always linked with anorexia, however they are associated with various abnormalities that trigger protein degradation and/or decrease of protein synthesis (Gordon, Kelleher and

Kimball, 2013). As CKD worsens, the reduction in kidney function activates pathways that cause endothelial damage, including inflammation, metabolic acidosis, insulin resistance, and disruption of anabolic hormone signalling. These processes often overlap with those seen in aging, diabetes, inflammation, and infections, all of which are contributing factors to protein-energy wasting (Garibotto, Bonanni and Verzola, 2012). Studies on experimental uraemia have reported how metabolic acidosis boosts amino acid oxidation and protein degradation by activating ubiquitin-proteasome pathway. Additionally, impaired insulin signalling can trigger catabolic processes, which leads to atrogen-related proteolysis. Uremic conditions further disturb muscle amino acid metabolism, that increases rapidly catabolic processes. Uremic patients show lower levels of branched-chain amino acids (BCAAs), such as leucine, valine, and isoleucine, in both blood and muscle cells. This decrease is caused by insufficient dietary intake, kidney impairment, and increased breakdown of BCAAs in muscle tissue (Dimou, Tsimihodimos and Bairaktari, 2022).

However, when metabolic acidosis is controlled and adequate energy is provided, individuals with advanced CKD can successfully adapt to LPD. Studies on nitrogen balance report that patients with renal failure can maintain a neutral or slightly positive nitrogen balance with protein intake as low as 0.55-0.6 g/kg/day. Studies including patients with CKD but without acidosis, showed that protein metabolism adaptation to LPD with 0.6 g/kg/day remains effective (BERNHARD *et al.*, 2001).

A study conducted by (Masud *et al.*, 1994) that explored the effectiveness of a very low-protein diet (VLPD) of 0.28 g/kg/day supplemented with isosmolar mixture of either ketoacids (KA) or essential amino acids (EAA) and energy requirements were at 35 kcals/kg/day in patients with CKD. After 3 weeks of the intervention, patients achieved neutral nitrogen balance with significant reductions in amino acid oxidation and protein degradation. Another study that investigated the effects of a VLPD with amino acid-ketoacid supplementation in individuals with advanced CKD showed that after more than a year following this diet, patients maintained neutral nitrogen balance, with protein synthesis, degradation, and leucine oxidation remaining similar to baseline (Tom *et al.*, 1995).

Clinical rationale for protein restriction in CKD is supported by a robust understanding of kidney pathophysiology and the metabolic burden that excess dietary protein imposes on damage kidneys. Protein restriction has been shown to positively influence other aspects of CKD progression, such as blood pressure control, reduced inflammation, and decreased

oxidative stress. All these factors contribute to slower kidney decline and better overall health outcomes for Individuals diagnosed with CKD. Reducing the glomerular filtration load, decreasing proteinuria, and lowering the production of toxin nitrogenous waste products, protein restriction offers an effective strategy to slow CKD progression, reduce the need for dialysis, and improve the quality of life for individuals with CKD. Thus, VLPDs are nutritionally safe for patients with advanced CKD, provided there is adequate energy intake, amino acid supplementation, and correction of metabolic acidosis.

2.3.2.2 Electrolytes Management

Disorders of sodium, chloride, potassium, calcium, and phosphorus commonly occurred in CKD, and some may be life-threatening. Sodium is considered an important mineral in maintaining the balance of body fluid, and according to WHO restriction of sodium intake to less than 2.3 g/day of sodium corresponding to 5.8 g of salt which can be considered as the most cost-effective measure to improve public health (Guideline: Sodium Intake for Adults and Children 2012). It is well established that increased sodium consumption links to higher blood pressure which increases the risk of developing cardiovascular disease. Individuals with impaired kidney function, elevated blood pressure is very common which is caused by sodium sensitivity; therefore, a low salt diet is considered a cornerstone of managing hypertension in these patients (Borrelli *et al.*, 2020). Recent meta-analysis summarized data from observational studies for the potential association between Dietary Approaches to Stop Hypertension (DASH) diet at the risk of developing CKD. Results showed that individuals who follow the DASH diet reduced the risk of CKD by 23%, suggesting a protective role of DASH diet. When DASH diet was categorized based on nutrients (such as potassium, calcium, magnesium), there was a significant association with a reduced risk of CKD by 22%, resulting in that nutrient-focused approach in DASH diet may be more effective in reducing CKD risk (Mozaffari, Ajabshir and Alizadeh, 2020). Regarding patients with CKD in a non-dialysis stage, several meta-analysis compared low versus high salt diet. Participants with moderate salt restriction of 4.4 g/day was linked with a significant lowering of 4.9 mmHg and 2.3 mmHg in systolic and diastolic blood of pressure respectively (Garofalo *et al.*, 2018).

Abnormalities in potassium metabolism are caused by several factors. Although since potassium metabolism is regulated in a large part by the kidneys, most cases of elevated or decreased potassium levels are caused by renal mechanisms. Kidney dysfunction increases the risk of developing abnormal potassium metabolism. Minimum daily requirement for potassium in the general population is based on its unavoidable loss through sweat, stool, urine, and other

sources, is about 1600 mg. However, WHO recommends a daily intake of 3510 mg to promote hypertension prevention. Thus, current recommendations for dietary potassium, for patients with CKD, intake mainly focuses on restriction when hyperkalaemia occurs. In 2010 Academy of Nutrition and Dietetics CKD guidelines recommend that patients with CKD from stages 3 to 5 with elevated potassium levels to limit their dietary potassium intake to <2.4 g/day (Academy of Nutrition and Dietetics, 2020). However, new guidelines of KDIGO highlighted the lack of evidence on potassium intake and CKD outcomes (Kidney Disease: Improving Global Outcomes (KDIGO) Diabetes Work Group, 2020). Systematic review by (Picard *et al.*, 2020) included 11 studies to investigate the relationship between potassium intake and the risk of disease progression in CKD varies depending on the stage of the disease and the level of potassium intake. In early renal stages, studies showed that high potassium intake was linked with a lower risk of renal failure progression, suggesting a beneficial effect of higher potassium intake in early stages, whereas in two out of the eleven studies, low potassium intake was linked to a higher risk of disease progression. In advanced renal stages, two studies reported that higher potassium intake could have a positive impact in slowing disease progression whereas only one study indicated that lower potassium intake might be beneficial (Picard *et al.*, 2020).

Observational studies describe associations between serum levels of these electrolytes and CKD progression, suggesting a possible role for diet. Standard Western diet, vegetarian foods might offer metabolic advantages in CKD. Hence, general restrictions of dietary habits might be no more sufficient in patients with CKD. Blood assessment should be integrated with urinary exams and food questionnaires to tailor dietary prescription to each patient based on biochemical and clinical needs.

2.3.2.3 Renal Diet Adherence

Renal diet is considered essential for optimal management of individuals living with CKD. However, data on the adherence to these restrictions and its implications for health-relevant biomarkers are limited. In a recent cross-sectional analysis estimated the adherence to CKD-specific dietary recommendations, to identify characteristics and lifestyle variables linked to poor adherence. Results showed that adherence to renal diet is mostly driven by gender, age, lifestyle, or socioeconomic factors instead than the prevalence of comorbidities such as hypertension, diabetes, hyperlipidaemia, and gout. Thus, lower adherence to renal diet associated with lower kidney function, elevated lipid profile, higher inflammation, and higher uric acid values, which are contributing factors to cardiovascular events to occur (Kaesler *et al.*, 2021). Another study examined whether knowledge of dietary recommendations impacts the

adherence of renal diet to patients with CKD without undergoing dialysis. Patients that were aware of dietary restrictions was not associated with reduced intake of these nutrients. Phosphorus intake was similar to among those with and without awareness of dietary restrictions 785 mg and 907 mg respectively. Protein intake was similar in both groups, 54.5 g/day and 57 g/day. These results suggests that knowledge alone is not sufficient to do dietary changes, other contributing factors such as psychosocial barriers, access to appropriate foods, costs, and patient support, influence adherence to renal diet more than just knowledge of nutrient sources (Betz *et al.*, 2021).

Strategies to overcome dietary barriers (e.g. affordable food, access to appropriate foods etc.) and to promote better dietary adherence were a support group and customized meal plans. Studies that focused on customized meals for dialysis patients found positive results, regardless of the meal interventions, nutritional status improved, and intradialytic weight gain decreased (Perez *et al.*, 2021). Thus, communication between providers and patients can create pathways for increased dietary adherence and compliance. Longer, or more intentional visits that focus on active listening between patients and healthcare providers will improve communication (Hunter, Shukla and Andrade, 2023).

2.3.3. KDIGO Nutritional Management Recommendations in CKD

KDIGO is the global nonprofit organization developing and implementing evidence-based clinical practice guidelines in kidney disease. As mentioned before, medical nutrition therapy is crucial for CKD progression, improve quality of life, and delay kidney failure. Current recommendations suggest maintaining a protein intake of approximately 0.8 g/kg/day in adults with CKD stages from 3 through 5, while avoiding excessive protein consumption more than 3 g/kg/day, which may increase the progression of the disease. Moreover, in selected patients at high risk of kidney failure, very low-protein diets supplemented with essential amino acids or ketoanalogues may be considered under close clinical supervision. In addition, restrictive protein interventions are not recommended in metabolically unstable patients due to the increased risk of protein-energy wasting and malnutrition.

The guidelines further highlight the importance of individualized nutritional prescriptions in vulnerable populations. For instance, children with CKD, protein restriction is discouraged due to potentially have a negative impact on grown and development to the child, whereas older adults with frailty or sarcopenia may require higher protein and energy requirements to preserve muscle mass and functional status.

Regarding protein management, KDIGO recommends sodium restriction to less than 2 g/day to the majority of patients suffering with CKD to support blood pressure control and to reduce cardiovascular and renal complications. However, sodium restriction should also be individualized, especially in patients with sodium-wasting nephropathies (such as Bartter and Gitelman syndromes, polycystic kidney disease, etc.) or other clinical conditions requiring modified electrolyte management.

Furthermore, an important evolution between earlier CKD nutritional recommendations and the updated KDIGO 2024 guidelines is the shift in emphasis from predominantly high biological value protein sources toward more plant-dominant dietary patterns. Previous dietary approaches for CKD frequently recommended that a substantial proportion of total protein intake should come from high biological value proteins, primarily animal-based sources, in order to maintain essential amino acids adequacy when following low-protein diet. However, updated KDIGO recommendations increasingly support greater consumption of plant-based foods and reduced intake of ultra-processed and animal-based foods, reflecting emerging evidence regarding the metabolic, cardiovascular, and renal benefits of plant-dominant dietary patterns (Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group, 2024) . This transition aligns closely with the principles of PLADO, which aims to achieve adequate nutritional intake while reducing dietary acid load, phosphorus bioavailability, and progression of the disease.

2.3.4. Nutritional Comparison of Plant-Based vs. Animal-Based proteins

Source of protein plays an important role in the management of CKD, where dietary modifications are often employed to slow disease progression and minimize renal workload. Proteins are essential macronutrients, vital for several physiological processes, including tissue repair, immune function, and muscle maintenance. However, patients with CKD, the type and quantity of protein consumed can significantly affect kidney function and disease progression.

2.3.4.1 Amino Acid Composition

Proteins are made of amino acids, which are divided into essential amino acids and non-essential amino acids. The differences between vegetarian protein and animal protein lie in the profiles of these amino acids, which are crucial for various physiological function, including muscle synthesis, immune function, and tissue repair. Several studies have examined the postprandial muscle protein synthesis (MPS) response to the ingestion of animal-based proteins

(dairy and meat) and plant-based proteins (such as soy, wheat, and rice). Increase of animal-based proteins leads to a significant increase in MPS, due to a rapid increase in plasma essential amino acids, particularly leucine. In contrast, plant-based proteins, such as soy and wheat, result in smaller MPS response. This is due to lower content of essential amino acids or the lack of specific amino acids such as leucine, lysine, and methionine, in plant-based proteins, therefore limiting protein synthesis. While vegetarian proteins have shown less anabolic potential, most studies have focused on only a few plant sources (e.g. soy, wheat, and rice), leaving the effects on other plant-based sources less explored (Gorissen *et al.*, 2018). The graph bellow compares the amino acid content of beef sirloin and several plant-based proteins (white beans, soybeans, cooked peas, and rice). Thus, it represents the amounts of essential amino acids (leucine, lysine, methionine, and others) in each protein source, showing that animal-based proteins contain higher levels of most essential amino acids compared to plant-based proteins. For example, beef sirloin, has significantly higher amounts of leucine, lysine, and valine, which are critical for muscle protein synthesis, compared to vegetarian proteins. Plant sources such as soybeans, tend to show higher values than others such as white beans and rice, but still generally lower compared to animal sources of protein.

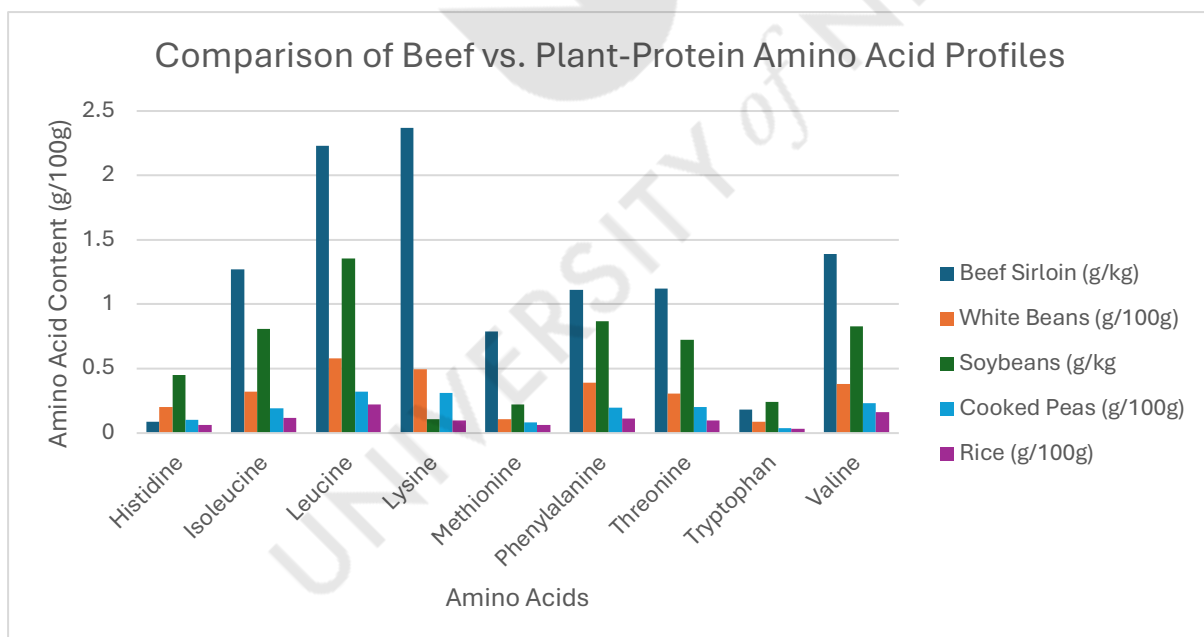


Figure 2.11: Comparison of Beef vs. Plant-Protein Amino Acid Profiles (Laleg *et al.*, 2016; Gorissen *et al.*, 2018).

Two studies by (Laleg *et al.*, 2016) and (Gorissen and Witard, 2018) have compared the essential amino acid scores of several plant-based and animal-based protein sources, as shown in figure

2.10. The graph indicates that on average, animal-based proteins generally have higher amino acids scores for most amino acids, especially lysine, threonine, and valine, whereas vegetarian proteins show comparable or higher scores for certain amino acids such as phenylalanine + tyrosine and histidine. More specifically, faba bean have a 231% histidine score whereas the highest % of histidine of animal based is milk with 180%. For isoleucine amino acid score animal-based proteins, specifically whey, has 213% amino acid score, whereas the higher score in plant-based is soybean at 157%. In general, animal sources (especially whey, beef, and casein) have a higher amino acid score, particularly lysine, leucine, isoleucine, valine, and methionine. These proteins are particularly strong in the BCAAs that are essential for muscle synthesis, growth, and repair. In addition, vegetarian protein (such as pea, faba bean, and soybean) perform better in certain areas like phenylalanine + tyrosine and histidine. However, they tend to fall short in terms of BCAAs compared to their animal counterparts. For individuals with CKD or individuals that have other dietary restrictions, it's essential to balance the intake of these proteins to ensure adequate levels of all essential amino acids, and often plant-based protein combinations, also known as protein complementation (like lentils with rice) are recommended to compensate for certain amino acid deficiencies.

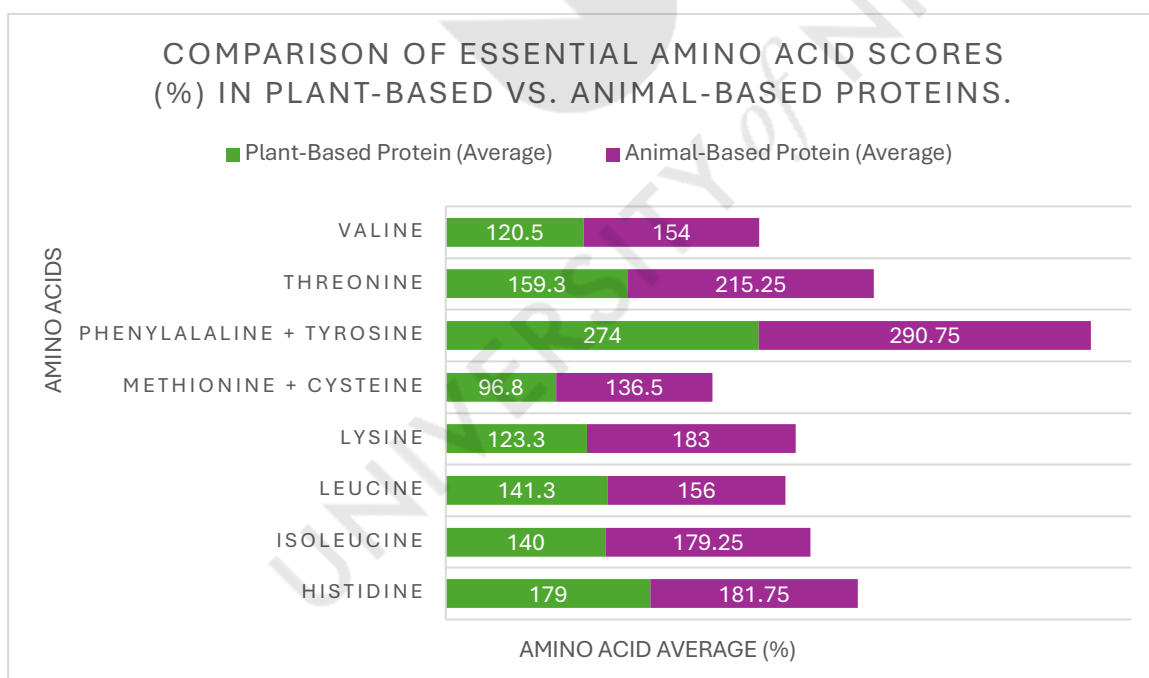


Figure 2.12: Comparison of Essential Amino Acid Scores (%) in Plant-Based vs. Animal-Based Proteins.

General dietary requirements for protein are defined as an estimated average requirement (EAR) and recommended dietary allowance (RDA). EAR is the daily intake level for a nutrient

that is estimated to meet the requirement for 50% of the target population, whereas RDA is calculated as the EAR plus two times the standard deviation, meets the requirement for 97-98% of the population (Institute of Medicine (US) Standing Committee on the Scientific Evaluation of Dietary Reference Intakes and its Panel on Folate, Other B Vitamins, and Choline and ., 1998). EAR for protein is 0.66 g/kg/day, and the RDA is 0.83 g/kg/day in adult healthy population. However, each group target has a different protein requirement based on their needs, for example protein requirements for elderly adults, and pregnant and lactating women are higher to minimize any possible complications (Joint WHO/FAO/UNU Expert Consultation, 2007). In addition, requirements for each indispensable amino acids have also been defined for each age group. Some examples of amino acid requirement for adults are: 10 mg/kg/day of histidine, phenylalanine + tyrosine require 25 mg/kg/day, and valine 26 mg/kg/day (Adhikari *et al.*, 2022).

2.3.4.2 Protein Quality

Protein quality refers to the amount and profile of amino acids in a protein source, as well as its digestibility. Food protein quality is assessed by digestibility, net protein utilization, and biological value. The Protein Digestibility-Corrected Amino Acid Score (PDCAAS) and the Digestible Indispensable Amino Acid Score (DIAAS) are the main methods used to assess protein quality (Dietary protein quality evaluation in human nutrition. Report of an FAO Expert Consultation 2013).

PDCASS is the most widely used measure of protein quality which considers both the amino acid profile (e.g. the presence and quantity of essential amino acids) and digestibility of the protein source. It is calculated by taking the amino acid score (reflecting the concentration of essential amino acids in a protein) and correcting it for the protein's digestibility (Wolfe *et al.*, 2016). A PDCASS score ranges from 0 to 1 where 1.0 shows that the protein is a high quality and meets all the essential amino acid requirements for humans in the necessary amounts and a score below 1.0 indicates that the protein lacks one or more essential amino acids in the required amounts or is poorly digested (Forester *et al.*, 2023). Protein sources from animals such as eggs, milk, meat, and fish, typically have high PDCASS values close to 1.0 meaning that they contain all nine essential amino acids in the right proportions to meet the human's body's needs and that they are highly digestible, meaning that the body can absorb and utilize most of the protein. For instance, egg protein has a PDCASS of 1.0 considering them as the gold standard for protein quality, as well as milk protein and beef protein (Hoffman and Falvo, 2004). Given dietary protein cannot fully meet the body's essential amino acids requirements when PDCASS is less than 100%, except for some soy protein isolates. Vegetarian protein sources

that have been tested to date are characterized by a PDCASS that is below 100% due to their lower digestibility and/or to an absence in certain essential amino acids compared to animal proteins (Dietary protein quality evaluation in human nutrition. Report of an FAO Expert Consultation 2013). Moreover, wheat protein has a PDCAAS of about 0.42, indicating that it lacks adequate amounts of lysine, therefore does not meet the complete amino acid needs for humans. The only plant-based protein that have a relatively complete amino acid profile and scores a PDCAAS close to 1.0 is soy protein. Digestibility of plant-proteins can also be affected by antinutritional factors such as phytates (which reduce the absorption of minerals) and fiber (which can reduce the bioavailability of amino acids) (Samtiya, Aluko and Dhewa, 2020). However, PDCASS method has some limitations, notably the ceiling effect, which means that proteins with a score higher than 1.0 (such as egg protein) are capped at a maximum score of 1.0, even though some proteins may have a greater amino acid balance. Although, it is still the standard tool used in many countries to assess the protein quality in foods (Schaafsma, 2012). Other limits in PDCAAS score are the use of faecal digestibility rather than the true ileal digestibility (TID), the restriction to only the first limiting amino acid, and the lack of consideration of the bioavailability of every single essential amino acid.

To increase the PDCASS, in 2011, the “FAO Expert Consultation on Protein Quality Evaluation in Human Nutrition” introduced another score, the DIAAS. Based on this score, protein sources, protein sources are divided into three categories: (1) DIAAS >100% are excellent sources; (2) DIAAS 100-75% are good sources; (3) DIAAS <75% are no claim sources (Ferrari *et al.*, 2022).

However, vegetarian proteins have lower DIAAS values, therefore lower PDCAAS values, and are defined as “low-quality protein sources”. Although, plant-based protein sources are complementary to each other, also known as protein complementation. An example is the combination of cereals and legumes, legumes have low levels of methionine and high levels of lysine, whereas cereals have exactly the opposite characteristics (Marinangeli and House, 2017). The main reason that plant-based proteins are less digestible than animal-based proteins is due to their protein structure. Vegetarian proteins have a higher content of β -sheet structure and lower proportion of protein α -helix which makes them more resistant to digestion in the gastrointestinal tract.

In addition, plant-based proteins contain fiber, therefore blocking the access of digestive enzymes to proteins, impairing digestion. Other antinutritional factors such as phytic acid,

protease inhibitors, hemagglutinins, and glucosinolates, can also have a negative impact in protein digestibility (Ferrari *et al.*, 2022). For example, grains, nuts, and seeds are rich in phytic acid which can bind to proteins and reduce their digestibility. Although, food processing methods such as soaking, sprouting, and germination can reduce the content of phytic acid, which can improve protein digestion (Multari, Stewart and Russell, 2015). Raw legumes, cereals, and vegetables are high in protease inhibitors which can also interfere with protein digestion by inhibiting enzymes such as trypsin. Methods to increase digestibility are drying, toasting, and autoclaving because they can deactivate these inhibitors (Gilani, Cockell and Sepehr, 2005). Pea protein concentrate treated with heat showed a 12% improvement in digestibility, which can increase its digestibility, same as casein, found in animal proteins (Rutherford *et al.*, 2015).

2.3.4.3 Plant-Based vs. Animal-Based Proteins in CKD

Quality and quantity of protein consumed play an important role in both CKD progression and overall kidney health. As mentioned above, high-protein intake, especially from animal-based sources, can increase the GFR, resulting in glomerular hyperfiltration and potentially increasing renal damage over time. In adults with kidney impairment, the kidneys struggle to filter and excrete the waste products of protein metabolism, such as urea and creatinine, which can build up in the blood (Rutherford *et al.*, 2015). Sulphur-containing amino acids include methionine, cysteine, homocysteine, and taurine. Methionine and cysteine are precursors of glutathione, which play a prominent role in oxidative stress, and is known that oxidative stress increases the development of CKD (Chen, C. *et al.*, 2023). Animal food sources generally have higher amounts of methionine + cysteine. For example, 100g whey has a methionine: cysteine ratio is 1.08:0.8 g whereas 100 g soy has a methionine: cysteine ratio is 0.3:0.2 g (Elango, 2020). Thus, these sulphur-containing amino acids are important determinants of dietary acid load due to sulphate production after oxidation. Western diet is characterized by high consumption of animal sources, beverages containing sugar and low consumption fruits, vegetables, and grains. It is known that following a western-style diet can led to low-grade metabolic acidosis and possibly cause metabolic disorders. However, consumption of fruits and vegetables can reduce the dietary acid load and decrease proteinuria and blood pressure in patients with macroalbuminuric hypertensive nephropathy and stage 2 CKD, which leads to decrease CKD progression (Goraya *et al.*, 2012). Figure 2.11 shows the comparison between the two types of protein the impact they have on renal dysfunction. The data is depicted on a scale ranging from negative (-5) to positive (+5), with negative values presenting negative effects and positive values indicating beneficial impacts. Each health aspect is represented by a horizontal bar,

illustrating the differences between the effects of animal-based and plant-based protein on health aspects in renal failure. Health aspects included were gut microbiota, cardiovascular risk inflammation, CKD progression, metabolic acidosis, and phosphorus load. Consuming more plant-based proteins showed a positive effect on those aspects whereas animal-based proteins showed a negative impact (Michail and Andreou, 2025). More specifically, phosphorus has a negative impact due to phosphorus absorbability from animal products being around 40–60% whereas in plant-based protein it is low, <40% in legumes and seeds (Itkonen and Lamberg-Allardt, 2023). Animal protein is high in saturated fat, endotoxins, and cholesterol; therefore, it increases the risk of cardiovascular disease as well as increases inflammatory markers, whereas vegetarian protein reduces the risk due to improved lipid profiles and lower oxidative stress and reduces inflammatory markers due to high fiber content, antioxidants, and phytonutrients (Wathanavasin, Kittiskulnam and Johansen, 2024). Moreover, animal protein has a higher acidic load due to sulfur-containing amino acids and can cause hyperfiltration and proteinuria, whereas vegetarian protein decreases acidosis and helps to maintain an acid-base balance (Darzi, Rouhani and Keshavarz, 2023).

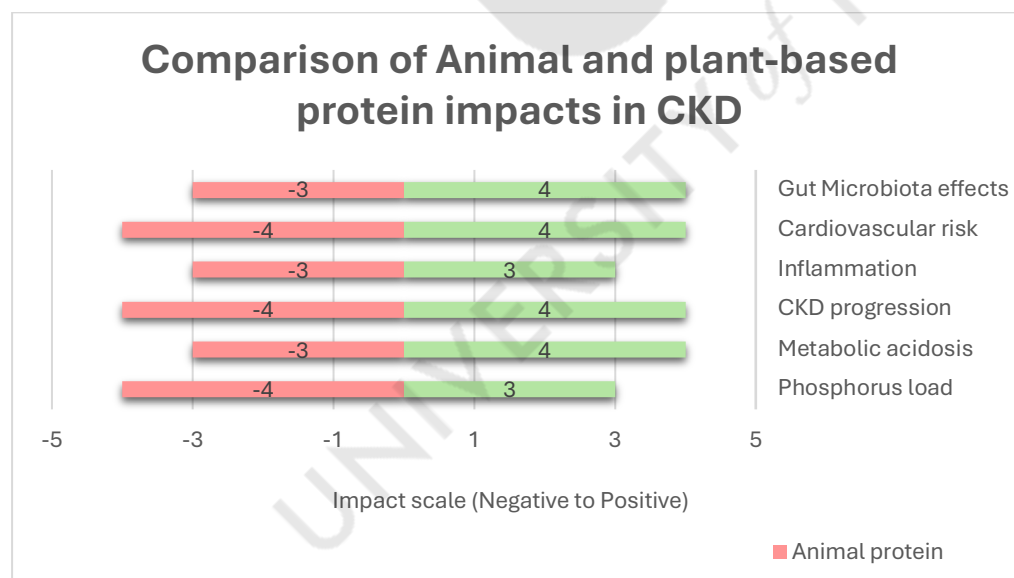


Figure 2.13: Comparison of the two types of protein and the impact in CKD.

Note: The graph compares the perceived impacts of animal protein and plant-based protein on several aspects of health in individuals with chronic kidney disease (CKD). The values on the impact scale range from -5 (most negative) to +5 (most positive), showing how each protein type is considered to affect factors like gut microbiota,

cardiovascular risk, inflammation, CKD progression, metabolic acidosis, and phosphorus load. Animal-based protein are indicated by red bars and plant-based protein (green bars).

Source: Self-made graph

A common complication in patients living with CKD is hyperphosphatemia which can contribute to renal osteodystrophy and cardiovascular disease. To manage elevated phosphorus in the blood, patients are often given phosphorus binders and advised following a low-phosphorus diet, that involved restricting high-phosphorus food sources. Foods are grouped together based on phosphorus bioavailability by source as plants, animals and food additives (Cupisti and Kalantar-Zadeh, 2013). Differences in phosphorus bioavailability between the two types of protein have been shown to be clinically relevant. Phosphorus from plant is thought to be poorly absorbed due to most of it exists as part of phosphorus storage molecules known as phytates, which cannot be broken down by human digestive enzymes. However, a portion of animal-based phosphorus is bound to digestible organic molecules, which are thought to be mostly bioavailable (St-Jules *et al.*, 2017). A study by (Moe *et al.*, 2011) wanted to determine whether the source of phosphorus (animal vs plant) has an impact on phosphorus metabolic in patients with CKD. Results showed that 72% of urinary phosphorus was noted in patients who followed animal-based diet whereas only 52% was observed in plant-based diet.

The comparison between plant-based and animal-based proteins highlights several key differences in terms of amino acids, protein quality, and digestibility. While animal proteins generally provide a complete and highly digestible source of protein, vegetarian proteins can still be beneficial, especially when consumed as part of a balanced diet that includes a variety of plant sources. For individuals with CKD, a plant-based diet can help reduce the renal burden associated with high animal protein intake, although careful planning is required to ensure adequate intake of essential amino acids and to overcome challenges related to digestibility and bioavailability.

2.3.5. Plant-based diets in CKD Management; Focusing on PLADO

Plant-based foods are recognized as important component of a nutritious diet across many dietary patterns. The main characteristic these diets have is the focus on plant-based protein sources within overall food intake. Examples of such dietary patterns include the Mediterranean diet, Mediterranean renal adaptation (MedRen), Flexitarian diet, Vegetarian diet, and PLADO.

MedRen diet is an adaptation of Mediterranean diet specialized for kidney patients with focuses on decreasing recommended daily intake of protein, sodium, and phosphorus compared to the recommended guidelines for the general population. Specifically, dietary guidelines for MedRen are total protein intake of 0.8g per kilogram per day, salt intake to 6 grams per day, and dietary phosphorus intake should not exceed the total of 800 mg per day (Naber and Purohit, 2021). While following the traditional Mediterranean diet and making minor adjustments promotes better kidney function and supports metabolic patterns. Moreover, primary dietary recommendations include focusing on white meat instead of red meat to reduce saturated fat and phosphorus load, increasing vegetarian foods such as legumes to increase dietary fiber thus, reducing net endogenous acid production, portion control as well as cooking methods should be individualized on patient's needs and wants. Regarding hyperkalemia occurrence, potassium management should include low-potassium fruits and vegetable intake should not exceed the two portions per day, with implementation of potassium-reducing cooking techniques (such as peeling the skin of, boiling with adequate water discard). High-phosphorus dairy products should be limited, while fresh cheeses should be consumed with caution (once every 7 to 10 days) to manage phosphorus complications (D'Alessandro *et al.*, 2023). Recent randomized crossover trial reported that patients with CKD in stages 3 and 4, maintain kidney function and had well tolerance with potassium levels when following a Mediterranean short-term intervention (Kwon *et al.*, 2024).

2.3.5.1 Concept of PLADO

While Mediterranean-based dietary interventions have been considered safe and capable of maintaining renal function in patients with CKD, one dietary intervention that has gained attention is the Plant-Dominant Low-Protein Diet (PLADO) in renal management. It is a specialized dietary regimen designed to manage CKD by restricting protein intake to 0.6-0.8 g/kg/day, with at least 50% of the total protein derived from plant-based sources (Kalantar-Zadeh *et al.*, 2020). This diet is intended to reduce the workload on the kidneys, slow the disease progression, and mitigate complications such as uremic toxins and high phosphorus levels. PLADO is beneficial due to its higher fiber content, anti-inflammatory effects, and alkalinizing properties, which are less likely to produce harmful byproducts compared to standard LPDs high in animal-based proteins. Thus, PLADO is linked with improved cardiovascular health, making it more sustainable long-term option for patients living with CKD, as it provides not only kidney protection but also provide health benefits. It emphasizes the consumption of vegetarian proteins while limiting total protein intake (Michail and Andreou, 2025).

As previously mentioned, standard LPD also aim to reduce protein intake but typically rely on animal-based products, which are higher in acid load and generate uremic toxins and AGEs. In contrast, PLADO, with its focus on plant-based foods, is less likely to contribute to these harmful byproducts and may offer better kidney protection and cardiovascular benefits (Kelly *et al.*, 2023). Studies mentioned that these diets can reduce the risk of certain health conditions including cardiovascular diseases, type 2 diabetes, and obesity, which are main risk factors for developing renal failure (Hertzler *et al.*, 2020).

Another nutritional therapy option in renal failure is the use of ketoanalogues, which are amino acid supplements designed to provide essential amino acids without the nitrogen burden linked with traditional proteins. Ketoanalogues are useful for preventing muscle wasting in individuals suffering with CKD, while avoiding excessive nitrogen waste, which can increase kidney damage (Li, A., Lee and Lin, 2019). While PLADO provides a broad range of beneficial compounds such as antioxidants, fiber, and polyphenols, it may not preserve muscle mass as efficiently as ketoanalogues, which are specifically designed for this specific reason. Despite this, PLADO's reliance on whole vegetarian sources offers long-term sustainability, as it provides a varied, nutrient-dense diet beyond just kidney protection, unlike ketoanalogues, which require ongoing supplementation and monitoring (Michail and Andreou, 2025).

PLADO regimens are customized based on the stage of CKD, with protein intake adjusted according to reduce the production of nitrogenous waste and support kidney function. In early stages, the focus is on preventing uremic toxin and metabolic complications, while advanced stages require careful management of electrolytes such as potassium, phosphorus, sodium, and calcium. For instance, in advanced renal disease, phosphorus control becomes particularly important as plant-based phosphorus is less bioavailable than animal-based phosphorus, reducing the risk of hyperphosphatemia. Potassium intake must also be carefully managed, especially since vegetarian products are richer in potassium, though it is less bioavailable than potassium from animal products. Cooking methods such as boiling and soaking vegetables can help to reduce potassium content, making it safer for patients at risk of hyperkalemia (Gluba-Brzózka, Franczyk and Rysz, 2017).

Other nutritional restrictions when following a PLADO diet include sodium intake should be <4 g/day, or <3 g/day if edema or hypertension is observed, and fiber content is around 25 g/day (Kalantar-Zadeh *et al.*, 2020). When conventional LPD and PLADO diet are compared, people with CKD total protein intake in PLADO is 24-32 g/day whereas in the standard renal

diet is 7.2-9.6 g/day, for an average 80 kg person (table 2.8). Based on the recent narrative review 10 studies, of which two were randomized controlled trials, explored the beneficial effects of PLADO diet in patients with CKD. Study by (Garneata *et al.*, 2016) examined the relation between VLPD supplemented with ketoanalogues compared with a conventional LPD in 207 individuals living with CKD for 15 months. Results showed that renal function was improved, and CKD progression rate was decreased with PLADO dietary patterns. Another RCT assessed the effect of vegetarian diets on cardiometabolic risk factors in patients with CKD. Results showed that participants who followed a vegetarian diet had a significant lower mean oxidized LDL compared to those who consumed meat diet. Thus, in the vegetarian diet group had lower mean value of triglycerides, body weight and BMI, compared to meat diet. Therefore, suggesting that plant-based diets, including PLADO, reduced cardiovascular risk markers in patients with CKD (Djekic *et al.*, 2020).

Table 2.9: Comparing standard diet in CKD and PLADO diet, in an 80kg person.

Protein Consumption	Standard Diet in CKD	PLADO in CKD
Proportion of plant-based protein (%)	15 %	50 %
Total protein (g/kg/day)	0.6 – 0.8 g/kg/day	0.6 – 0.8 g/kg/day
Total protein intake (g/day)	48-64 g/day	48-64 g/day
Plant-based protein (g/day)	7.2-9.6 g/day	24 – 32 g/day
Animal-based protein (g/day)	40.8 – 54.4 g/day	24 – 32 g/day
Total fiber intake, g/day	25 – 30 g/day	25 – 30 g/day

PLADO regimens involve protein restriction to 0.6–0.8 g/kg/day depending on the stage of renal failure. This is mainly to achieve the intake of the essential amino acid requirements while reducing the production of nitrogenous waste products that damage the kidneys. As mentioned above, plant-based proteins have high nutritional value while producing fewer toxic byproducts compared to animal-based proteins (Xiao *et al.*, 2023). Moreover, since plant proteins are more

likely to contain lower amounts of specific essential amino acids, including lysine and sulfur-containing amino acids, it has been questioned as to whether these plant-based LPDs may be adequate in some essential nutrients. Previous research did not mention an increased prevalence of protein-energy wasting or malnutrition in patients with CKD not undergoing dialysis when followed a vegetarian LPDs with a protein intake of 0.7-0.75 g/kg/day. Although, assessment of nutritional status included body weight and several serum protein markers, whereas patients' amino acid, vitamin, mineral, and trace element status were not included (Barsotti *et al.*, 1996) and (Cupisti *et al.*, 2002). PLADO is CKD-patient-centric and flexible with respect to the targeted dietary goals and is based on the preferences of the patients compared to strict dietary regimens. Although there is a lack of information regarding the adequacy of essential nutrients, including essential amino acids, of vegetarian or PLADO providing 0.5-0.6 g/kg/day. Close monitoring of key macro and micronutrients is essential in order to promote better adherence and clinical outcomes to the patient. A frequent concern is the perceived risk of elevated potassium levels. However, there is no scientific evidence to support that dietary potassium restriction in CKD improved outcomes. Evidence suggests that dietary potassium, especially from whole, vegetarian foods, does not contribute to elevated potassium (Morris *et al.*, 2020). Fiber intake plays a major role in the modulation of intestinal microbiota metabolic toward saccharolytic direction and in decreasing proteolytic-derived uremic toxins. In contrast, when constipation occurs it worsens microbiota dysbiosis and contributes to the uremic status and to elevated potassium levels. Therefore, suggesting that high fiber diet promotes bowel motility and preventing higher potassium absorption, and alkalization with vegetarian sources also decreases the risk of hyperkalaemia (Cupisti *et al.*, 2017). Although, additional consideration and nutritional education should be given to the patients regarding fruits and vegetables, and sources with high potassium concentrations as well as cooking techniques to lower their potassium content.

PLADO regimen on each stage of renal failure, is presented on the table 2.9. Protein intake represents the total daily protein intake adjusted for CKD stage. As the disease advances, the lower protein intake is in order to reduce uremic toxin products and metabolic complications on kidneys. Plant-based protein portion represents the percentage of protein derived from plant-based sources, and therefore, as renal disease progresses, the higher the amount of plant-based protein is. This will help to improve phosphorus and acid load management. Electrolytes (potassium, phosphorus, and sodium) are also represented on the table and should be monitored carefully as the disease progresses. Calcium is vital to prevent bone disease. In advanced stages,

supplementation may be needed due to reduced dietary sources and impaired absorption. Thus, frequency monitoring is also shown to help professionals to have regular visits. For early stages, there are fewer follow-ups, as kidney function is still relatively preserved; however, basic blood samples, such as eGFR, BUN, and electrolytes, are advised to monitor to detect early abnormalities. Dialysis increases protein needs, although the process removes toxins and excess nutrients; therefore, weekly to monthly monitoring is important to balance dietary intake or prevent any malnutrition.

Table 2.10: PLADO regiments specifications.

CKD Stage	Protein Intake	Plant-Based Protein Portion	Potassium Intake	Phosphorus Intake	Sodium Intake	Calcium Intake	Monitoring
Stage 1–2	~0.8 g/kg/day	~70–80% of total protein	Normal (~3,500 mg/day), avoid excess	Moderate restriction (~700 mg/day)	<2,300 mg/day	Adequate (~1,000 mg/day), prefer plant sources	Every 6–12 months (basic labs: eGFR, Urea, BUN, electrolytes)
Stage 3	~0.6–0.8 g/kg/day	~80% of total protein	Moderate restriction (~2,000–3,000 mg/day)	Restriction begins (~600 mg/day)	<2,300 mg/day	Adequate with possible supplements (~1,000 mg/day)	Every 3–6 months (labs + dietitian check-ins)
Stage 4	~0.6 g/kg/day	~90% of total protein	Careful selection (~1,500–2,000 mg/day, limit high-potassium foods)	Low (~400–500 mg/day)	<2,000 mg/day	Supplementation if required (~1,000–1,200 mg/day)	Every 1–3 months (labs + close dietitian oversight)

Stage 5 (non-dialysis)	~0.4– 0.6 g/kg/day	~90– 100% of total protein	Low (~1,000– 2,000 mg/day)	Very low (<400 mg/day)	<2,000 mg/day	Supplementation likely needed (~1,200 mg/day)	Monthly (labs + individualized dietary adjustments)
Dialysis	~1.0– 1.2 g/kg/day	~50– 60% of total protein	Increased (~2,500– 3,500 mg/day)	Increased allowance (~800 mg/day), dialysis removes excess	2,000– 3,000 mg/day	Increased need (~1,200–1,500 mg/day)	Weekly to Monthly (labs + dialysis team review)

Note: The table outlines the recommended protein intake, plant-based protein portions, and specific nutrient intake targets for renal individuals across different stages, including dialysis. It also provides monitoring frequencies and suggests nutrient management strategies (potassium, phosphorus, sodium, and calcium). Protein intake and specific nutrient guidelines are adjusted according to the severity of CKD, with more stringent restrictions as the disease progresses. Monitoring is tailored based on disease stage, ranging from basic labs every 6-12 months for earlier stages to weekly or monthly check-ins for dialysis patients.

2.3.5.2 Evidence of PLADO regimens

The benefits of the Plant-Dominant Low-Protein Diet (PLADO) in chronic kidney disease (CKD) management are multifaceted, as demonstrated by several studies. The study by (Di Iorio *et al.*, 2013) involved 99 patients with CKD with proteinuria who followed either a conventional diet (0.6 g/kg/day) or a very-low-protein diet (0.3 g/kg/day) with keto-analogues supplementation for 12 months. Results showed that patients with moderate to severe proteinuria and increased phosphate levels reported a significant decrease in proteinuria, by 50%, in patients who consumed 0.3 g/kg/day of protein with keto-analogues regimen. Thus, an RCT reordered the survival and reduction of CKD progression, involved 207 patients with stage 4 CKD and were divided into two groups, with group A following a VLPD + keto-analogues and group B, following a conventional LPD renal diet. Findings suggest that only group A showed correlation of metabolic abnormalities, and the decline in eGFR was slower in that group compared to group B (Garneata *et al.*, 2016). Therefore, suggesting the

effectiveness of a vegetarian, VLPD with ketoanalogues supplementation, however there is a lack of randomized controlled trials comparing animal-based and plant-based low-protein diet.

Based on the narrative review by (Michail and Andreou, 2025) highlighted pivotal studies that underline the benefits of PLADO as an emerging dietary strategy in the management of CKD. The studies listed on table 2.10 demonstrate PLADO's efficacy in addressing critical aspects of CKD care, such as reduction of CKD progression, improving metabolic and cardiovascular markers, and improving overall patient outcomes. Reviews by Saeed *et al.*, (2023) and Cupisti, Gallieni *et al.*, (2020) highlighted the potential of PLADO, as medication-like intervention, in reducing cardiovascular risks and improving CKD outcomes. Kalantar-Zadeh *et al.*, (2020) and Mocanu *et al.*, (2021) found that PLADO improves quality of life, delays dialysis, and offers metabolic and cardiovascular benefits compared to animal-based LPD. Thus, (Joshi, Shah and Kalantar-Zadeh, 2019) confirmed PLADO's ability to maintain nutritional adequacy while reducing uremic toxins. RCT by Garneata *et al.*, (2016) demonstrate PLADO's effectiveness in slowing CKD progression and improving renal function. Additionally, guidelines from Ikizler *et al.*, (2020) recommended plant-based proteins for better kidney outcomes, and studies by Zarantonello and Brunori (2023) and Djekic *et al.*, (2020) further emphasized PLADO's positive impact on inflammation, gut microbiota, and cardiovascular risk markers in patients with kidney impairment. Overall, based on the studies, PLADO appears to be an effective dietary approach in managing CKD, with several studies supporting its benefits across several health aspects.

However, the successful implementation of PLADO requires a multidisciplinary approach, integrating dietary expertise with clinical monitoring to address individual variability and potential challenges. Future research should aim to refine these interventions further, exploring long-term outcomes and strategies to enhance adherence.

Table 2.11: Relevant Trials of PLADO's efficacy.

Author/s	Year	Study Design	Aims	Results
Saeed et al.	2023	Review	Explore the link between chronic kidney disease (CKD) and cardiovascular health.	Highlighted the role of dietary interventions like PLADO in reducing cardiovascular risks.
Cupisti, A. et al.	2020	Review	Assess low-protein diets (LPD), including PLADO, as a therapeutic option for patients with CKD.	PLADO was identified as a medication-like intervention, improving CKD progression and patient outcomes.
Kalantar-Zadeh, K. et al.	2021	Review	Evaluate PLADO in CKD management.	Demonstrated improved quality of life and delayed need for dialysis in patients with CKD.
Mocanu, C. et al.	2021	Review	Compare plant-based versus animal-based low-protein diets in CKD management.	PLADO provided similar benefits to animal-based LPDs with added metabolic and cardiovascular advantages.

Joshi, S. et al.	2019	Review	Assess the adequacy of plant-based proteins in CKD management.	PLADO was sufficient in maintaining nutritional adequacy while reducing uremic toxins.
Garneata, L. et al.	2016	Randomized Controlled Trial (RCT)	Study the effects of a very low-protein diet supplemented with keto-analogues in CKD.	Improved renal function and slowed CKD progression with PLADO-like dietary patterns.
Ikizler, T.A. et al.	2020	Practice Guidelines	Develop KDOQI guidelines for nutrition in CKD.	Recommended incorporating plant-based proteins for metabolic benefits and better kidney outcomes.
Zarantonello, D. et al.	2023	Review	Explore benefits of plant-based diets in preventing and mitigating CKD progression	Identified significant benefits of PLADO in reducing inflammation and improving gut microbiota.
Kalantar-Zadeh, K. et al.	2016	Letter	Investigate North American experiences with low-protein diets for CKD.	Found PLADO effective in CKD management, emphasizing the role of dietitian-led interventions.
Djekic, D. et al.	2020	Randomized crossover study	Assess the effects of vegetarian diets on cardiometabolic risk	Plant-based diets, including PLADO, reduced cardiovascular

			factors in patients with CKD..	risk markers in patients with CKD.

2.3.5.3 Challenges of PLADO

Despite the potential benefits of PLADO, several challenges exist to implement it. For instance, concern regarding amino acid deficiency in PLADO. Vegetarian foods often provide lower levels of amino acids than omnivorous diets, however they do not contain low protein in themselves. Although, a study using an exploratory analysis using linear programming aimed to explore whether combinations of protein ingredients could reproduce amino acid profile that meets specific nutritional goals, and to identify the potential solutions and limitations of such combinations. Results showed that it was easy to create a balanced profile using plant-protein combinations, and they also identified several plant protein mixtures that met more specific amino acid requirements, such as mimicking the amino acid profile of animal proteins. Plant-protein sources such as legumes (lima beans, pea, winged beans isolates), starchy vegetables and vegetables (potato, radishes), cereal grains (corn and brown rice), fruits, nuts and seeds (Napin, Brazil nut) were found to have amino acid profiles that complemented each other and helped to achieve amino acid compositions similar to those found in animal proteins. More specifically, potato, lima beans, winged beans protein isolates were particularly rich in BCAAs, which are essential for muscle synthesis and repair. Napin protein isolate was high in cysteine and histidine, and corn protein was rich in leucine, which brown rice protein isolate was high in both leucine and valine, two amino acids for muscle protein synthesis (Dimina *et al.*, 2022).

Another challenge in implementing PLADO is dietary adherence. Several studies have reported that LPDs and low adherence rates are common. A study conducted by (Bellizzi *et al.*, 2022) compared the effectiveness of a VLPD with ketoanalogues and LPD in patients with CKD for six months. Results showed that adherence to protein restriction is low however risk of renal death did not differ between the groups. Low dietary adherence could be due to the unappealing taste of protein-free alternatives, such as starch-based bread and pasta, meat alternatives are more expensive, and patients may have face challenges in maintaining the diet when away from home. Thus, large dietary changes can be difficult to maintain in the long term. In contrast, PALDO could be a promising alternative because it's natural composition may improve adherence whereas conventional LPDs do not (Kaimori *et al.*, 2025). Moreover, adherence and feasibility differ among dietary approaches, even though PLADO is beneficial, it requires

significant dietary adaptation, especially for patients that follow more animal-based diets. Thus, adherence can be affected by taste preferences, food accessibility, and sociocultural factors. For instance, vegetarianism is a long tradition in Indian cultures due to at least partly to religious interdictions against taking living creatures' lives. 40% of India's population, traditionally adheres to vegetarian diets, which primarily include fermented milk, lentils, and fresh sprouting seeds. Like India, China is also encouraged by Buddhism and Daoism, therefore are following a vegetarian diet that includes soybean products, such as tofu (Khor *et al.*, 2021).

On the other hand, there is a high prevalence of overweight and obesity, especially in low and low-middle income countries. These countries are also facing a shift from traditional diets to "Western" diets, also known as "nutrition transition", characterized by high saturated fats, sodium, sugar, and meat intake (Viroli, Kalmpourtzidou and Cena, 2023). Following a Western diet leads to unbalanced nutrient intake which then leads to adverse health effects such as obesity, non-communicable diseases and early all-cause mortality (Popkin, Corvalan and Grummer-Strawn, 2020). Globally, unbalanced dietary patterns are ranked at top risk factors for mortality and disability-adjusted life-years lost mainly caused by cardiovascular diseases, type 2 diabetes and cancer (GBD 2019 Risk Factors Collaborators, 2020).

2.3.5.4 Implementation strategies of PLADO

PLADO regimens are a vital component of nutritional therapy for individuals with CKD, providing benefits that exceed symptom management to addressing the main causes of the disease's progression. Proper implementation of PLADO is critical to achieving these beneficial outcomes while reducing potential risks. This requires careful planning, patient education, and consistent monitoring.

Key component to achieve overcoming challenges are providing nutritional adequacy, creating individualized meal plans, and promoting dietary adherence. The reduction of protein, especially animal-based, PLADO reduces the production of nitrogenous waste and uremic toxins, therefore eases the burden on the kidneys which reduces the disease's progression rate. Thus, it helps to reduce the need for dialysis or kidney transplant. Additionally, PLADO helps to manage several complications including hyperphosphatemia, metabolic acidosis, and cardiovascular disease, due to its plant-based composition, which is rich in fibre, antioxidants, and unsaturated fats. When correctly implemented, PLADO can meet the nutritional needs of patients living with CKD by providing low protein intake while ensuring sufficient calories, healthy fats, and complex carbohydrates to prevent protein-energy wasting.

Although, several challenges can be observed, such as patient's difficulty adjusting to plant-based diets due to taste preferences, cultural norms, or misconceptions about the adequacy of plant-based diets. Studies have shown that adherence to a plant-based diet is linked to reduction of mortality risk and CKD progression, whereas unhealthy plant-based foods, such as sugar-sweetened beverages and refined sugars can increase the disease risk (Amir *et al.*, 2024). Another challenge is managing micronutrients such as potassium, phosphorus, and vitamin B12. Due to plant-based products having more potassium, though less bioavailable, as well as added phosphates it's essential to carefully monitor them (Kalantar-Zadeh *et al.*, 2020).

Thus, personalized meal plans and careful nutrient management are essential, and patients should receive guidance from registered dietitians to ensure their diets are both nutritionally adequate and culturally acceptable. Moreover, nutritional counselling, support and education to the patient as well as to a family member is crucial for successful implementation of PLADO diet. PLADO should be tailored to individual patient needs, considering factors such as the disease stage, comorbidities, dietary preferences, and cultural background. Therefore, supervision by a multidisciplinary team is recommended, comprising nephrologists, specialty-trained dietitians, and other medical professionals. Weakness or sarcopenia may occur in patients with CKD that follow PLADO with poor adherence, especially older individuals living with CKD should be monitored frequently (Massini *et al.*, 2023). Moreover, practical implementation of PLADO can be demonstrated through structured visual nutrition education tools. For instance, similar to MyPlate nutrition education tool, PLADO can demonstrate a similar education tool for recommended daily servings, and identifying foods to exclude, such as highly processed products and fruit juices due to their increased sodium and potassium content, respectively. Figure 2.12 represents the PLADO plate which is designed for educational purposes that includes macronutrient distribution with 50% of non-starchy vegetables, 25% protein with emphasis on plant-based, and 25% of whole-grains and starchy vegetables and sodium intake should not exceed more than 2,300 mg/day. Moreover, it adopts Mediterranean cultural adaptation that includes water consumption and olive oil as the main oil consumption. Importantly, portions and food choices should be based on patient's preferences, availability, biochemical markers, CKD stage, and possible comorbidities.

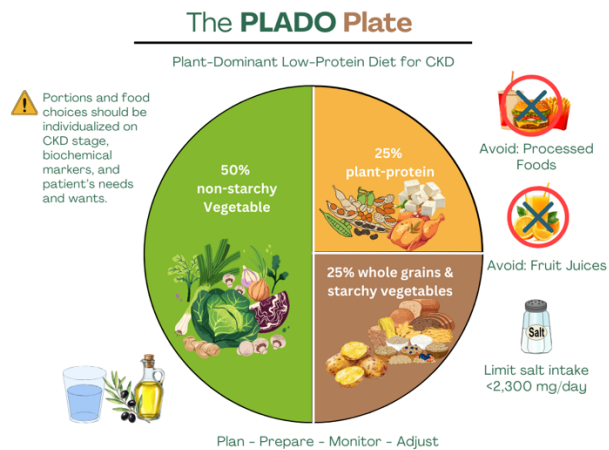


Figure 2.14: Visual representation of PLADO Plate for renal nutrition framework.
Source: Created by the author

Other strategies to implement PLADO in patients with CKD involve nutrition education on protein substitutions as well as protein exchange list. Food exchange list, mainly carbohydrate exchange list, have been used to assist patients diagnosed with diabetes and patients that aim for weight loss to organize their meals (H Ibrahim *et al.*, 2023). Using the Expedited 10 g protein counter (EP-10), dietary protein quantification and education tool, in nutrition education in dialysis patients demonstrated significant improvement in nutritional status while having no negative impact on potassium and phosphorus levels (Lim, S. and Lye, 2012).

Educating patients with CKD regarding potassium and phosphorus management is also important. Educational materials that include low-potassium vegetables and fruit lists as well as low-phosphorus sources should be given to the patients in plain language. Moreover, understanding dietary patterns rather than isolating foods is essential, and consider the significance of culture and socioeconomic barriers of food. Thus, PLADO can be easily adopted to Mediterranean countries due to easier access of legumes, olive oils, traditional vegetable-based meals which limits the consumption of processed meats and salty cheeses (Rhee *et al.*, 2023).

2.4 THE MEDITERRANEAN DIET & CYPRIOT DIETARY PATTERNS

Dietary pattern is one of the most modifiable risk factors for adverse health outcomes, being an effective albeit neglected strategy for the prevention, and against the development and progression of several diseases. A recent systematic review analysed four specific dietary patterns in relation to the development and progression of CKD in adults. Dietary patterns

were: Prudent diet, characterized by higher intake of fruit, vegetables, whole grains, fish and poultry; Western diet; DASH diet, rich in fruit and vegetables, low-fat dairy products, whole grains, fish, poultry, beans, seeds, and nuts, low in sodium, added sugars, fats, and red meat; and Mediterranean diet. Results showed that Prudent, Mediterranean, and DASH diets are linked with higher levels of GFR, lower levels of albuminuria and inflammatory markers (C-reactive protein) marking these diets as protective to nephrons, lower cardiovascular and CKD risk. Western diet was associated with worsening renal function and rapid disease progression which was linked to elevated levels of microalbuminuria and lower GFR (Quintela *et al.*, 2021).

Cyprus, a Mediterranean country, follows the Mediterranean diet that incorporates a significant proportion of plant-based foods such as legumes, whole grains, nuts, and olive oil. A recent study explored the effects of COVID-19 lockdown on all lifestyle medicine pillars, diet, physical activity, sleep, stress, social support and use of risky substances on Cypriot population. Results showed that participants during lockdown reported significantly higher perceived stress score, lower social support score, and worse sleep quality score. Adherence to Mediterranean diet was moderate and increased significantly only in those practicing religious fasting (Kolokotroni *et al.*, 2021). Another study was conducted that examined the differences in dietary and lifestyle habits during and after the lockdown, in COVID-19, in Cyprus. During the lockdown, the Cypriot population, had a greater daily intake of fruits, vegetables, legumes, fish and poultry as well as higher consumption of olive oil and lower consumption of alcohol compared to the period after the lockdown (Kyprianidou *et al.*, 2022). A recent study by Deligiannidou *et al.*, (2024) examined the associations between adherence to Mediterranean diet, subjective well-being, and several socioeconomic factors in Cypriot and Greek population. The study found that higher adherence to Mediterranean diet was positively associated with several aspects of subjective well-being, especially when comparing participants with low Mediterranean diet adherence to those with high adherence to the diet. This indicates that individuals who followed more closely to the Mediterranean diet reported better life satisfaction, happiness, and mental health, which results that dietary habits are closely linked to emotional well-being. A recent study analysed Food-Based Dietary Guidelines (FBDGs) of different countries and assess how well they align with a plant-based diet approach, including animal-based products. An index was developed, Balanced Food Choice Index (BFCI), to assess how well FBDGs encourage plant-based diets. Cyprus reported a BFCI score of 30, suggesting that the recommendations in Cyprus' dietary guidelines are somewhat aligned with a plant-based approach, however there is still significant emphasis on animal-based products.

Netherlands showed a BFCI score of 94 (closer to 100) which indicates a stronger emphasis on plant-based foods, and the lowest BFCI score of 3 being Slovakia (Klapp, Feil and Risius, 2022). While Cyprus has a rich variety of plant-based protein sources, there is a widespread reliance on animal-based proteins such as halloumi, lamb, and seafood which can affect the PLADO adherence (Michail and Andreou, 2025). Availability and affordability of high-protein vegetarian options, such as tofu and tempeh, remain limited in Cypriot markets, which may affect patient compliance. Therefore, overcoming these barriers requires culturally tailored dietary recommendations, integrating local food products, mainly plant-based, which ensuring nutritional adequacy for Cypriot individuals with CKD (Andreou *et al.*, 2025).

Narrative Review as Foundational Scholarly Contribution

Summary of Published Narrative Review

As part of the preparatory and conceptual phase of this doctoral research, a narrative review entitled:

“A Plant-Dominant Low-Protein Diet in Chronic Kidney Disease Management: A Narrative Review with Considerations for Cyprus” was conducted and published in *Nutrients* (Michail & Andreou, 2025) .

The purpose of this review was to systematically examine the existing scientific evidence surrounding plant-dominant low-protein diets (PLADO) in chronic kidney disease (CKD) management prior to the implementation of the present empirical investigation. Conducting this review allowed for a comprehensive evaluation of current knowledge, identification of methodological inconsistencies, clarification of clinical controversies, and determination of evidence gaps relevant to the Cypriot and Mediterranean context.

The review critically analyzed:

- The pathophysiological rationale for protein restriction in CKD
- Comparative effects of animal-based versus plant-based protein sources
- Impacts of PLADO on renal function, metabolic acidosis, cardiovascular risk, and uremic toxin production
- Nutritional adequacy and safety concerns, including potassium and phosphorus management

- Adherence challenges and implementation considerations
- Cultural adaptation within Mediterranean dietary frameworks

Importantly, the review highlighted persistent uncertainties regarding long-term outcomes, patient adherence, protein quality, and regional applicability. These identified gaps directly informed the design, objectives, and methodological structure of the present doctoral study.

Thus, the narrative review served not merely as a literature summary, but as a **conceptual and scientific foundation** for the empirical phases of this PhD research. It ensured that the intervention framework, research questions, and hypotheses were grounded in a critical synthesis of contemporary evidence.

- **Scholarly Impact and Article Metrics**

The published review has demonstrated measurable academic impact:

- **Citations:** 7
- **Article Views:** 13,922

These metrics indicate both scholarly recognition and substantial international interest in the topic of plant-dominant dietary management of CKD. The visibility and citation activity further support the relevance of PLADO as an emerging area in nutritional nephrology and underscore the timeliness of the present doctoral investigation.

In December 2025, the article was then got a certificate from Editor's Choice article, which reflected high quality, originality, and scientific value of the research (Appendix 2).

Review

A Plant-Dominant Low-Protein Diet in Chronic Kidney Disease Management: A Narrative Review with Considerations for Cyprus

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Abstract: Chronic kidney disease (CKD) is a major global health challenge, significantly contributing to morbidity and mortality due to its strong association with cardiovascular complications, metabolic imbalances, and reduced quality of life. Among the various interventions for CKD management, nutrition therapy plays a critical role in slowing disease progression and improving patient outcomes. The Plant-Dominant Low-Protein Diet (PLADO) has emerged as a promising dietary strategy that prioritizes plant-based protein sources while restricting overall protein intake, offering potential renal, cardiovascular, and metabolic benefits. This review evaluates current evidence on the efficacy of PLADO in CKD management, analyzing its impact on renal function, cardiovascular health, and systemic inflammation. Key findings suggest that PLADO can delay CKD progression, reduce dialysis dependence, and mitigate cardiovascular risks through lower dietary acid load, increased fiber intake, and anti-inflammatory properties. Additionally, PLADO has been shown to support gut microbiota diversity and reduce uremic toxin production, offering metabolic advantages beyond kidney health. While PLADO appears nutritionally adequate, concerns remain regarding protein sufficiency, potassium management, and long-term adherence. Its successful implementation requires tailored meal planning, patient education, and regular clinical monitoring to optimize outcomes and mitigate potential risks. This review highlights the importance of integrating PLADO into CKD management as a holistic, patient-centered dietary approach, particularly in regions like Cyprus, where no studies have evaluated its applicability. By synthesizing existing research, this review provides insights for clinicians, dietitians, and researchers to further explore long-term outcomes, adherence strategies, and feasibility across diverse healthcare settings. Future studies should focus on large-scale randomized controlled trials (RCTs) to establish PLADO's role in CKD dietary guidelines and clinical practice.

Keywords: chronic kidney disease (CKD); plant-dominant low-protein diet (PLADO); renal nutrition; plant-based protein; metabolic acidosis; dietary adherence; nephrology care; CKD dietary practices in Cyprus

As part of the methodological framework of this doctoral research, an original research article entitled:

“Development and validation of a questionnaire for the knowledge assessment and management of PLADO diet in kidney and healthy population in Cyprus” was published in *Frontiers in Nutrition* (Michail et al., 2025) .

The purpose of this study was to develop and psychometrically validate a culturally adapted instrument designed to assess knowledge, perceptions, sustainability beliefs, and protein-source understanding related to plant-dominant low-protein diets (PLADO), with a particular focus on kidney health.

The development of this instrument was undertaken prior to and in preparation for the interventional phase of the present PhD study. The rationale was to ensure that any evaluation of adherence, perceptions, or educational impact within the Cypriot CKD population would be supported by a scientifically validated and culturally appropriate measurement tool. Given the absence of validated instruments specifically addressing PLADO knowledge and protein-source perceptions within Mediterranean populations, the creation of this tool addressed a clear methodological gap.

Methodological Rigor and Psychometric Strength

The questionnaire development followed a structured multi-phase validation process:

- Comprehensive literature review and domain identification
- Expert panel evaluation for content validity (I-CVI > 0.78; S-CVI/Ave = 0.89)
- Cognitive pretesting
- Pilot testing (n = 120)
- Exploratory Factor Analysis (EFA)
- Confirmatory Factor Analysis (CFA)
- Internal consistency assessment (Cronbach's α = 0.71–0.82 across subscales)
- Criterion validity assessment

Exploratory factor analysis supported construct validity, explaining 36% of total variance, while confirmatory factor analysis demonstrated adequate model fit indices (RMSEA, TLI, BIC). Internal consistency values confirmed acceptable-to-good reliability across domains, including sustainability beliefs, dietary behaviors, and CKD-specific protein knowledge.

The final instrument comprised 42 items across eight thematic domains and incorporated structured educational elements such as glossary terms and explanatory prompts, allowing assessment of both baseline knowledge and learning progression.

Scientific and Practical Significance

This validated tool represents a novel contribution to renal nutrition research by:

- Providing the first culturally tailored PLADO-focused knowledge instrument in Cyprus
- Enabling reliable measurement of dietary perception shifts
- Supporting evaluation of intervention effectiveness beyond biochemical markers
- Bridging behavioral nutrition research and clinical nephrology

Importantly, this methodological foundation strengthened the integrity of the present doctoral intervention study by ensuring that adherence, knowledge acquisition, and perception outcomes were measured using a validated, psychometrically sound instrument.



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Development and validation of a questionnaire for the knowledge assessment and management of PLADO diet in kidney and healthy population in Cyprus

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Chronic kidney disease (CKD) requires dietary strategies that balance protein restriction, nutritional adequacy, and sustainability. As plant-dominant dietary models gain prominence in renal nutrition, understanding public perceptions of protein sources and their health impacts is increasingly critical. However, no validated assessment tool exists to evaluate such perceptions within the Cypriot population. This study presents the development and validation of a novel questionnaire designed to assess perceptions of sustainability, nutritional value, and health impacts of plant- and animal-based proteins, with a focus on kidney health. The instrument was developed through literature review, expert input ($n = 10$), cognitive pretesting, and pilot testing ($n = 120$). Validation included content validity indexing (I-CVI), Modified Kappa statistics, internal consistency via Cronbach's alpha, and exploratory factor analysis (EFA). Expert agreement was high, with an S-CVI/Ave of 0.89 and 93% of items achieving I-CVI ≥ 0.83 . Internal consistency across subscales ranged from $\alpha = 0.71$ to 0.82. EFA supported construct validity, explaining 36% of the variance. The final 42-item questionnaire covers eight domains, including sustainability beliefs, dietary behavior, and protein knowledge. A unique feature is its embedded educational content—glossary terms, visuals, and explanatory prompts—designed to evaluate baseline knowledge and learning outcomes. Pilot results revealed knowledge gaps and uncertainty about the sustainability of plant-based proteins among CKD respondents. This validated tool fills a significant gap in renal nutrition education and research and offers a reliable, culturally relevant means to assess dietary perceptions. It supports patient education, public health interventions, and clinical practice in promoting sustainable, kidney-friendly diets. Broader application and cross-cultural adaptation are recommended to enhance global utility.

2.5 CONCLUSION

This chapter critically examined the existing body of literature surrounding chronic kidney disease (CKD) pathophysiology, dietary management strategies, and the evolving role of plant-dominant low-protein diets (PLADO) in renal care. The review highlighted the central role of protein intake in CKD progression, emphasizing both the therapeutic potential and the clinical challenges associated with protein restriction.

Evidence supports the use of low-protein dietary approaches in slowing CKD progression; however, considerable heterogeneity exists across studies in terms of design, duration, outcome measures, and patient populations. While conventional low-protein diets often prioritize high-biological-value animal proteins to prevent protein-energy wasting, emerging research suggests that plant-dominant approaches may confer additional metabolic benefits, including reduced dietary acid load, lower phosphorus bioavailability, improved cardiovascular risk profiles, and potential modulation of the gut–kidney axis.

Despite promising findings, several limitations in the current literature were identified. Many studies are short-term, observational, or lack rigorous comparative frameworks. Long-term effects on renal function decline, dialysis initiation, and patient-centered outcomes remain insufficiently established. Furthermore, mechanistic exploration of microbiota-mediated pathways in dietary interventions for CKD remains limited. Importantly, Mediterranean populations, including Cyprus, are substantially underrepresented in interventional renal nutrition research, raising questions regarding the transferability and cultural feasibility of plant-dominant dietary models in these contexts.

The review also underscores the growing relevance of implementation science in renal nutrition. Biological efficacy alone is insufficient if dietary interventions are not sustainable within patients' cultural, social, and economic environments. Thus, integrating clinical effectiveness with adherence assessment and contextual feasibility represents an essential advancement in CKD dietary research.

Collectively, the literature demonstrates that while plant-dominant low-protein diets hold theoretical and emerging empirical promise, robust, context-specific, and multidimensional investigations are required to clarify their long-term clinical impact and real-world applicability. These identified gaps provide the scientific rationale for the present study, which

seeks to evaluate both the effectiveness and feasibility of PLADO within the Cypriot CKD population using a structured and comprehensive methodological framework.

The following chapter outlines the research design and methodological approach adopted to address these unresolved questions.

CHAPTER 3 METHODOLOGY

3.0 METHODOLOGY OVERVIEW

This chapter outlines the comprehensive methodological framework of the PLADO study, designed to assess the effect of a plant-dominant low-protein diet on Cypriot individuals with CKD. This study adopts a primary, quantitative, and longitudinal research approach providing a comprehensive evaluation of the effectiveness of PLADO in CKD management. The investigation of the effects of a plant-dominant dietary approach on clinical, biochemical, and behavioral impact in renal individuals. The methodology was developed to monitor baseline and after a 6-month intervention to assess any changes attributed by dietary alternation as well as nutrition education while maintaining feasibility and ethical practices in a clinical population.

A total of 30 participants with renal failure were recruited according to inclusion and exclusion criteria and were divided equally to a control group who received a conventional low-protein dietary plan based on the KDOQI renal guidelines or an intervention group who received PLADO regimes guidelines. The intervention was delivered a 6-month period, with assessments conducted at baseline and at the end of the study. This controlled pre-post intervention design enabled evaluation for all participants over time as well as between group differences.

Both groups followed a structured 7-day meal plan which was developed by the main clinical dietitians which were based on existing evidence based renal dietary guidelines, alongside structured nutrition education sessions were delivered throughout the intervention period. Data collection included body composition analysis, biochemical markers important to kidney disease progression such as urea, creatinine, electrolytes etc., and assessments of protein related dietary knowledge and dietary adherence. Validated tools and standardized protocols were used to enhance reliability and consistency for all individuals.

Quantitative data analyzed using the right pre and post comparative statistical approaches to assess possible changes within and between groups which may occurred. Methodological rigor was ensured through standardized data collection procedures, consistent assessment timing, and use of validated measurement tools.

All study procedures were conducted with ethical principles based on research ethics that involves human participants. Ethical approval was obtained prior to the beginning of the study, written informed consent was obtained from all participants, and confidentiality was maintained through anonymized data handling and secure data storage.

Overall, the controlled pre-post intervention design method used in the present study was appropriate for addressing the research hypotheses supporting the investigation. The following chapter presents the exact methodology used followed by figure 3.1 demonstrating the infographic methodology used.

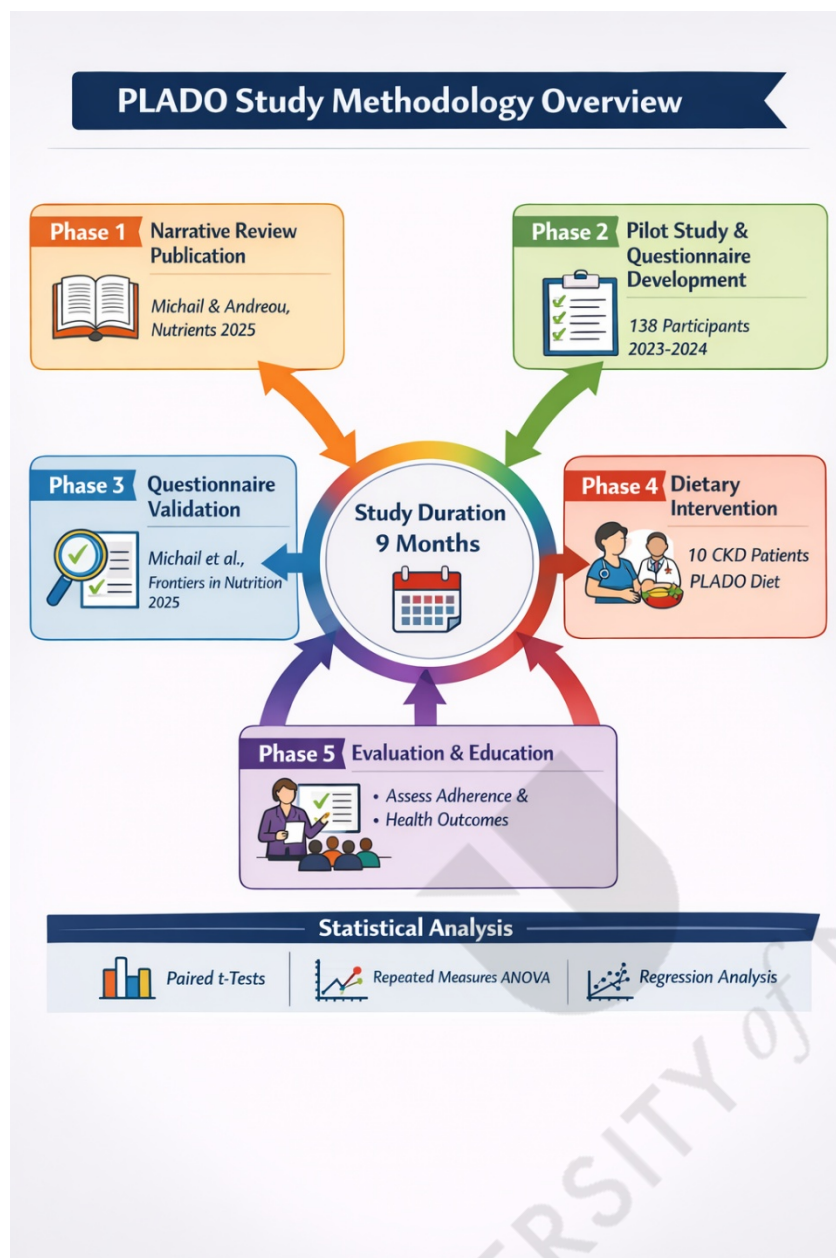


Figure 3.1: Methodology infographic.

Source: Created by the author

3.1 METHODOLOGY FRAMEWORK AND RESEARCH DESIGN

Clinical research requires a systematic approach with diligent planning, executing and sampling to obtain reliable and validated results, as well as understanding of each research methodology is important for researchers (Kiani et al., 2022). Moreover, medical research can be divided into primary, where studies are conducted, and secondary research, where raw data is analyzed and evaluated (Röhrig et al., 2009). Formulating the research questions is the first step in the research process which is the foundation for framing the hypothesis. Research

questions should be feasible, interesting, novel, ethical, and relevant (FINER). To structure each research question utilization of the population, intervention, comparison, and outcome, also known as PICO format, should be used (Willis, 2023).

Based on the above, four research questions were formed:

- **Research Question 1:** PLADO will significantly slow CKD progression compared to a conventional low-protein diet.
- **Research Question 2:** PLADO will lead to lower urea, creatinine, and phosphorus levels.
- **Research Question 3:** Patients following PLADO will report better quality of life scores.
- **Research Question 4:** Adherence to PLADO will be influenced by cultural factors and food accessibility.

Quantitative research focuses on testing the validity of hypotheses established by the research to identify the causal relationships between specific phenomenon and discovering practices to predict that phenomenon. Data used in quantitative research can be expressed as numerical values, and data accumulated through questionnaire surveys and tests are often used in this method, whereas qualitative research uses narrative data with words and images collected by participant observations, in-depth interviews, and focus group discussions (Pyo *et al.*, 2023). They have both advantages and disadvantages, for example quantitative research has the advantages of reliability and generalizability of the results and advances in data collection and analysis methods although, quantitative research shows difficulties with an in-depth analysis of dynamic phenomena that cannot be expressed by numbers alone. However, qualitative research takes a holistic perspective addressing the “why” and “how” questions. It has the advantage of validity, referring how accurately or appropriately a phenomenon was measured, although it presents weak generalizability, therefore it cannot be observed whether the phenomenon applies to other cases (Lakshman *et al.*, 2000).

Longitudinal studies perform continuous or repeated measures to follow specific individuals over prolonged periods of time. They are mainly observational in nature, with quantitative and/or qualitative data, without any external influenced being applied. This type of research evaluates the relationship between risk factors and the development of the disease, and the outcomes of treatments over a period (Kothari *et al.*, 2023). The advantages of using longitudinal

studies are the ability to identify and relate event to specific exposures, and further define these exposures with regards to presence, timing and chronicity. Although there are some cons regarding this type of study such as the incomplete and interrupted follow-up of participants, therefore loss to follow-up over time, difficulty in separation of the reciprocal impact of exposure and outcome, and lastly the inaccuracy in conclusion if adopting statistical techniques that fail to report the intra-individual correlation of measures (Caruana *et al.*, 2015). Examples of well-known longitudinal studies are the Framingham heart study which developed to identify the risk factors for cardiovascular disease in 1948 (DAWBER, KANNEL and LYELL, 1963).

Promoting healthy and sustainable diets is one of the key priorities for the prevention and management of chronic diseases, such as CKD. Health literacy is characterized by knowledge, motivation, and competencies to access, understands, appraise, and apply health information to make judgments and take decisions in everyday life (Sørensen *et al.*, 2012). Any type of intervention that aimed to change the practices of food outlets to promote healthier menu offerings are important. Nutrition education interventions can help improving the dietary behaviors of low socio-economic adults. Basic components of educational research intervention trials include experimental variables, such as novel curriculum; strong research questions valid and reliable instruments for documenting change; strong data analysis plan; experimental design that minimizes threats to internal validity (Sullivan, Gail M., 2011).

For nutrition education researchers a key challenge is to select the appropriate treatment for the control group that matches the research question, ethical considerations, and availability of standard care (Lindquist *et al.*, 2007).

The overall methodological structure of the study is presented in Figure 3.2. The research was conducted in five sequential phases, integrating exploratory, validation, interventional, and analytical components within a mixed-methods framework.

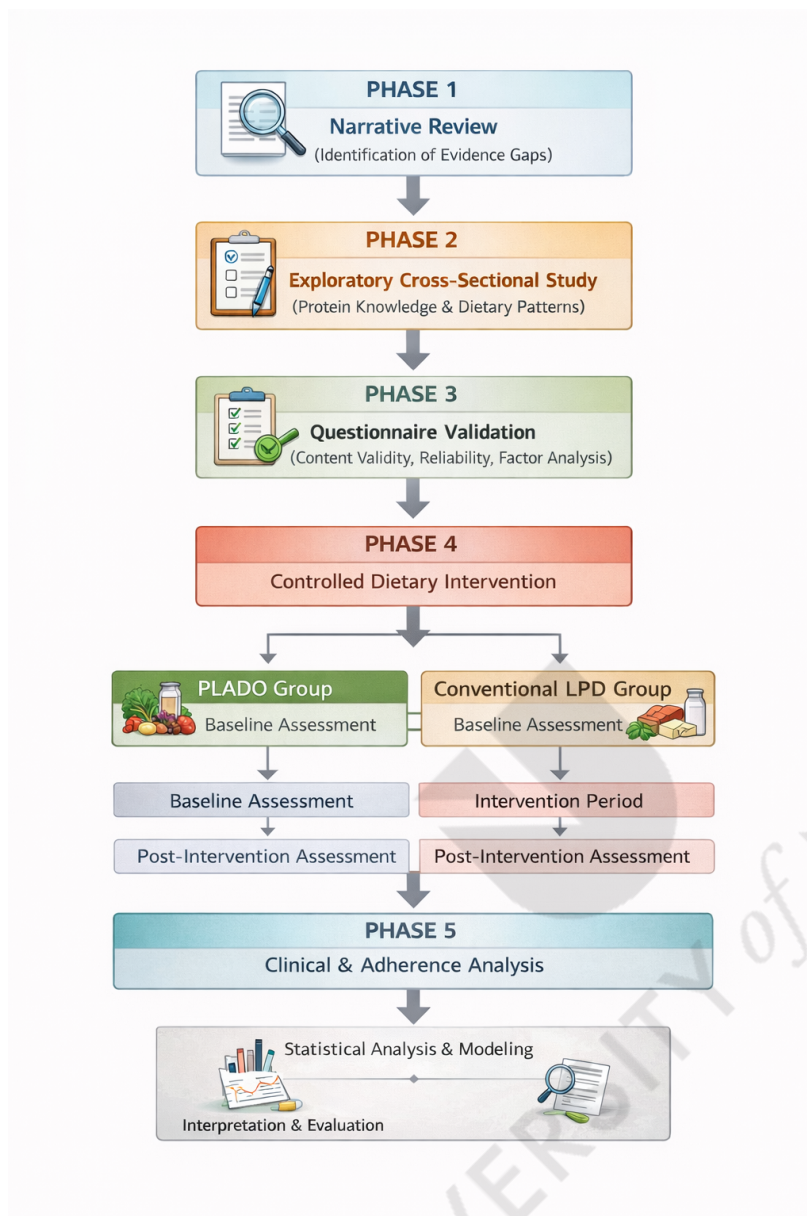


Figure 3.2: Overview of the Multi-Phase Methodological Framework.
Source: Created by the author

3.2 DETAILED METHODOLOGY OF THE PLADO STUDY (5 PHASES)

The purpose of this chapter is to present the research strategy and the methodology used. It provides information concerning the method that was used in undertaking this research as well as justification for the use of each method. Furthermore, this chapter describes each method in detail regarding the description of the research design, several stages of the research, including

selecting the intervention group, sources of data and data collection process, research tools, steps taken before and during the tests, and data analysis techniques.

The methodology of this PhD research is organized into five distinct but interrelated phases. Each phase is designed to investigate the impact of the Plant-Dominant Low-Protein Diet (PLADO) on Cypriot individuals with kidney impairment, evaluate their dietary adherence, and validate a novel questionnaire developed to assess nutritional knowledge and behavioral outcomes over time.

3.2.1. Phase 1 – Narrative Review Publication

The first phase involved the publication of a narrative review in the journal *Nutrients* (February 2025), with a focus on the clinical benefits and potential risks of the PLADO diet, particularly within the Cypriot population. This review summarized existing literature and served as the scientific foundation for the empirical investigation by outlining the rationale for using a plant-dominant dietary approach in the management of chronic kidney disease (CKD) (Michail and Andreou, 2025).

More specifically, a comprehensive search strategy was developed to identify relevant studies, focusing on randomized controlled trials, cohort studies, and observational studies that examined the impact of PLADO on renal outcomes. Databases such as PubMed, Scopus, and UNIC library were utilized to retrieve recent literature. Keywords included through search included “PLADO diet”, “chronic kidney disease”, “plant-based nutrition”, “low-protein diet”, “medical nutrition therapy”, and “renal nutrition”. Articles published in English within the least 10 years were prioritized. The review evaluated evidence regarding:

- Slowing CKD progression
- Preservation of renal function
- Reduction of uremic toxins
- Cardiovascular benefits
- Nutritional adequacy and risk of malnutrition
- Patient adherence and quality of life

Evidence highlighted that PLADO may offer benefits in slowing CKD progression, reducing cardiovascular risks and improving metabolic health. However, the review also reported the

challenges related to protein sufficiency, potassium management, and long-term adherence. The findings underscored the necessity for tailored meal planning, patient education, and frequent clinical monitoring to optimize PLADO's implementation in CKD management.

Emphasis was given to the potential application of PLADO in Cyprus, where dietary patterns traditionally include a Mediterranean lifestyle however there is a high intake of animal-based proteins and foods rich in sodium and phosphorus. Therefore, this review highlights the importance of adapting PLADO to focal food culture, integrating common Cypriot foods, and providing education to improve patient adherence. Thus, it also mentions the need for further research on how PLADO could be effectively incorporated into Cypriot healthcare practices and dietary guidelines.

A Plant-Dominant Low-Protein Diet in Chronic Kidney Disease Management: A Narrative Review with Considerations for Cyprus. *Nutrients*, 17(6), 970. <https://doi.org/10.3390/nu17060970>.

3.2.2. Phase 2 – Exploratory cross-sectional study; Pilot Study and Questionnaire Development

3.2.2.1 Exploratory cross-sectional study

After identifying the importance of nutrition intervention in CKD and the impact of PLADO with the disease's progression, questionnaire has been developed to assess the perception of consumers regarding dietary protein. It was an exploratory cross-sectional study which aimed to assess the baseline knowledge and perceptions regarding dietary protein types among Cypriot individuals with or without kidney failure. Thus, the questionnaire aimed to identify gaps in awareness for the two types of protein, investigate Cypriots perception on protein consumption and health risks, assessing self-reported dietary habits, and gather preliminary data to inform the development of a comprehensive assessment tool for Cypriot individuals. Therefore, findings from this initial cross-sectional study helped the refinement, expansion, and structuring of the final questionnaire used in following phases of the research.

After conducting the research questions the development and adaptation of an online questionnaire was developed. Based on literature review, preexisting theory, subject-matter expert input, and input from the target population were assessed in order the development of the survey. Online questionnaires collect information from participants responding to the study link using internet-based communication technology (e.g. email, Google Forms). After

COVID-19 pandemic there has been a growing interest among researchers for using internet-based data collection, due to the relative ease of online data collection instead of traditional face-to-face interviews (Akintunde *et al.*, 2021). Advantages of using an online survey includes the possibility of reaching a wider geographical area in a shorter timeframe, limited burden to the patient, participants are flexible to complete the questionnaire from the environment of their choice and in their own time, and the opportunity to include multimodal educational tools to improve communication with and comprehension by the patient participants (Oliveri *et al.*, 2021). Although several limitations were also reported and should be taken into consideration, such as potential lack of inclusiveness, limited representativeness of the research due to lack of physical access to web-based surveys, digital literacy levels, inability to provide immediate feedback and clarify potential elements of confusion, and lastly completing the survey remotely instead of physical research may lead to lower levels of engagement with the study (Singh, S. and Sagar, 2021). Considering the above, the present study gave the option to individuals who wanted to fill the questionnaire but had limited access to internet or had low digital literacy levels, students of the MSc Clinical Dietetics helped them completing the survey. Using self-reporting questionnaires may facilitate more accurate answers due to the anonymity they offer, whereas researcher-reported questionnaires allow the researcher to have a better understanding of how the data are collected and how answers are negotiated, however they require more training from the researchers (Ranganathan and Caduff, 2023).

The questionnaire was administered online using Google Forms and included the following domains:

1. Demographic Characteristics: Participants provided information regarding:

- Age
- Gender
- Educational level
- Occupation
- Marital Status
- Smoking Status
- Physical activity levels

2. Mediterranean Diet Adherence: Adherence to the Mediterranean dietary pattern was assessed using the Mediterranean Diet Score (Medi Diet Score). A total of 14-item

questions. Higher scores indicated greater adherence to the Mediterranean dietary pattern. The score evaluated consumption frequency of:

- Fruits and vegetables
- Whole grains
- Olive oil
- Fish
- Legumes
- Dairy products
- Red and processed meat

3. Dietary Habits and Protein Consumption: Participants reported:

- Frequency of animal protein intake
- Frequency of plant-based protein intake
- Following Dietary patterns (DASH, PLADO, lacto-ovo vegetarians etc.)

4. Anthropometric Measurements

- Weight (kg)
- Height (cm)
- Waist circumference (cm)

5. Medical History

- Presence and stage of CKD
- Medical conditions (Hypertension, Diabetes, Stroke, etc.)
- Medications

6. Knowledge Assessment

- Protein-containing and non-protein containing food groups
- Protein quantity in commonly consumed foods
- Differences between animal and plant-based foods
- Biological function of proteins
- Health effects associated with excessive animal protein intake
- Plant-based dietary sustainability and environment impact
- Dietary modifications following CKD diagnosis
- Examples of knowledge-assessment questions included:
 - Identification of food groups that do not contain protein
 - Estimation of protein content in foods such as white bread and red meat
 - Understanding the concept of protein complementation

- Classification of foods and nutrients as animal or plant protein sources
- Recognition of protein functions in the human body, including tissue repair, antibody production, oxygen transport, and hormone regulation
- Identification of potential health outcomes linked with excessive intake of animal protein, including kidney problems, elevated cholesterol, and liver complications.
- Awareness of gastrointestinal effects such as constipation associated with-low fiber dietary patterns.
- Understanding of sustainability concepts related to plant-based dietary patterns

7. A qualitative dietary recall question was also included, where participants were asked to describe a 24h-recall diet.

Educational material was embedded within the questionnaire and visible immediately before the related knowledge questions. The education material included infographic information which showed different foods on each type of protein (e.g. plant-based foods with a soy picture, lentils etc.). Definitions were also given (e.g. protein complementation, amino acids), and also tables with the carbohydrate exchange list, where participants could see how much protein, carbohydrate, fat, and kilocalories each food group has. Materials remained visible within the form structure.

Adherence to the Mediterranean dietary pattern was assessed using the Medi Diet screening tool. The questionnaire assessed:

- Olive oil consumption
- Vegetable and fruit intake
- Red meat consumption
- Intake of butter, margarine, and sugary beverages
- Wine consumption
- Legumes
- Fish and seafood
- Industrial sweets and pastries
- Nuts
- Preference for white meat or plant-based protein sources
- Consumption of traditional Mediterranean-style dishes prepared with tomato, onion, garlic and olive oil.

Each item was scored as either 0 or 1 according to predefined criteria. A score of 1 indicated adherence to the Mediterranean dietary recommendation for that item, while 0 indicated non-adherence. The total scoring system ranged from 0 to 14, with higher scores reflecting greater adherence to the Mediterranean diet. Moreover, lower consumption of red meat, processed foods, butter, sweetened beverages, and industrial pastries were also positively scored (García-Conesa *et al.*, 2020). The full 14-item Medi Diet score is in appendix 12

Knowledge score was calculated based on participants responses with the correct answer. Correct answers were scored as 1 point and incorrect answers as 0 points. Total knowledge score ranged from 0 to 11. Participants were categorized into three knowledge groups based on tertile distribution:

- Low knowledge
- Moderate knowledge
- High knowledge

The questionnaire was open to the public for 3 months, February 2021 to May 2021, and participation was anonymous and voluntary. To assess participants knowledge regarding protein, they were first provided with standardized nutrition education materials with definitions and infographic information. Eligibility criteria included Greek-speaking adults, who were able to complete the online questionnaire therefore have an internet access. Renal and non-renal participants were included in the study, with focus group being individuals with CKD. Participants were recruited through social media platforms, university mailing lists, and word to mouth. As this was an exploratory study which aimed to investigate perceptions and knowledge gap, no formal sample size calculation was performed.

Independent variables included age, gender, education level, BMI, renal status, dietary pattern whereas dependent variables were knowledge score, perception responses, and frequency of protein consumption.

Statistical analysis for this phase included descriptive statistics, Mann-Whitney U to compare two sample and test whether they have the same distribution. This was applied for gender and knowledge score, gender with BMI, food group assessment with knowledge score. Other statistical tests were Kruskal-Wallis to determine any statistically significant differences between three independent variables with ordinal variables. This test was made for assessing

knowledge score with age and education level. Linear regression analysis was also conducted to examine demographic predictors of protein related knowledge score. Significant level was set with a p value lower than 0.05.

Exploratory cross-sectional study was conducted due to lack of contextual information, and the aim is to develop hypotheses and identify important domains for further organized research. To get preliminary comprehension of Cypriots nutritional knowledge, perceptions of protein sources, and behavioural patterns this initial phase was developed. This aimed to identify information gaps and establish a framework for later tool development, as PLADO-specific data was absent in the Cypriot renal setting. Additionally, it was not subjected to formal validation process, as its primary role was exploratory. The findings of this initial phase directly influence the questionnaire's development and enhancement. Targeted questions assessing protein-dominance patterns, CKD-related dietary changes, and PLADO-specific knowledge were developed based on reported misunderstandings and behavioural confusions.

In addition, this initial phase had some limitations that should be mentioned. Firstly, the use of an online, self-administered questionnaire introduces the possibility of risk of bias as well as social desirability bias, especially when anthropometric and dietary intake frequencies were self-reported. Participants could have reported less unhealthy dietary behaviours or over report healthy habits. Secondly, educational materials were provided prior to the knowledge assessment, therefore some patients could not have engaged with the material therefore not evaluating their comprehension regarding protein knowledge. Lastly, due to the cross-sectional design, results should be interpreted as exploratory and were subsequently used to develop and further validate the questionnaire applied in later phases of the study.

3.2.2.2 Pilot study & 2nd assessment of Questionnaire

This research has chosen to use a quantitative method. A quantitative method was used, part of the study, to evaluate the awareness of Cypriot population regarding the sustainability of plant-based protein. For this part of the research a focus group was developed.

Second part of the research involved conducting a pilot study in March 2024, in collaboration with MSc students of Clinical Dietetics of the University of Nicosia. The study aimed to develop and test a questionnaire designed to assess the knowledge and attitudes of patients diagnosed with CKD and the general population regarding dietary protein sources and the impact of PLADO on their health.

The questionnaire included the following domains:

- Demographics (e.g., age, gender, occupation, education level)
- MED Diet Score (Mediterranean Diet Adherence)
- Dietary habits (animal vs. plant-based protein consumption)
- Medical history (specifically CKD)
- Nutritional knowledge and perceptions of PLADO
- Adherence to dietary guidelines
- Patient-reported outcomes related to health and kidney function

The tool was distributed electronically via Google Forms. It was piloted with 20 participants and later administered to 138 subjects between 2023–2024.

Table 3.1: Questionnaire Research Objectives, Statistical Tests and Possible Correlations.

Objective/Research Question	Questionnaire Reflection	Statistical Tests	Correlations
Objective 1: Describe the demographic, socioeconomic, anthropometric (weight, height, BMI) and lifestyle behaviors (Dietary patterns, sleep duration, exercise, protein supplementation) in Cypriot and Greek non-renal and renal adults.	(1)-(9) & (11)-(13) & (18) -(24.1) Gender, age group, ethnicity, educational level, marital status, number in the household, country and city of residence, occupation, weight, height, BMI, smoking, exercise, sleep duration	Descriptive and frequency statistics, crosstabulations	- Correlation between BMI and dietary pattern.
Objective 2: To assess consumer perceptions on the nutritional value and	(36) What is the usefulness of proteins in the	- Descriptive statistics (mean, mode,	- Correlation between understanding of

sustainability of animal and plant-based proteins in relation to kidney health.	human body based on their type? Proteins are used by the body for many functions. (37) Do you believe that long-term overconsumption of protein could cause serious effects on the body? And if "YES," which type of protein? (35) A plant-based or vegetarian diet results in less meat, fewer greenhouse gas emissions, more love for the planet's animals, less waste of water and land aimed at food for all. Considering the above, can it be considered that plant-based proteins are a sustainable alternative?	percentage of responses. - Chi-Square Test	protein types and perceived health benefits in patients with CKD. - Correlation between sustainability ratings and preference for plant-based proteins
Objective 3: To evaluate how patients with CKD vs. patients without CKD perceive	(14) Do you currently suffer from any kind of kidney disease? (Yes/No)	- Descriptive statistics (for patients with CKD vs. patients	- Correlation between protein type perception and CKD status

protein sources and the impact on kidney health.	(14.1) If yes, report the kidney disease stage	without CKD responses.) - T-test (comparing the perception of protein in patients with CKD vs. patients without CKD)	- Correlation between diet changes and perceived health improvements
Objective 4: To explore the cultural factors and dietary habits that influence the adoption of plant-based vs. animal-based proteins in Cyprus.	- How often do you consume plant-based vs. animal-based protein in your diet? - Do you consider the impact of protein type (animal vs. plant) when selecting your diet for health reasons? (Yes/No) - What factors influence your choice of protein source (e.g., cultural, health, taste)? - Are plant-based foods readily available to you? (Yes/No)	- Descriptive statistics (for food accessibility, protein type consumption) - Chi-Square Test (for Yes/No responses) - Logistic Regression (if predicting plant-based diet adoption based on cultural factors)	- Correlation between cultural factors (e.g., food accessibility) and adherence to plant-based protein diet - Correlation between health perception and dietary choices (plant vs. animal protein)
Objective 5: To understand how dietary preferences and health	- What dietary pattern do you follow (e.g.,	- Descriptive statistics (dietary patterns	- Correlation between dietary preferences

conditions (like CKD) influence protein selection.	Mediterranean, Omnivore, Vegan, etc.)? - Do you think a plant-based protein diet is beneficial for patients with CKD? (Yes/No) - Do you think an animal-based protein diet is beneficial for patients with CKD? (Yes/No)	distribution) - ANOVA (comparing responses between groups following different dietary patterns)	(Mediterranean, Vegan, etc.) and perceived health benefits in patients with CKD.
Objective 6: To assess public awareness of the relationship between dietary proteins and kidney health.	- Have you heard about the Plant Dominant Low Protein Diet (PLADO)? (Yes/No) - Would you consider trying PLADO for health reasons (if available)? (Yes/No)	- Chi-Square Test (for Yes/No responses) - Descriptive statistics (for frequency of PLADO awareness)	- Correlation between awareness of PLADO and willingness to try it for health reasons

3.2.3. Phase 3 – Questionnaire Validation

Following the pilot, the questionnaire underwent a formal validation process conducted by a multidisciplinary expert panel, including nephrologists, clinical dietitians, and public health researchers. The panel assessed:

- Content validity (relevance to renal nutrition and PLADO)
- Construct validity (alignment with theoretical frameworks)
- Linguistic clarity and ease of comprehension

According to (Saw and Ng, 2001) questionnaires are one of the most used tools for data collection in clinical research and based on the type of the questionnaire specific issues of content, construct and criterion validity should be addressed accordingly. Validation is a critical step to ensure that the questionnaire accurately and reliably captures the constructs it is designed to measure. Without validation, the tool may yield inconsistent or biased results, limiting its scientific value. Given that the questionnaire assesses both pre-existing knowledge and perception changes following educational exposure, it must demonstrate content accuracy, clarity, reliability, and construct validity (Tsang, Royse and Terkawi, 2017).

Content Validity refers to the extent to which the items in a questionnaire are representative of the entire theoretical construct the questionnaire is designed to assess (Schultz, Whitney and Zickar, 2005). A panel of experts who are familiar with the construct that the questionnaire is aimed to measure should be tasked with evaluating the content validity of the tool. Therefore, the expert panel review the tool to ensure comprehensive and accurate coverage of key themes—sustainability, nutrition, and CKD-related health impacts. If relevant dimensions are omitted or poorly framed, the tool cannot yield meaningful insights. Expert validation ensures that the items and educational content are scientifically grounded and relevant.

Clarity and readability are essential. Ambiguously phrased items can lead to misinterpretation, undermining data quality (Yaddanapudi and Yaddanapudi, 2019). As the questionnaire includes educational materials, these must also be clear, accessible, and effectively communicated to all participants. If educational content is not understood, observed shifts in perception may be misleading.

Reliability or precision of a research tool refers to the consistency of the measure. Differences in results between repeated measurements on the same individual under similar conditions or between different observers of the same individuals could indicate a lack of reliability (Ranganathan and Caduff, 2023). Reliability is assessed through internal consistency (Cronbach's alpha) to ensure that items within subscales reflect the same underlying construct. Test-retest reliability will assess whether results are stable over time, further supporting the questionnaire's robustness.

Construct validity, assessed via exploratory factor analysis (EFA), determines whether items cluster as expected under theoretical domains. This is particularly critical in a tool that

integrates an intervention component, as it must distinguish between existing knowledge and educational effects.

Criterion validity, in quantitative research, measures how well the research instrument agrees with another measured criterion or the gold standard assessment, if present. Criterion validity is usually evaluated by comparing the research tool with an existing validated indicator measured at the same (Baker, 1991). This step confirms that the questionnaire measures align with existing dietary assessment tools and health perception scales.

Constructs of the questionnaire included assessing awareness of environmental impacts of protein sources, dietary habits using the 14 items modeled on the Med Score framework as well as dietary patterns classifications (e.g. DASH, vegan, PLADO diet), examining the knowledge of protein choices and health impacts, as well as how protein roles in the body and nutrient composition. Items were generated using a systematic literature review from PubMed and the University of Nicosia Library. Search terms included: (Animal protein OR vegetarian protein OR plant-based) AND (Health populations OR Kidney patients) AND (Questionnaire OR Tool) AND (Health impact). From 84 articles, 11 used questionnaires and only two involved developments of knowledge-based tools (Gokce *et al.*, 2019) (Othman *et al.*, 2019).

It was an original questionnaire combined with already validated questionnaires such as the MedScore questionnaire. The structure of the survey aimed to fulfill all the areas of interest and constructs. It was also designed for the participants to complete it easily and within the time given in the consent information before accepting them to participate. The types of questions were used; open-ended questions, close-ended questions, multiple choice questions, and single-answer questions.

All items of the questionnaire should have internal reliability and therefore be consistent in the sense that they all should measure the same thing. Specifically, validation of the questionnaire was performed by an expert panel, a total of 10 experts. With the permission of the experts their names are presented here (Mr. Christoforos Christoforou, Mr. Demetris Papamichail, Prof Andonis Zampellas, Dr. Christoforos Giannaki, Dr. Hileti Dona, Dr. Elena Philippou, Dr. Nikoleta Ntorzi, Prof. Dimtrios Papandreou, Miss Anna Latzia, Dr. Evaggelos Latzourakis). An internal validity test (Cronbach's Alpha) was applied using SPSS24 for the results of the pilot study. After assessing the questionnaire's validation final changes were made and the final form of it was updated.

Exploratory Factor Analysis (EFA) was performed to determine whether items cluster as expected under theoretical domains. It's widely used in medical education research in the early phases of instrument development, to measure variables that cannot be assessed directly. Using EFA, the researchers investigate the results of factor loading, along with other criteria to refine the measure. Factor loadings are the correlation between the item and the factor; a factor loading of more than 0.30 usually indicates a moderate correlation between the item and the factor (Royce, 1963).

Content validity was measured by the expert panel for each item to assess relevance, clarity, and simplicity using a 5-point Likert scale. Item-level CVI (I-CVI) was calculated; $I-CVI \geq 0.78$ was considered acceptable. Scale-level CVI (S-CVI/Ave) was also computed. To adjust for chance agreement, Modified Kappa was calculated as shown below: $\kappa = (I - CVI - pc) / (1 - pc)$ where pc is the probability of chance agreement. Kappa values were interpreted as: ≥ 0.74 excellent, 0.60–0.74 good, 0.40–0.59 fair, < 0.40 poor.

Face validity was conducted among undergraduate nutrition students ($n=10$) with minimal prior knowledge of protein. Students reviewed definitions and visuals. Feedback indicated definitions were clear, but more context was needed for protein knowledge. Images and brief explanations were added accordingly.

Internal consistency was evaluated using Cronbach's alpha ($\alpha \geq 0.70$ acceptable). Item analysis included: Missing value analysis (Bennett, 2001); Critical value analysis (Goh, Stavropoulos and Adeli, 2021); Item-total correlations and coefficient alpha (Baethge, Goldbeck-Wood and Mertens, 2019); Homogeneity testing (Deng and Chan, 2017).

Criterion validity was examined by comparing MedScore-derived results with the validated Mediterranean Diet Adherence Screener (Bekar and Goktas, 2023).

Pilot testing was conducted to evaluate clarity, usability, and feasibility of the questionnaire. Ten participants (5 healthy, 5 individuals living with CKD) were recruited from nephrology clinics and community ads. Inclusion: age ≥ 18 , Greek-speaking, internet access. Exclusion: dialysis patients, transplant recipients, cognitive impairment. Average completion time: 15 minutes.

Revisions based on feedback included: clearer definitions, simplified language, added visuals, and a progress bar. Cultural examples (e.g., lentils with rice) enhanced engagement.

A larger pilot study (n=120) was then conducted via Google Forms to assess psychometric performance. Participants completed a 42-item version across eight domains. Data on demographics, health status, dietary habits, and knowledge were collected. This pilot enabled formal testing of validity and reliability prior to main study rollout.

Statistical analyses, including reliability (Cronbach's alpha), item-total correlations, and exploratory factor analysis, were performed using Python-based libraries such as `pandas`, `scipy.stats`, and `statsmodels`. Confirmatory factor analysis and model fit evaluations were performed using `sklearn` and visualized via `matplotlib` and `seaborn`.

Scoring procedures were standardized across constructs. The MedDietScore was calculated based on 14 binary (Yes/No) questions, with higher scores indicating greater adherence to the Mediterranean diet. Knowledge scores were computed as a sum of correct responses across 15 multiple-choice items, while protein perception and sustainability awareness were treated as categorical variables for analysis.

The initial tool was developed in Greek to ensure cultural appropriateness. It underwent refinement through pilot feedback and expert input, leading to the addition of CKD-specific questions, clarification of terminology, and expansion of protein knowledge items. The final version was professionally translated and back translated into English to maintain conceptual fidelity. It consists of 42 items grouped into eight domains and has demonstrated strong psychometric validity in a Cypriot context.

Table 3.2: Evolution of Questionnaire Content.

Component	Initial Greek Version	Final English Version
Title	Questionnaire for proteins & kidney diseases	Questionnaire on Protein Perception & Sustainability
Language	Greek	English (back translated)
Structure	36 core items, ungrouped	42 items, grouped into 8 domains
Key Additions	CKD stage, physical activity, protein knowledge	Supplement intake, medical history, blood biomarkers
Clarity of Instructions	Basic	Simplified and itemized

Completion Time	~15–18 minutes	~10–12 minutes

The validated questionnaire was used in subsequent phases (Michail *et al.*, 2025) .

Michail, A., Zesimos, C., Sergiou, I., Tzini, K., & Andreou, E. (2025). Development and validation of a questionnaire for the knowledge assessment and management of PLADO diet in kidney and healthy population in Cyprus. *Frontiers in Nutrition*, 12, 1619237. <https://doi.org/10.3389/fnut.2025.1619237>.

3.2.4. Phase 4 – Dietary Intervention with in Patients with CKD.

The fourth part of the study involved the inclusion of a total of 60 patients with several types of nephropathies attending private office of Dr. Eleni Andreou and the first researcher, as well as Nefrozoi Medical Center. Participants were divided into two groups (n=30 each).

Both groups were composed of patients at several stages of renal failure, providing a broad representation of renal impairment. Specifically:

- CKD Stage 3a: 20 patients
- CKD Stage 3b: 10 patients
- CKD Stage 4: 10 patients
- CKD Stage 5: 10 patients
- CKD Dialysis: 10 patients

These stages were determined based on the eGFR and clinical assessment. The inclusion of patients at different CKD stages allowed for the investigation of how the PLADO diet might impact patients at several points in the disease progression.

Inclusion criteria:

- Adults aged (>18 years)
- Diagnosis of renal failure at several stages, referred to a clinical dietitian
- Were clinically stable
- Willing to participate in the study, and to follow a structured dietary intervention

Exclusion Criteria:

- Had severe comorbidities affecting nutritional status
- Were pregnant or lactating
- Were unable to comply with dietary recommendations.

Patients undergo dialysis were included to the study to broader representation of advanced renal disease and to evaluate whether adherence to the PLADO dietary approach and nutrition education strategies could be applicable in patients receiving renal replacement therapy. Moreover, including dialysis patients allowed comparison across different stages of CKD severity and enabled assessment of dietary challenges, adherence patterns, and patient-reported outcomes in more clinically diverse renal population.

3.2.4.1 Study Groups and Randomization

In the present study, participants were allocated into either a Control Group, also known as “Usual or Standard Treatment”, receiving standard nutritional management according to the guidelines of the KDOQI Guidelines or an Intervention Group receiving a PLADO intervention.

Participants were randomly assigned to one of the two study groups:

- Intervention Group (PLADO)
- Control Group (KDOQI standard care)

Each group included 15 participants, with equal gender distribution to ensure balanced representation of males and females across groups. Baseline demographic and clinical characteristics were assessed prior to the intervention to ensure comparability between groups regarding age, sex, CKD stage, anthropometric characteristics, renal function, and renal health indicators.

Participants in both groups received structured nutrition education throughout the intervention period. Educational sessions and dietary counseling were conducted at baseline and at each trimester follow-up (months 0,3, and 6). The validated questionnaire was administered at each assessment point to evaluate dietary knowledge, adherence, and patient-reported outcomes.

3.2.4.2 Nutritional Risk Assessment

To assess the nutritional status of participants throughout the study, diagnostic criteria for protein-energy wasting (PEW), malnutrition, and sarcopenia were included using established international guidelines.

Protein-Energy Wasting (PEW)

PEW was assessed according to the criteria proposed by the International Society of Renal Nutrition and Metabolism (ISRNM). These criteria include biochemical parameters, body composition measurements, muscle mass indicators, and dietary intake assessment to identify nutritional deterioration in patients with CKD. The diagnostic criteria used in this study are summarized below.

Table 3.3: Diagnostic Criteria for Protein-Energy Wasting (PEW) in CKD Patients.

Category	Criteria for Protein-Energy Wasting (PEW)
Serum Chemistry	Serum albumin <3.8 g/100 ml (Bromocresol Green method)
	Serum prealbumin (transthyretin) <30 mg/100 ml (maintenance dialysis patients only)
	Serum cholesterol <100 mg/100 ml
Body Mass	BMI <23 kg/m ²
	Unintentional weight loss: 5% over 3 months or 10% over 6 months
	Total body fat percentage <10%
Muscle Mass	Muscle wasting: reduced muscle mass 5% over 3 months or 10% over 6 months
	Reduced mid-arm muscle circumference area (>10% reduction compared to 50th percentile reference population)
	Reduced creatinine appearance
Dietary Intake	Unintentional low dietary protein intake (DPI): <0.80 g/kg/day for at least 2 months in dialysis patients or <0.6 g/kg/day in CKD stages 2–5

	Unintentional low dietary energy intake (DEI): <25 kcal/kg/day for at least 2 months

Note: Adapted from the diagnostic criteria proposed by the International Society of Renal Nutrition and Metabolism (ISRNM) for the identification of Protein-Energy Wasting (PEW) in patients with CKD (Fouque *et al.*, 2008) . BMI: Body Mass Index; DPI: Dietary Protein Intake; DEI: Dietary Energy Intake; CKD: Chronic Kidney Disease; GFR: Glomerular Filtration Rate.

Malnutrition Assessment

Nutritional risk was assessed using the Malnutrition Universal Screening Tool (MUST), a validated screening instrument commonly used to identify adults at risk of malnutrition prior to the intervention (Oshima and Tsutsumi, 2025). The tool was applied during the examination phase as part of the nutritional assessment of renal patients.

Muscle health/body composition indicators

Muscle-related nutritional indicators were assessed using the CHARDER MA601 body composition analyzer. Muscle mass, muscle quality, and phase angle were used to monitor changes in muscle health, cellular integrity, and potential indicators of muscle wasting during the intervention. However, these parameters were not used to diagnose sarcopenia but provided supportive information regarding nutrition and functional status.

3.2.4.3 Intervention Group (PLADO)

Participants assigned to the intervention group received a 7-day cyclic plant-dominant low-protein diet (PLADO) for 6 months.

The dietary intervention was individualized based to each participant's estimated energy and protein requirements, taking into consideration:

- CKD stage
- Age
- Gender
- Body weight
- Physical activity level
- Metabolic Status
- Nutritional Needs

Energy intake was prescribed to maintain adequate nutritional status and prevent protein-energy wasting. However, on average, female participants followed meal plans providing approximately 1600 kcals/day, while male participants followed meal plans providing approximately 2000 kcals/day, although calorie intake varied individually according to patient needs.

Protein intake was prescribed according to CKD stage and current renal nutrition guidelines, ranging from approximately 0.6-0.8 g/kg/day. Thus, based on PLADO framework, approximately 50-70% of total protein intake was derived from plant-based protein sources.

Nutritional Targets of the PLADO Meal Plans

Meal plans were individualized for each participant, However, the PLADO meal plans generally followed the following dietary framework:

- Energy intake individualized according to estimated requirements, using Harris-Benedict formula.
- Protein intake: ~0.6-0.8 g/kg/day depending on CKD stage
- Approximately 50-70% of total protein derived from plant-based sources.
- Moderate fat intake primarily from unsaturated fat sources
- Carbohydrate intake adjusted to meet total energy requirements
- Sodium restriction tailored according to renal and blood pressure status, generally targeting less than 1000-2300 mg/day.
- Potassium intake adjusted individually according to serum potassium levels and CKD stage.
- Phosphorus intake controlled through limitation of processed foods, phosphate additives, and high-phosphorus animal products
- Adequate dietary fiber intake through increased consumption of plant-based foods.
- Minimal intake of added sugar, preservatives, and ultra-processed foods.

For participants diagnosed with diabetes, meal plans were further modified to include low glycemic index carbohydrate options and controlled carbohydrate distribution throughout the day to support glycemic management. Food choices emphasized whole grains, legumes, vegetables, and other fiber-rich carbohydrate sources compatible with both diabetic and renal recommendations.

Individualized meal plans were developed for each participant based on:

- Personal food preferences
- Cultural dietary habits
- Food tolerances
- Existing dietary restrictions
- CKD stage
- Presence of comorbidities such as diabetes

Particular emphasis was placed on incorporating traditional Cypriot foods to improve cultural acceptability and long-term dietary adherence.

Meal plans were developed using Dietplan7 software (Forestfield Software Ltd), which enabled individualized nutrient analysis and dietary planning. All meal plans were analyzed for:

- Energy content
- Macronutrient composition
- Dietary fiber
- Sodium
- Potassium
- Phosphorus
- Calcium
- Vitamins and minerals
- Water

Nutrient analysis ensured that the meal plans met renal-friendly nutritional targets consistent with PLADO dietary principles.

Nutritional compositions were obtained from:

- S. Yiannopoulos, M. Christodoulidou, K. Kontoghiorghes, E. Ioannou-Kakouri and P. Nicolaidou-Kanari (2013)
- Food product nutritional labels where applicable

Foods included in the meal plans were further categorized according to their primary protein source as:

- Plant-based protein
- Animal-based protein
- Mixed protein source

This categorization enabled evaluation of the plant-dominant characteristic of the intervention meal plans. The nutritional composition of the Cypriot PLADO meal plan and representative sample menus are presented in the Results section and Appendix 9.

Nutrition Education Materials

Participants in the intervention group received structured educational materials throughout the intervention period

Education materials included:

- Renal exchange lists
- MyPlate dietary guide
- Educational infographics regarding plant and animal protein sources
- Information regarding complementary proteins
- Educational leaflets categorizing foods according to phosphorus and potassium content
- Portion guidance materials
- Food-label interpretation guidance.

The educational intervention aimed to improve participants' understanding of renal nutrition and support adherence to the PLADO dietary pattern.

Monitoring During the Intervention

Dietary Adherence Monitoring

Dietary adherence was monitored regularly throughout the intervention period. Participants attended monthly follow-up sessions with the dietitians. During these sessions:

- Dietary recalls were conducted
- Food diaries were reviewed
- 24-hour dietary recalls were collected
- Nutritional counseling and behavioral support were provided

Anthropometric and Body Composition Measurements

Anthropometric and body composition measurements were performed during follow-up visiting using calibrated CHARDER body composition analyzers (models MA601 and MA801).

The following measurements were recorded:

- Body weight (kg)
- Height (cm)
- Body Mass Index (BMI)
- Body fat percentage and in kg
- Skeletal muscle mass
- Fat-free mass
- Total body water
- Intracellular water
- Extracellular water
- Visceral fat
- Phase angle
- Overall health score

Intracellular and extracellular water measurements were additionally used to calculate the edema index, which was used as an indicator of fluid balance and hydration status. The formula used (Sasmita *et al.*, 2024).

$$\text{Edema Index (EI)} = \frac{\text{Extracellular Water (ECW)}}{\text{Total Body Water (TBW)}}$$

Height was measured to the nearest 0.1 cm using a stadiometer, with participants standing barefoot in an upright position. Body weight was measured to the nearest 0.1kg with participants wearing light clothing and no shoes. The body composition analyzer automatically adjusted for light clothing by subtracting 1.0 kg from the recorded body weight.

Body composition analysis was conducted using bioelectrical impedance analysis (BIA) technology integrated within the CHARDER MA601 and MA801 analyzers. To improve measurement consistency and reliability, participants were instructed:

- To avoid food and fluid intake for at least 2 hours prior to assessment
- To remove shoes and heavy outer clothing
- To remove metallic objects, stainless steel accessories, and electronic devices prior to measurement.
- To stand still during the assessment procedure

Participants with implanted electronic medical devices, including cardiac pacemakers, were excluded from BIA body composition analysis due to safety considerations and possible device interference. For these participants, only body weight, height, and BMI measurements were recorded.

Additionally, some participants attending the Nephrozoia clinic were unable to undergo BIA assessment because body composition equipment was not available at that clinical site. In these cases, only anthropometric measurements including body weight, height, and BMI were collected.

Measurements were performed under standardized conditions where possible, including similar hydration status and measurement timing, to improve consistency across follow-up assessments.

Anthropometric and body composition measurements were collected at baseline and during follow-up assessments throughout the intervention period to evaluate changes in nutritional status, hydration status, and body composition.

Laboratory Analysis and Biomarker Monitoring

Participants were referred to the study through nephrologists within the General Healthcare System of Cyprus (GeSY). Biochemical and clinical laboratory measurements were obtained from patients' routinely scheduled nephrology follow-up assessments.

Participants typically attended nephrology appointments every 3 to 6 months depending on:

- CKD stage
- Disease progression
- Clinical condition
- Treating nephrologist recommendations

Laboratory analysis used in the study were therefore based on routinely collected clinical blood test results available during the intervention period.

The following biochemical and clinical markers were recorded where available:

Renal Function Biomarkers

- Serum Creatinine
- Estimated glomerular filtration rate (eGFR)
- Serum Urea

Nutritional and Metabolic Biomarkers

- Serum albumin
- Sodium
- Potassium
- Phosphorus
- Calcium
- Bicarbonate (HCO_3^-).

Hematological and Inflammatory Biomarkers

- Hemoglobin
- C-reactive protein (CRP)

Lipid Profile

- Total cholesterol
- Low-density lipoprotein (LDL)
- High-density lipoprotein (HDL)
- Triglycerides

All laboratory analysis were performed in certified clinical laboratories using standardized automated biochemical methods according to routine nephrology practice. Estimated glomerular filtration rate (eGFR) values were obtained directly from routine laboratory reports provided during nephrology follow-up assessments. The reported eGFR values were used as indicators of renal function and CKD progression throughout the study. eGFR measurements were generated by certified clinical laboratories using standardized automated laboratory calculations routinely applied in nephrology clinical practice. The eGFR value were additionally used for CKD staging and evaluation of renal disease progression during the intervention period.

Additional renal biomarkers, including urinary creatine measurements and urine protein-to-creatinine ratio assessment, were available for some participants during the initial assessment phase depending on nephrologist requests and routine clinical monitoring. However, these measurements were not consistently available for all participants during follow-up assessments due to variability in nephrology monitoring schedules and laboratory requests. Consequently, these urinary biomarkers were not included in the final statistical analysis to maintain consistency and comparability across all study participants.

3.2.4.4 Control Group (KDOQI Standard Care)

The control group consisted of patients receiving standard nutritional management according to the 2020 Kidney Disease Outcomes Quality Initiative (KDOQI) Clinical Practice Guidelines for Nutrition in Chronic Kidney Disease.

Participants in the control group were recruited from the first supervisor's existing patient pool and continued to receive routine nutritional care typically provided in nephrology clinical practice. Similar to the intervention group, participants received individualized nutrition counseling throughout the intervention period; however, dietary recommendation followed conventional CKD dietary management principles rather than the PLADO framework.

Nutritional therapy in the control group were individualized according to:

- CKD stage
- Age
- Gender
- Body weight
- Biochemical profile

- Comorbidities
- Nutritional requirements

Protein intake recommendations followed KDOQI guidelines for CKD management were adjusted according to disease stage and clinical status. Unlike the intervention group, no specific emphasis was placed on increasing plant-based protein intake, and participants were given flexibility regarding the source of dietary protein.

Standard nutritional counseling in the control group focused on:

- General protein restriction
- Sodium reduction
- Potassium and phosphorus management where clinically indicated
- Adequate caloric intake
- Fluid management guidance where applicable
- General healthy eating recommendations for adults with CKD

For participants diagnosed with diabetes, individualized dietary modifications included low glycemic index carbohydrate options and carbohydrate distribution guidance to support glycemic control.

As with the intervention group, educational materials were provided throughout the study and included renal exchange lists, portion guidance, food-label interpretation guidance, and information regarding foods high or low in sodium, potassium, and phosphorus.

Participants in the control group attended follow-up nutritional counselling sessions at the same frequency as the intervention group. Educational sessions and dietary assessments were conducted at baseline and during follow-up sessions throughout the intervention period.

Dietary adherence and nutritional intake were monitored using

- Dietary recalls
- Food diaries
- Follow-up dietary interviews
- Questionnaire assessments

Anthropometric measurements, body composition analysis (where available), laboratory biomarkers monitoring, and questionnaire administration were conducted using the same procedures as those applied in the intervention group.

The primary distinction between the two study groups was the emphasis on plant-dominant protein sources and PLADO-specific dietary education provided exclusively to the intervention group.

Biochemical monitoring for the control group included the same renal, metabolic, inflammatory, and lipid markers collected in the intervention group. Laboratory measurements were obtained through routine nephrology follow-up assessments within the GeSY.

Medication Recording

Information regarding participants' prescribed medications was recorded at baseline in order to document concurrent pharmacological treatment during the intervention period.

Medication data were obtained from participants' medical records and nephrology documentation where available. Recorded medication included:

- Angiotensin-converting enzyme (ACE) inhibitors
- Angiotensin receptor blockers (ARBs)
- Statins
- Diuretics
- Calcium channel blockers
- Xanthine oxidase inhibitors
- Antidiabetic medications where applicable

Participants continued their routine medical treatment throughout the study period under the supervision of their treating nephrologists. No dietary-related medication adjustments were performed by the research team during the intervention.

No major changes in medication regimens were reported during the intervention period. Medication use was documented as a potential confounding factor; however, due to the relative stability of pharmacological treatment throughout the study, medication variables were not included in the primary statistical analysis.

The clinical workflow and decision-making pathway implemented in this study are illustrated in Figure 3.3. The algorithm outlines the eligibility screening, nutritional assessment procedures, biochemical monitoring, intervention allocation, and follow-up protocol applied throughout the study period.

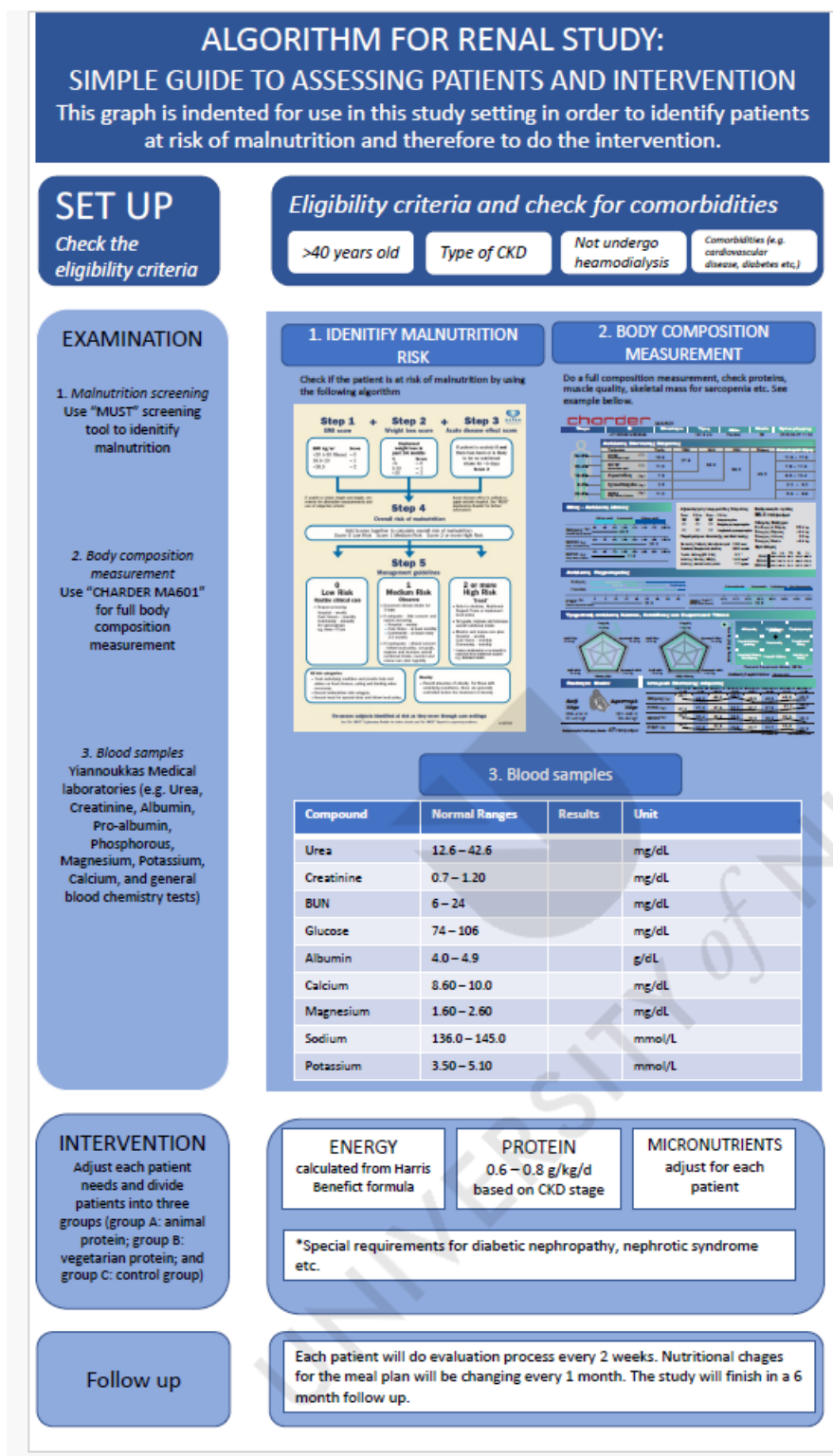


Figure 3.3: Clinical Algorithm for Patient Assessment and PLADO Intervention Implementation
Source: Created by the author

3.2.5. Phase 5: Evaluation of Diagnostic Outcomes and Nutrition Education

Data were collected at two points: baseline and the end of the intervention. Follow-up evaluations conducted throughout the intervention period. Follow-up evaluations included reassessment of anthropometric measurements, body composition parameters, dietary adherence, nutrition knowledge, and routinely collected renal biochemical markers.

Participants received structured nutrition education and individualized dietary counseling throughout the study period. Educational sessions were conducted at baseline and during follow-up visits. The educational intervention aimed to improve participants' understanding of renal nutrition, plant-based protein sources, complementary proteins, portion control, and dietary management of chronic kidney disease.

Dietary adherence was evaluated using the validated questionnaire, dietary recalls, and food diary assessments collected throughout the intervention period. The questionnaire was used to assess participants' adherence behaviors, compliance with dietary recommendations, and changes in nutrition knowledge over time.

3.2.5.1 Outcome Measures

The study outcomes were categorized into primary and secondary outcome measures to evaluate the effects of the PLADO intervention on renal function, dietary adherence, nutritional status, and patient-related outcomes throughout the intervention period.

Primary Outcomes

The primary outcomes of the study included:

- Estimated glomerular filtration rate (eGFR)
- Serum Creatinine levels
- Dietary adherence to prescribed nutritional recommendations

These outcomes were selected to evaluate renal function progression and participants' compliance with the dietary intervention.

Secondary Outcomes

Secondary outcomes included:

- Body composition parameters
- Edema index

- Phase angle
- Nutritional knowledge score
- Lipid profile parameters

Secondary outcomes were evaluated to assess the broader nutritional, metabolic, and behavioral effects of the intervention.

3.3 STATISTICAL ANALYSIS

Variables analyzed included eGFR, creatinine, dietary knowledge, and psychosocial indicators. Blood biomarkers and clinical indicators were measured to assess the impact of both the PLADO diet and the conventional KDOQI diet on kidney function and other health outcomes.

Quantitative data were analyzed using:

- Paired t-tests for pre-post comparisons
- Repeated measures ANOVA for longitudinal changes
- Regression models to identify predictors of adherence and renal improvement

1. **Repeated Measures ANOVA/ Mixed-Effects Models:** These tests were used to compare pre/post changes across multiple time points or groups. The repeated measures analysis was particularly useful for tracking changes in biomarkers (such as creatinine) over time within subjects. Mixed-effects models were used to account for intra-subject variance and were better suited than t-tests for repeated data, allowing for analysis of interactions between group (PLADO vs. KDOQI) and time (baseline vs. 6 months).
2. **ANCOVA (Analysis of Covariance):** ANCOVA was used to compare post-test values adjusted for baseline differences. This method helped isolate the treatment effect by controlling for potential confounding variables such as age, gender, and BMI.
3. **Mann-Whitney U test:** This non-parametric test was used to compare medians between two independent groups, particularly useful when biomarker data was not normally distributed or had outliers (e.g. CRP, Triglycerides, Urea).
4. **Wilcoxon Signed-Rank Test:** This test was used for within-group comparisons (pre vs. post for a single group) when the data was skewed or ordinal, providing an alternative to the paired t-test for small sample sizes or non-normal data.

5. **Chi-Square Test/ Fisher's Exact Test:** These tests were employed to compare categorical outcomes between the two groups, such as the proportion of patients who showed improvement in albumin levels (e.g. >3.5 g/dL) or normalized CRP levels (<5 mg/dL) after intervention.
6. **Logistic Regression:** Logistic regression models were used to predict binary outcomes (e.g. "CRP normalized? Yes/No") based on predictors such as group (PLADO vs. KDOQI), stage (CKD stages 3a-5), gender, and adherence.
7. **Effect Size Measures (Cohen's d, η^2 , Odds Ratios):** These measures were calculated to quantify the magnitude of the intervention effect, beyond p-values, providing insights into the clinical significance of the findings.
8. **Correlation Analysis (Pearson or Spearman):** Correlation analysis was used to explore relationships between continuous variables, such as protein intake vs. eGFR change or eGFR vs. CRP, to better understand how dietary intake might influence kidney function or other biomarkers.
9. **Binary Logistic Regression Analysis:** A multivariable binary logistic regression model was constructed to examine the association between Mediterranean diet adherence and CKD status. The dependent variable was CKD status (Question 14, recoded), coded as 1 = CKD and 0 = No CKD. Participants who responded "I don't know" were excluded from the regression analysis.

The primary independent variable was Mediterranean Diet Score (continuous). Age group was entered as a categorical variable, and gender was included as a binary variable. The reference categories were Female for gender and the youngest age group (18–25 years) for age.

Odds ratios (OR) with 95% confidence intervals (CI) were calculated using maximum likelihood estimation. Statistical significance was defined as $p < 0.05$.

Multivariable linear regression models were constructed to evaluate the effect of the PLADO intervention on renal and metabolic outcomes. All models were adjusted for age and biological sex to account for potential confounding due to demographic and physiological differences known to influence CKD progression and protein metabolism.

If repeated measures were used: A linear mixed-effects model with random intercepts was applied, adjusting for age and biological sex.

Table 3.4: Intervention Study main hypothesis and suggested statistical tests.

Hypothesis	Suggested Test
PLADO vs. KDOQI at baseline	Independent t-test or Mann-Whitney
Pre-Post within group	Paired t-test or Wilcoxon signed-rank
Pre-Post vs. between groups	Repeated Measured ANOVA or Mixed-Effects
Adjust for covariates (age, gender)	ANCOVA or Linear Regression
Categorical thresholds (e.g. CRP <5 mg/dL)	Chi-Square or Logistic Regression

3.3.1 Size and Power Calculation

Statistical power analysis was conducted using G*Power software (Faul et al., 2007) to assess the adequacy of the intervention sample size. The dietary intervention phase included 60 participants with CKD, randomized into the PLADO intervention group and the conventional KDOQI low-protein diet control group (30 participants per group).

Based on repeated-measures comparisons for primary renal outcomes (eGFR and serum creatinine), assuming a moderate effect size ($f = 0.25$), alpha level of 0.05, and power ($1-\beta$) of 0.80, the required total sample size was estimated to range between 54 and 58 participants. Therefore, the final recruited sample was considered sufficient to detect clinically meaningful intervention effects.

However, for secondary exploratory outcomes and subgroup analyses by CKD stage, statistical power may have been reduced due to smaller subgroup sample sizes. This limitation should be considered when interpreting non-significant findings.

3.4 ETHICAL CONSIDERATIONS

All procedures performed in this study involving human participants were in accordance with the ethical standards of the Cyprus National Bioethics Committee. Ethical approval was granted by the Cyprus Bioethics Committee under protocol number EEBK EII 2024.01.53. The ethical principles of the Declaration of Helsinki were followed throughout the study. All participants received verbal and written information about the study and provided informed consent. Participants were informed that the study involved body composition assessments,

dietary interventions, nutrition education sessions, and follow-up assessments at baseline, 3, 6, and 9 months.

All participants provided written informed consent. The study adhered to the ethical guidelines set forth by the Declaration of Helsinki, ensuring that participants' rights and privacy were protected throughout the study. Confidentiality was maintained by anonymizing the data, and participants were free to withdraw from the study at any time without changing their treatment care and plan.

Participants in this study being vulnerable group, due to CKD diagnosis, special care was taken to ensure the participation did not cause any physical, psychological, or nutritional burden. The dietary intervention and meal plans were designed in line with established renal nutrition guidelines and were monitored to avoid any possible complications such as malnutrition or any adverse health outcomes.

Any risks associated with participation to the study were considered minimal. Body composition assessments were non-invasive, and nutritional education sessions posed no physical risk. Potential risks related to dietary modification were closely monitored and individualized adjustments were made when necessary. Benefits included improved nutritional knowledge, better dietary adherence, improvements in body composition, renal biomarkers, and health outcomes.

Participants' confidentiality was strictly followed. Each participant was assigned a unique identification code, and all data were anonymized prior to analysis. Personal identifying information was stored separately from research data in locked cabinets accessible only to the research team.

Participants were allocated to either the control or to the intervention group based on the critical thinking of the clinical dietitian that ensured fairness and minimized bias. Both groups received individualized meal plans and the same nutrition education material, with the only difference being the total amount of animal protein per day. No special treatment was given to either group to minimize bias.

Participants were monitored throughout the 6-month intervention study for any adverse effects or concerns due to dietary intervention. Regular follow-up sessions gave the opportunity to patients to ask questions, do meal plan adjustments or report any difficulties.

As mentioned above, participants could withdraw from the study any point without providing a reason. Withdraw did not affect their ongoing treatment or relationship with the healthcare team. Data collected prior to withdraw were handled in accordance with ethical approval and participant consent.

Data will be securely stored for the duration required by institutional policy and then destroyed in a secure manner. Study findings will be disseminated through peer-reviewed publications and academic presentations. Participants were informed that no personal data would be disclosed in any result publication.

The researchers declared no conflicts of interest that could influence the conduct, outcomes, or interpretation of the study.

3.5 DESIGN CONSIDERATIONS

The study included a multiphase mixed-method approach using observational and interventional research. Observational framework was used through the validated questionnaire to assess the consumers' perception on protein knowledge which included both CKD and healthy Cypriot individuals. Interventional framework was used to assess the effectiveness of a new dietary approach, PLADO, in slowing CKD progression rate. This mixed-method approach prompts a better understanding and assessment of nutritional, clinical, and behavioral outcomes for a real emerging problem, renal failure.

The study population was consisted of adults who were diagnosed with renal failure. Clear inclusion and exclusion criteria were defined to ensure participant safety, clinical stability, and relevance to the research objectives. Eligibility criteria were applied consistently across both study groups, and all participants met the same baseline requirements prior entering the study.

The study included validated tools and metrics to promote mythological rigor. Dietary adherence and quality were assessed using established scoring systems such as MedScore, as well as the validated questionnaire to assess protein awareness and knowledge.

Study design incorporated longitudinal repeated measures and between-group comparisons, allowing for evaluation of within-participant changes over time as well as differences caused by the intervention.

A 6-month intervention period was selected to allow sufficient time for dietary behavior modification and physiological changes to occur. Reported outcomes were mainly pre and post intervention in order to assess long-term effects.

The intervention included a structured 7-day individualized meal plan developed by clinical dietitians based on renal nutrition guidelines as well as to the patients' wants and needs. Nutrition education sessions were delivered on each assessment which was handout materials in simple language, with pictures, definitions, tips, food options, and possible questions that might occurred.

3.6 PROTOCOL

The purpose of the protocol for this study is to provide a structured, transparent, and scientifically rigorous plan for **evaluating the impact of a Plant-Dominant Low Protein Diet (PLADO)** on kidney function, dietary adherence, and nutritional outcomes in Cypriot patients with chronic kidney disease (CKD).

Specifically, the protocol serves to:

1. Define Clear Research Objectives

Primary Goal: To determine whether the PLADO intervention can stabilize or improve eGFR, a key marker of kidney function.

Secondary Goals: To assess changes in clinical markers (e.g., albumin, phosphorus), adherence levels, and dietary knowledge.

2. Ensure Standardization Across Participants

By specifying inclusion/exclusion criteria, dietary education methods, and lab assessments, the protocol ensures consistency and reproducibility across all participant experiences.

3. Guide Data Collection and Intervention Delivery

It outlines:

- The duration and frequency of measurements
- The content of dietary counseling
- The use of specific tools (e.g., adherence checklists, biomarker labs)

4. Provide a Predefined Statistical Plan

- This protects against post-hoc bias by predefining:
- What tests will be used
- What constitutes a significant result
- How sample size and power will be handled

5. Ensure Ethical Compliance

It confirms that the study:

- Adheres to the Declaration of Helsinki
- Has ethical approval
- Uses informed consent and data protection principles

6. Enable Replication and Peer Review

With full transparency, this protocol allows:

- Other researchers to replicate or adapt the intervention
- Reviewers and committees to evaluate feasibility and validity

Therefore, the protocol is a blueprint that ensures the study is ethically sound, scientifically valid, and methodologically consistent — from recruitment to analysis. The complete protocol for the study is presented in Box 3.1.

Box 3.1. Study Protocol

Study Design

This study follows a prospective, longitudinal observational design, implemented over a 6-month period. The design is strengthened by a controlled dietary intervention, comparing two parallel groups: an intervention group receiving a Plant Dominant Low Protein Diet (PLADO) and a control group continuing with usual dietary practices. The study also includes cross-sectional components: a validated knowledge questionnaire pilot and main survey assessing awareness and attitudes toward dietary protein sources among Cypriot renal patients.

Protocol of the Study:

Study Objectives

Primary Objective:

To assess the effect of the PLADO intervention on estimated glomerular filtration rate (eGFR) among Cypriot renal patients with CKD.

Secondary Objectives:

1. Evaluate changes in renal biomarkers (e.g., creatinine, albumin, potassium, phosphorus).
2. Assess feasibility and adherence to PLADO.
3. Explore baseline protein knowledge and post-intervention behavior change.

Participants

Inclusion Criteria:

1. Adult Cypriot residents aged 18–75
2. Diagnosed with Chronic Kidney Disease (CKD) all stages and dialysis
3. Stable medical status
4. Able to provide informed consent

Exclusion Criteria:

1. Pregnancy/lactation
2. Severe comorbidities
3. Kidney transplant history
4. Participation in other clinical trials
5. PLADO component allergies
6. Severe cognitive impairment.

Sample Size and Power

Sample size will be determined using power analysis based on expected effect size for eGFR improvement, standard deviation of renal markers, and desired power (80%) with alpha set at 0.05.

Recruitment & Allocation

Participants will be recruited via renal clinics and allocated to:

Control: Usual diet with standard CKD care

Intervention: PLADO plan delivered by dietitians.

Allocation method: Random or purposive depending on recruitment feasibility.

Dietary Intervention (PLADO)

PLADO focuses on plant-based protein, total protein intake control (0.6–0.8 g/kg/day), and nutrient monitoring. Includes meal plans, dietitian education, and follow-up for 6 months.

Data Collection Procedures

Assessments at baseline and 6 months:

Renal Function: eGFR, Creatinine

Nutritional Status: Albumin, Hemoglobin

Electrolytes: Potassium, Phosphorus

Anthropometry: Weight, BMI

Knowledge: Questionnaire

Adherence: Monthly checklist.

Statistical Analysis

Paired t-tests or Wilcoxon for within-group change; independent t-tests or Mann–Whitney for between-group. Chi-square/Fisher's test for binary outcomes. Effect sizes: Cohen's d, Hedges' g. Stratified analysis by CKD stage.

Ethical Considerations

Approved by the University of Nicosia Ethics Committee. Informed consent obtained. Data confidentiality and participant autonomy ensured per Helsinki Declaration.

Timeline

Jan–Feb 2024: Pilot questionnaire

Mar 2024: Main analysis

Apr–Jul 2024: Intervention & Control trial

Aug–Oct 2024: Follow-up & analysis.

Data Management

All data will be encrypted, coded, and stored securely. Access limited to approved research team.

Dissemination Plan

Findings will be submitted to journals, presented at conferences, and shared with the Renal Association of Cyprus and study participants.

The clinical workflow and decision-making pathway implemented in this study are explained Step -By Step in Table 3.4 and illustrated in Figure 3.3. The algorithm outlines the eligibility screening, nutritional assessment procedures, biochemical monitoring, intervention allocation, and follow-up protocol applied throughout the study period.

Table 3.5: What it does (STEP-BY-STEP EXPLANATION)

1. SET-UP (Eligibility & Comorbidities)

Defining:

Age > 40

Type of CKD

Not undergoing haemodialysis

Comorbidities assessed

This establishes your inclusion/exclusion criteria.

It should align exactly with Section 3.3 Participants.

2. EXAMINATION PHASE

A. Malnutrition Screening

Using:

MUST screening tool

Purpose:

Identify patients at risk of malnutrition before intervention.

This strengthens your ethical and clinical rigor.

B. Body Composition Measurement

Using:

CHARDER MA601 (bioimpedance)

Purpose:

Baseline nutritional status and lean mass assessment.

Good for avoiding protein-energy wasting.

C. Blood Samples

Measured:

Urea

Creatinine

BUN

Albumin

Electrolytes

Glucose

These support:

Primary outcome and metabolic monitoring.

3.INTERVENTION PHASE

Patients allocated into:

Group A: Animal protein

Group B: Vegetarian protein

Group C: Control

Then dietary prescription includes:

Energy via Harris–Benedict

Protein 0.6–0.8 g/kg (CKD stage-based)

Micronutrient adjustment

Special cases (DKD, nephrotic syndrome)

This is the interventional protocol in applied form.

4.FOLLOW-UP

Evaluation every 2 weeks

Diet adjusted monthly

6-month duration

This is the study timeline.

CHAPTER 4 RESULTS

4.0 OVERVIEW

This section presents the findings of the study, focusing on the impact of PLADO on the renal function, dietary adherence, and clinical biomarkers of Cypriot patients with renal failure. The results are organized according to research questions and hypotheses, with an emphasis on comparing outcomes between the intervention group (PLADO) and the control group (KDOQI guidelines).

Key findings include improvements in kidney function, as indicated by changes in eGFR and serum creatinine, as well as changes in serum urea, albumin levels, and electrolyte balance. Additionally, the analysis of dietary adherence revealed notable differences between the two groups, with the PLADO group showing higher levels of compliance to the dietary regimen. The statistical analysis also evaluated secondary outcomes, such as inflammation markers (e.g. CRP) and lipid profile changes, to assess the broader effects of PLADO on CKD-related health parameters.

The following sections provide a detailed breakdown of the data collected at baseline and after six months of intervention, including tables, figures, and statistical analysis. In addition to the primary results, the validation of the questionnaire and the context of existing literature are briefly discussed to enhance the understanding of the findings.

Main findings:

- **Kidney Function:** Significant improvements in eGFR and serum creatinine were observed in the PLADO group compared to the control group, aligning with findings from previous studies discussed in Chapter 2.
- **Dietary Adherence:** The PLADO group demonstrated significantly higher adherence to dietary recommendations, as measured by self-reports and 24-hour dietary recalls, compared to the KDOQI group.

Validation of Questionnaire:

- The validation process for the dietary adherence questionnaire, conducted with an expert panel, confirmed its high reliability and content validity, ensuring its appropriateness for use in this study. Minor revisions were made based on expert

feedback to improve clarity and comprehensiveness, which were implemented prior to the full study.

4.1 EXPLORATORY CROSS-SECTIONAL QUESTIONNAIRE STUDY

4.1.1. Participants characteristics

Results of the initial cross-sectional study are presented in this subsection. A total number of 120 Cypriot adults completed the exploratory questionnaire. Table 4.1 presents the descriptive characteristics of the participants, with the total count, percentage and standard deviation. The questionnaire included 63 males (52.5%) and 57 females (47.5%). Majority of the population were males in the 31 to 45 age group (26.67%) and 10.83% being females. Equal number of both genders were observed in 18 to 25 age group, with both genders having 19 participants each within the group. Higher proportion of females were observed in the other age groups, 9.17% of females were above 61 years, 5% of females were aged from 26 to 30. Out of the total of participants, eight adults prefer not to disclose their age group.

Majority of participants were Cypriots which contributed to the 82.5% of the total population whereas 21 adults were identified with Greek ethnicity. Nicosia was the main city of residence which contributed to the total of 94 participants (*SD*: 35.34) with the second highest city being Limassol which included a total of 7 participants (*SD*: 29.43). 12.5% reported other for their current residency (*SD*: 32.43).

Education levels varied from secondary to tertiary undergraduate level and tertiary postgraduate level. Most of participants were at undergraduate level with 47.5% (*SD*: 34.23) then followed by postgraduate level which reached 45% (*SD*: 57.41), which left only 9 participants (7.5%) being on secondary education level. Marital status was also included in descriptive statistics which showed the majority of the total participants being single (70.83%), 19.17% were married, 5.83% have been divorced, and 4.17% prefer not to disclose. Moreover, majority of the sample was consisted of employed or single participants, with 60% and 30% respectively.

Table 4.1: Descriptive Statistics for exploratory cross-sectional questionnaire (n=120).

Variable	Category	n (%)

Gender	Male	63 (52.5)
	Female	57 (47.5)
Age group (years)	18–25	38 (31.7)
	26–30	8 (6.7)
	31–45	45 (37.5)
	46–60	3 (2.5)
	>61	18 (15.0)
	Prefer not to say	8 (6.7)
Ethnicity	Cypriot	99 (82.5)
	Greek	21 (17.5)
Education level	Secondary education	9 (7.5)
	Undergraduate degree	57 (47.5)
	Postgraduate degree	54 (45.0)
Marital status	Married	23 (19.2)
	Single	85 (70.8)
	Divorced	7 (5.8)
	Prefer not to say	5 (4.2)
Employment status	Employed	72 (60.0)
	Student	36 (30.0)
	Other	12 (10.0)

Descriptive statistics for this hypothesis showed that average value of total protein score in females was 1.98 whereas in males was 1.17. This suggests that females in this sample had on

average of higher value of the total protein knowledge score than males. Therefore Mann-Whitney U was conducted to compare total protein scores between the two genders. further investigate the association and find statistically significant results. Results in table 4.2, showed that the difference between females and males with respect to the dependent variable, total knowledge score, was statistically significant with $U=1154$, $n_1 = 57$, $n_2 = 63$, $p = .001$. The effect size which is also presented was $r=0.32$ which demonstrated a medium effect.

Table 4.2: Mann-Whitney analysis for gender and knowledge score.

Variable	U	z	p -value	Effect size (r)
Total knowledge score	1154.00	-3.47	.001	0.32

Note: U = Mann–Whitney U statistic; z = standardized test statistic; p -values are two-tailed. Effect size (r) was calculated using the formula $r = z/\sqrt{N}$. Statistical significance was set at $p < .05$.

Further assessment was made to compare knowledge scores with the ordinal variable age groups. A Kruskal-Wallis test, results presented in table 4.3, was used which showed a statistically significant difference in total knowledge scores across the six age groups ($\chi^2 = 11.37$; $df=5$; $p = 0.044$).

Table 4.3: Kruskal-Wallis test assessment for age and knowledge score.

Variable	χ^2	df	p -value
Total knowledge score	11.37	5	.044

Note: χ^2 = Kruskal–Wallis chi-square test statistic; df = degrees of freedom; p -values are two-tailed. Statistical significance was set at $p < .05$.

Due to Kruskal-Wallis test being statistically significant, post-hoc pairwise comparisons were conducted to determine which age group differed from each other. Post-hoc analysis, shown in table 4.4, using Tukey's test identified a significant difference in knowledge score between participants aged 26–30 years and those aged 31–45 years (mean difference = 1.53, $p = .023$, 95% CI: 0.14-2.92). No other pairwise age-group comparisons reached statistical significance. Although the overall effect of age group on knowledge score was statistically significant, post-hoc analysis indicated that differences were limited to a single age-group comparison.

Table 4.4: Tukey's Test (post-hoc) assessment.

Comparison	Mean difference	p-value	95% CI
>61 vs. 26–30	1.08	.328	-0.46 to 2.63
>61 vs. 31–45	0.44	.799	-0.57 to 1.46
>61 vs. 46–60	0.67	.956	-1.60 to 2.93
>61 vs. 18–25	0.04	1.000	-1.00 to 1.07
>61 vs. Prefer not to say	0.29	.994	-1.25 to 1.83
26–30 vs. 31–45	1.53	.023*	0.14 to 2.92
26–30 vs. 46–60	0.42	.996	-2.04 to 2.87
26–30 vs. 18–25	1.12	.204	-0.29 to 2.53
26–30 vs. Prefer not to say	1.38	.247	-0.44 to 3.19
31–45 vs. 46–60	1.11	.672	-1.05 to 3.27
31–45 vs. 18–25	0.41	.675	-0.39 to 1.21

Comparison	Mean difference	<i>p</i> -value	95% CI
31–45 vs. Prefer not to say	0.15	1.000	-1.24 to 1.55
46–60 vs. 18–25	0.70	.937	-1.47 to 2.88
46–60 vs. Prefer not to say	0.96	.868	-1.50 to 3.42
18–25 vs. Prefer not to say	0.26	.995	-1.16 to 1.67

Comparison	Mean difference	<i>p</i> -value	95% CI
>61 vs. 26–30	1.08	.328	-0.46 to 2.63
>61 vs. 31–45	0.44	.799	-0.57 to 1.46
>61 vs. 46–60	0.67	.956	-1.60 to 2.93
>61 vs. 18–25	0.04	1.000	-1.00 to 1.07
>61 vs. Prefer not to say	0.29	.994	-1.25 to 1.83
26–30 vs. 31–45	1.53	.023*	0.14 to 2.92
26–30 vs. 46–60	0.42	.996	-2.04 to 2.87
26–30 vs. 18–25	1.12	.204	-0.29 to 2.53
26–30 vs. Prefer not to say	1.38	.247	-0.44 to 3.19
31–45 vs. 46–60	1.11	.672	-1.05 to 3.27
31–45 vs. 18–25	0.41	.675	-0.39 to 1.21
31–45 vs. Prefer not to say	0.15	1.000	-1.24 to 1.55
46–60 vs. 18–25	0.70	.937	-1.47 to 2.88
46–60 vs. Prefer not to say	0.96	.868	-1.50 to 3.42
18–25 vs. Prefer not to say	0.26	.995	-1.16 to 1.67

Note: Values represent pairwise comparisons between age groups following the Kruskal–Wallis analysis. *p*-values were adjusted for multiple comparisons. CI = confidence interval. Statistical significance was set at $p < .05$. *Significant result.*

Further investigation was conducted regarding education and knowledge score, shown in tables 4.5 through table 4.7, which showed no statistically significant difference due to $\chi^2 = 2.75$, df

= 2, $p = .253$. Same results were observed for total knowledge score and changes in plant and animal-based protein with $\chi^2 = 0.4$, $df = 2$, $p = .819$ and $\chi^2 = 0.52$, $df = 3$, $p = .915$, respectively.

Table 4.5: Kruskal-Wallis assessment for education and knowledge score.

Variable	χ^2	df	p -value
Total knowledge score	2.75	2	.253

Note: χ^2 = Kruskal–Wallis chi-square test statistic; df = degrees of freedom; p -values are two-tailed. Statistical significance was set at $p < .05$.

Table 4.6: Knowledge score and plant protein change.

Variable	χ^2	df	p -value
Total knowledge score	0.40	2	.819

Note: χ^2 = Kruskal–Wallis chi-square test statistic; df = degrees of freedom; p -values are two-tailed. Statistical significance was set at $p < .05$.

Table 4.7: Knowledge score and animal protein change.

Variable	χ^2	df	p -value
Total knowledge score	0.52	3	.915

Note: χ^2 = Kruskal–Wallis chi-square test statistic; df = degrees of freedom; p -values are two-tailed. Statistical significance was set at $p < .05$.

However, a statistically significant difference has been observed in total knowledge score across categories with plant-based sustainability perception $\chi^2 = 6.28$, $df = 2$, $p = .043$, suggesting that protein related knowledge varied according to sustainability awareness.

Table 4.8: Sustainability perception and knowledge score.

Variable	χ^2	df	p -value
Total knowledge score	6.28	2	.043*

Variable	χ^2	df	p -value
Total knowledge score	6.28	2	.043*

Note: χ^2 = Kruskal–Wallis chi-square test statistic; df = degrees of freedom; p -values are two-tailed. Statistical significance was set at $p < .05$. *Significant result.*

Table 4.9 shows further descriptive statistics regarding plant-based sustainability perception has been further investigated. Out of 120 participants, 71 adults (59.2%, SD : 1.26) have considered plant-based diets to be sustainable, while 16.7% (SD : 1.20) disagreed with the argument, more than those who disagreed, 24.17% (SD : 1.33) indicated that they were unsure with the statement.

Table 4.9: Descriptive Statistics for Plant-based protein sustainability.

Response	n (%)
Yes	71 (59.2)
No	20 (16.7)
I do not know	29 (24.2)
Total	120 (100.0)

Note: Data are presented as frequency and percentage: n (%). No missing or invalid responses were recorded.

Anthropometric data were also collected and therefore analyzed. Descriptive statistics regarding BMI for both genders are shown in table 4.10, whereas table 4.11 shows the Mann-Whitney U test. The test indicated that the BMI scores for females (Median= 21.97) were significantly lower than the BMI scores in males (Median = 25.14), $U = 780.50$, $z = -5.33$, $p < 0.01$ with the effect size being large ($r = 0.49$) suggesting a substantial gender difference.

Table 4.10: Descriptive Statistics regarding BMI and gender.

Gender	n	Mean	Median	SD
Female	57	22.41	21.97	2.98
Male	63	25.83	25.14	3.78

Note: SD = standard deviation.

Table 4.11: Mann-Whitney analysis regarding BMI and gender distribution.

Variable	U	z	p -value	Effect size (r)
BMI	780.50	-5.33	< .001*	0.49

Note: U = Mann–Whitney U statistic; z = standardized test statistic; p -values are two-tailed. Effect size (r) was calculated using the formula $r = z/\sqrt{N}$. Statistical significance was set at $p < .05$. *Significant result.*

Linear regression model was used to investigate predictors, such as demographic, of protein related knowledge score, presented in table 4.12, with reference group being females, ages 18 to 25 years, at undergraduate level of education. The first significant predictor was gender, with males scoring significantly lower than females ($B = -0.59$, $p = .017$). Another predictor to assess was age with the total knowledge score, where results showed that participants aged 26 to 30 years showed higher knowledge score compared to reference group ($B = 1.03$, $p = .034$). However, no significant relations were reported for education level or for other age groups.

Table 4.12: Linear Regression (Females; 18-25 age group; Undergraduate).

Predictor	B	β	SE	t	p -value	95% CI
Constant	1.90	—	0.25	7.50	< .001*	1.40 to 2.40
Male gender	-0.59	-0.23	0.24	-2.43	.017*	-1.08 to -0.11
Age 46–60 years	0.58	0.07	0.73	0.79	.428	-0.86 to 2.02
Age 26–30 years	1.03	0.20	0.48	2.15	.034*	0.08 to 1.98
Age 31–45 years	-0.32	-0.12	0.28	-1.15	.254	-0.87 to 0.23
Age >61 years	-0.11	-0.03	0.35	-0.30	.765	-0.81 to 0.60
Age group: Prefer not to say	-0.10	-0.02	0.53	-0.19	.847	-1.16 to 0.95
Postgraduate education (Master's/PhD)	0.16	0.06	0.24	0.64	.521	-0.32 to 0.64
Secondary education	-0.55	-0.11	0.49	-1.12	.266	-1.51 to 0.42

Predictor	B	β	SE	t	p -value	95% CI
Constant	1.90	—	0.25	7.50	< .001*	1.40 to 2.40
Male gender	-0.59	-0.23	0.24	-2.43	.017*	-1.08 to -0.11
Age 46–60 years	0.58	0.07	0.73	0.79	.428	-0.86 to 2.02
Age 26–30 years	1.03	0.20	0.48	2.15	.034*	0.08 to 1.98

Age 31–45 years	- 0.32	- 0.12	0.28	- 1.15	.254	-0.87 to 0.23
Age >61 years	- 0.11	- 0.03	0.35	- 0.30	.765	-0.81 to 0.60
Age group: Prefer not to say	- 0.10	- 0.02	0.53	- 0.19	.847	-1.16 to 0.95
Postgraduate education (Master's/PhD)	0.16	0.06	0.24	0.64	.521	-0.32 to 0.64
Secondary education	- 0.55	- 0.11	0.49	- 1.12	.266	-1.51 to 0.42

Note: Reference categories were female gender, age 18–25 years, and undergraduate education. B = unstandardized regression coefficient; β = standardized regression coefficient; SE = standard error; CI = confidence interval. Statistical significance was set at $p < .05$. *Significant result.*

Following table, 4.13, shows the protein knowledge for all participants included in this study. Results showed that Cypriot participants have low protein-related knowledge. 70% of the total sample were in the low knowledge category (mean SD: 0.87 ± 0.85), while only 30% demonstrated moderate knowledge score (mean SD: 3.17 ± 0.38). Notable, there were no participants that have achieved scores to be included to the high protein-knowledge category. This was an important finding due to despite educational materials presented, protein-related knowledge was predominantly low, therefore highlight the knowledge gap in the study population.

Table 4.13: Protein Knowledge across all participants.

Knowledge category	<i>n</i>	Mean	SD	Minimum	Maximum	Mean $\pm$ SD
Moderate knowledge	36	3.17	0.38	3	4	3.17 ± 0.38
Low knowledge	84	0.87	0.85	0	2	0.87 ± 0.85

Note: *n* = number of participants; SD = standard deviation. Mean $\pm$ SD represents the average total knowledge score and its corresponding standard deviation within each knowledge category.

Another knowledge assessment was when participants were asked to indicate whether they knew which food groups do not contain protein. The total of 72 ($SD = 1.21$) participants has reported that they knew whereas 48 ($SD = 0.98$) participants did not know. Mann-Whitney was performed which showed that adults who positively answered regarding food groups and protein demonstrated significantly higher total knowledge scores compared to those who did not know (Mann–Whitney $U = 998.00$, $z = -4.03$, $p < .001$). Median knowledge score was 2.00 among those who reported protein awareness, compared with 0.00 among those who did not have protein awareness.

Table 4.14: Question regarding which food groups do not contain protein.

Response	<i>n</i>	Mean	Median	SD
Yes	72	1.94	2.00	1.21
No	48	0.98	0.00	1.19

Note: *n* = number of participants; SD = standard deviation.

Low protein-related knowledge was evident both at the scale level and at the item level, with participants lacking basic awareness of protein-containing food groups also demonstrating significantly lower knowledge scores.

Table 4.15: Mann-Whitney regarding assessing protein knowledge in food groups with total knowledge score.

Variable	<i>U</i>	<i>z</i>	<i>p</i> -value	Effect size (<i>r</i>)
Total knowledge score	998.00	-4.03	< .001*	0.37

Note: *U* = Mann–Whitney *U* statistic; *z* = standardized test statistic; *p*-values are two-tailed. Effect size (*r*) was calculated using the formula $r = z/\sqrt{N}$. Statistical significance was set at $p < .05$. *Significant result.*

4.2 QUESTIONNAIRE VALIDATION

4.2.1. Expert Panel Content Validation

The content validity of the questionnaire was evaluated by a panel of six domain experts who assessed each item using a 5-point Likert scale. Item-Level Content Validity Index (I-CVI) values were calculated for each item, and a Scale-Level CVI (S-CVI/Ave) was computed to evaluate overall agreement. The S-CVI/Ave was 0.89, indicating excellent content coverage and relevance. Notably, 68% of items achieved a perfect I-CVI score of 1.00, while 93% scored $I\text{-CVI} \geq 0.83$. These results suggest a high level of consensus among experts on the relevance of the questionnaire items. Modified Kappa values, which adjust for chance agreement, confirmed that most items fell within the 'excellent' (≥ 0.74) or 'good' (0.60–0.74) categories, further substantiating the validity of the questionnaire content. Details of the I-CVI and Modified Kappa values for each item are presented in table 4.16.

Table 4.16: Item-Level Content Validity Index (I-CVI) and Modified Kappa.

Q. No	Abbreviated Question Text	I-CVI	Modified Kappa
1	Gender	1.00	1.00

2	Age Group	1.00	1.00
3	Ethnicity	1.00	1.00
4	Education Level	1.00	1.00
5	Marital Status	1.00	1.00
25	Dietary Patterns and Definitions	1.00	1.00
30	Do you know what food groups don't have protein	1.00	1.00
36	Use of protein in the human body	0.73	0.70
37	Long-term effects of protein overconsumption	0.82	0.81
39	24h-recall	1.00	1.00
60	Protein effects on CKD – perception	0.83	0.66
61	Typical 24-hour diet recall	0.83	0.66

Note: This table presents the I-CVI and Modified Kappa values for each item in the questionnaire, rated by a panel of six domain experts. I-CVI values represent the proportion of experts rating each item as highly relevant (≥ 4 on a 5-point Likert scale). Modified Kappa adjusts for chance agreement. Items with $I-CVI \geq 0.78$ and $Kappa \geq 0.60$ were considered acceptable. Full item breakdown is available upon request or in supplementary spreadsheet format.

4.2.2. Face Validity and Pretesting

The face validity of the questionnaire was further assessed through feedback from a small pilot group of nutrition students. They highlighted issues with terminology and conceptual clarity, particularly around protein-related knowledge items. Based on their feedback, adjustments

were made, such as simplifying definitions and incorporating educational visuals. These enhancements contributed to improved accessibility and comprehensibility of the tool.

4.2.3. Pilot Study Demographics

A pilot validation study was then conducted among 120 participants to examine demographic representation and psychometric performance of the questionnaire. The sample had a balanced gender distribution (52.5% male, 47.5% female) and was predominantly composed of young adults with tertiary education. Employment status was also diverse, with 60% employed and 30% students. The full demographic profile is presented in Table 4.17.

Table 4.17: Demographic Characteristics of Pilot Sample (n = 120).

Characteristic	Distribution
Gender	63 males (52.5%), 57 females (47.5%)
Mean Age	Approximately 28 years (majority under 30)
Education Level ⁽¹⁾	92.5% with tertiary education
Employment Status ⁽²⁾	60% employed, 30% students
BMI Categories ³⁾	Self-reported, classified per WHO standards

(1)Education level was assessed by a multiple choice of primary education, lower secondary education, upper secondary education, post-secondary education.

(2)Employment status was assessed by a multiple choice of Student, Unemployed for the whole year, Unemployed for part of the year, Employee, Retired.

(3)Body Mass Index (BMI) categories was calculated based on self-reported height and weight: BMI= weight (kg) / height (m²). Then they were divided into categories Underweight (BMI <18.5 kg/m²), Normal weight (BMI 18.5-24.9 kg/m²), Overweight (BMI 25.0–29.9 kg/m²), Obese (BMI>30 kg/m²).

4.2.4. Internal Consistency and Reliability

Table 4.18 shows the Psychometric validation metrics supported the internal reliability of the questionnaire and table 4.19 represents the internal consistency of questionnaire subscales. The MedDietScore subscale, consisting of 14 binary items, showed good internal consistency with

Cronbach's alpha of 0.82. The Sustainability Beliefs subscale had an alpha of 0.76, and the CKD Protein Knowledge subscale yielded 0.71, both considered acceptable. The Food Frequency subscale demonstrated borderline acceptability at $\alpha = 0.69$, suggesting potential for refinement. Overall, these results support the use of the questionnaire in assessing consumer perceptions related to sustainability, nutrition, and protein intake in CKD.

Overall, the validation results indicate that the questionnaire is reliable and valid for the most part, especially in terms of content validity and scale with higher Cronbach's alpha values (like the MediDiet score). However, areas with lower Cronbach's alpha values, such as the FFQ scale, needed further attention to improve internal consistency and overall reliability.

Table 4.18: Questionnaire Validation Metrics from Pilot Study.

Validation Metric	Value/Range	Interpretation
I-CVI ⁽¹⁾	0.80 – 1.00	High content validity
Modified Kappa ⁽²⁾	Majority ≥ 0.74	Excellent agreement among experts
Cronbach's Alpha – MedDietScore ⁽³⁾	0.82	Good internal consistency
Cronbach's Alpha – Sustainability Beliefs ⁽³⁾	0.76	Acceptable internal consistency
Cronbach's Alpha – CKD Protein Knowledge ⁽³⁾	0.71	Acceptable internal consistency
Cronbach's Alpha – Food Frequency Scale ⁽³⁾	0.69	Borderline acceptable

(1)I-CVI (Item-Level Content Validity Index) was calculated based on expert feedback with values above 0.80 indicating high content validity.

(2)The Modified Kappa statistic was used to measure agreement among experts, with values ≥ 0.74 indicating excellent agreement.

(3)Cronbach's alpha was used to assess internal consistency, with values ≥ 0.70 deemed acceptable for reliability. Cronbach's alpha for each scale (MedDietScore, Sustainability Beliefs etc.) reflect internal consistency across the respective sets of items. The analysis was based on a sample of 120 participants.

Table 4.19: Internal Consistency of Questionnaire Subscales.

Subscale	Number of Items ⁽¹⁾	Cronbach's Alpha (α) ⁽²⁾	Interpretation
MedDietScore	14	0.82	Good
Sustainability Beliefs	6	0.76	Acceptable
CKD Protein Knowledge	8	0.71	Acceptable
Protein Source Frequency	10	0.69	Borderline Acceptable
24-hour Recall Consistency	5	0.65	Moderate

(1)Number of items represents the total number of questions assessing the subscale (e.g. MedDietScore was assessed by a 14-item questions).

(2)Cronbach's alpha (α) measures the internal consistency of a scale, indicating how closely the items in a subscale are to one another. An alpha value greater than 0.70 is generally considered acceptable, indicating good reliability. Values closer to 1 indicate stronger consistency, while values closer to 0 indicate poor reliability.

Construct validity was evaluated through exploratory factor analysis (EFA). The clarity-related variables yielded a dominant factor (MR1) explaining 35.9% of total variance. Factor loadings exceeded 0.40 for most clarity items, indicating meaningful grouping. Model fit indices such as RMSEA (0.00) and BIC (-4336.11) suggested an acceptable fit, although TLI (0.461) indicated room for improvement. These results support the presence of interpretable latent

structures within the clarity construct. Reliability testing of the clarity, relevance, and simplicity sections yielded high Cronbach's alpha scores (0.92, 0.91, and 0.89, respectively), confirming internal consistency of the validation ratings.

Table 4.20: Exploratory Factor Analysis for Clarity.

Metric ⁽¹⁾	Value
Factor Loadings (MR1)	0.268
SS Loadings	17.607
Proportion of Variance	0.359
RMSR	0.28
RMSEA	0
TLI	0.461
BIC	-4336.11
Mean Item Complexity	1

(1) **Factor Loadings (MR1)** represent the correlation between the individual items and the dominant factor, with higher values indicating stronger associations. **SS Loadings** refer to the sum of squared factor loadings, which reflects the amount of variance explained by the factor. The **Proportion of Variance** indicated the percentage of total variance accounted for by the dominant factor (MR1). **RMSR (Root Mean Square Residual)** is a measure of the model's residuals with lower values indicating a better fit. **RMSEA (Root Mean Square Error of Approximation)** evaluates the goodness of fit of the model, with values closer to 0 indicating an excellent fit. **TLI (Tucker-Lewis Index)** is a fit index where values closer to 1 indicate better model fit, though a value of 0.461 suggests improvement. **BIC (Bayesian Information Criterion)** is used for model comparison, with lower values indicating a better model fit. **Mean Item Complexity** refers to the average complexity of the items in the factor model, with a value of 1 suggesting a relatively simple model structure.

4.3 QUESTIONNAIRE RESULTS

4.3.1. Participant Characteristics

Regarding the questionnaire developed assessing the consumer's perception on sustainability, nutritional value, and the impact of animal and plant-based alternative proteins on the health of both general and renal Cypriot population, results presented below. On tables 4.21 and 4.22

descriptive statistics of the demographics of the questionnaire are shown. The first table 4.21 demonstrates the descriptive statistics (rounded to 1 decimal place). The total number of participants were 137, of whom 59.9% (n=82) and 40.1% (n=55) were females and males respectively. The average age of participants was 41.4 years (SD = 17.7), as shown in table 4.22. Number in the household was also reported with 2.9 mean participants and highest being 9 participants in total in the household (SD = 1.4)

Table 4.21: Descriptive Statistics (Rounded to 1 Decimal Place).

Statistic	Gender	Age group	Ethnicity	Education level	Marital status	Household members	Country of residence	City of residence
Count	137	137	137	137	137	137	137	137
Unique values	—	—	—	—	5	—	3	7
Most frequent category (<i>top</i>)	—	—	—	—	—	—	—	—
Frequency of top category	—	—	—	—	63	—	123	102
Mean	1.6	3.0	1.1	3.1	—	2.9	—	—
Standard deviation	0.5	1.6	0.3	0.9	—	1.4	—	—
Minimum	1.0	1.0	0.0	1.0	—	1.0	—	—
25th percentile	1.0	2.0	1.0	3.0	—	2.0	—	—

Median (50th percentile)	2.0	3.0	1.0	3.0	—	3.0	—	—
75th percentile	2.0	5.0	1.0	4.0	—	4.0	—	—
Maximum	2.0	5.0	2.0	4.0	—	9.0	—	—

Note: Results based on total number of participants (n=137). Each variable was decoded in order to perform the statistical analysis.

(1)Gender decoded: 1=Male; 2=Female; 0=Other; (2)Age group decoded: 1= 18-25 years; 2=26-30 years; 3=31-45 years; 4= 46-60 years; 5= +61 years; 0= Prefer not to say.; (3)Ethnicity decoded: 1= Cypriot; 2= Greek; 0= Other.; (4)Education Level decoded: 1= Primary (Elementary school); 2= Secondary (High School and/or High School); 3= Tertiary (University/College at undergraduate level); 4= Tertiary (University/Collegeat master's or PhD level.; (5)Marital Status decoded: 1= Married; 2= Divorced; 3= Single; 4= Widowed; 0= Prefer not to say. ; (6)Number in the household was including the participant as well.; (7)Country of Residence decoded: 1= Cyprus; 2= Greece; 3= United Kingdom; 4= United States of America; 0= Other.; (8)City of Residence decoded: 1= Nicosia; 2= Limassol; 3= Larnaca; 4= Paphos; 5= Famagusta; 6= Other in Cyprus; 7= outside Cyprus.

Thus, the second ethnicity observed were Greek, with the total percent reaching 10.9% (n=15), whereas only 1.5% (n=2) reported “Other” as their ethnicity. Regarding level of education, shown in figure 4.1, the highest percent was observed at the “Higher/postgraduate” level, which reached 40.9% (n=56) of the total population. Second highest level of education was reported in “Higher/University” level, that reached the 34.3% (n=47) of the total population, whereas “Secondary” and “Primary” level of education was equivalent to 19.0% (n=26) and 5.8% (n=8) respectively. Thus, 46.0% (n=63) reported they were married, whereas 41.6% (n=57) reported being single. 5.1% (n=7) reported being widowed, and the same percentage, 3.6%, of the total number of participants were observed in participants reporting being divorced (n=5) and five participants prefer not to say. Occupational status was also demonstrated below, reporting that 40.9% (n=56) were employed. Student and retired participants had almost similar percentages, 29.2% (n=40) and 28.5% (=39) respectively. There were only two unemployed participants, which was equivalent to 1.5% of the total participant.

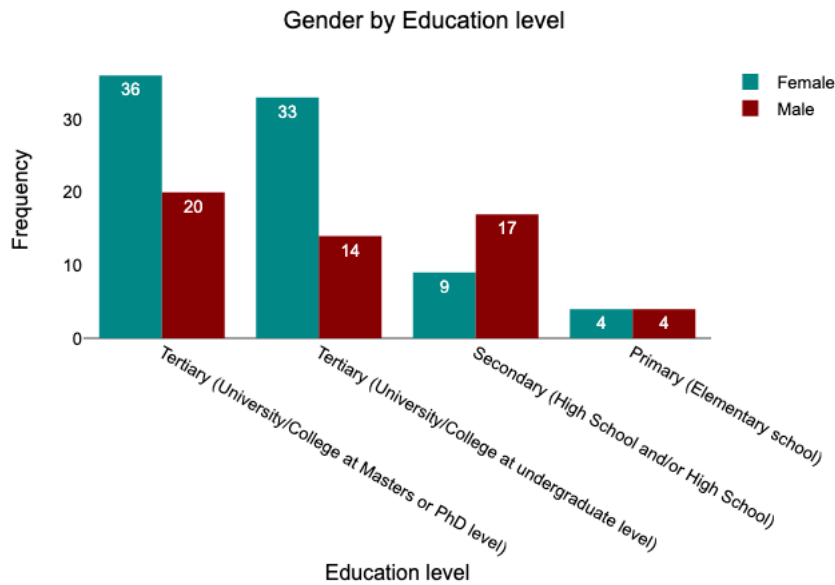


Figure 4.1: Bar chart demonstrating education level for both genders.

Thus, figure 4.2 shows the frequency of the city of residence of the participants, in a pie chart. The first common city of residence was Nicosia that reached up to 74.5% of the participants, with the second most common city of residence being Larnaca, Famagusta, Paphos and Limassol at 3.65%, 2.92% and 2.19% respectively.

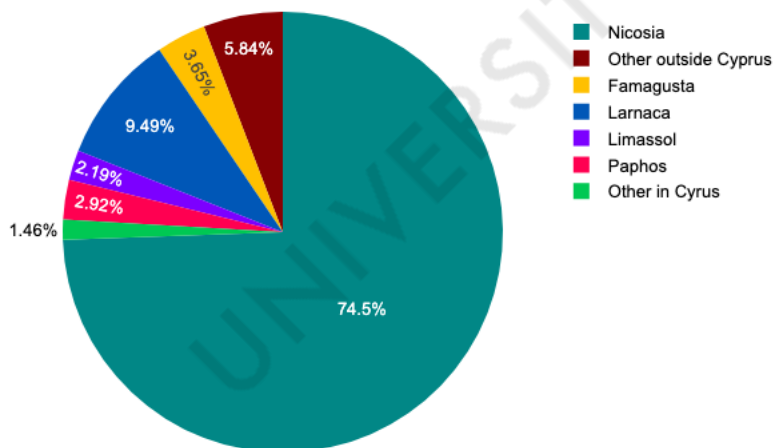


Figure 4.2: Pie chart demonstrating participants city of residence.

Moreover, the following table 4.22 shows other descriptive demographics including ethnicity, level of education, marital status, and occupation status. Most of the participants were Cypriots,

which contributed to 87.6% (n=120) of the total number of participants. Participants were represented across all age groups with the largest proportion aged 61 years and older (27.7%, n=38), followed by those in the 18 to 25 age group (24.8%, n=34), and participants in the 26 to 30 age group were consisted of 21.9% (n=30) of the total number of participants. Smaller proportions were observed in the 31 to 45 years age group reaching 10.9%, and 46 to 60 age group which was 14.6%.

The sample was mainly consisted of females (59.9%, n=82), and 40.1% of males. Regarding marital status, nearly half of participants were married (46.0%, n=63), while single individuals were 41.6% (n=57). Regarding professional status, most of the participants, 40.9%, were employed, 29.2% were retired, and 28.5% were students.

Table 4.22: Demographic Distribution of the Questionnaire.

Variable	Category	<i>n</i> (%)
Age group (years)	18–25	34 (24.8)
	26–30	30 (21.9)
	31–45	15 (10.9)
	46–60	20 (14.6)
	≥61	38 (27.7)
Gender	Male	55 (40.1)
	Female	82 (59.9)
Ethnicity	Other	2 (1.5)
	Cypriot	120 (87.6)
	Greek	15 (10.9)
Education level	Primary education	8 (5.8)
	Secondary education	26 (19.0)
	Higher education (University)	47 (34.3)

	Higher/Postgraduate education	56 (40.9)
Marital status	Divorced	5 (3.6)
	Married	63 (46.0)
	Prefer not to say	5 (3.6)
	Single	57 (41.6)
	Widowed	7 (5.1)
Professional/occupational status	Student/University	39 (28.5)
	Unemployed	2 (1.5)
	Employed	56 (40.9)
	Retired	40 (29.2)

Note: Data are presented as frequency and percentage: n (%).

In table 4.23 comparison of the relation between gender, age, and education level was conducted by chi-square (χ^2) test. The first assumption was whether there is an association between gender and age. Both gender and age group are independent variables of one another shown by $\chi^2(4, N=137) = 13.06, p = 0.01$. Gender and education level association was also found significantly linked with $\chi^2(3, N=137) = 9.77, p = 0.02$. Thus, the other two variables that were tested for independence were age group and education level, which found $\chi^2(12, N=137) = 66.86, p = 0.00$ suggesting a significant correlation between these two variables.

Table 4.23: Chi-Square Test Results for Demographics.

Variable 1	Variable 2	χ^2	df	p -value
Gender	Age group	13.06	4	.011*
Gender	Education level	9.77	3	.021*
Age group	Education level	66.86	12	< .001*

Note: χ^2 = chi-square test statistic; df = degrees of freedom; p -values are two-tailed. No cells had expected counts less than 5, indicating that chi-square assumptions were met. Statistical significance was set at $p < .05$. *Significant result.*

Moreover, table 4.24 shows the chi-square across all five age groups and both genders. Null hypothesis is rejected by $\chi^2 = 13.06$, $df = 4$ (p -value=0.01) suggesting there is a significant association between age group and gender distribution.

Table 4.24: Age Group Distribution.

Age group (years)	Male, n (%)	Female, n (%)	Total, n (%)
18–25	5 (14.7)	29 (85.3)	34 (24.8)
26–30	14 (46.7)	16 (53.3)	30 (21.9)
31–45	6 (40.0)	9 (60.0)	15 (10.9)
46–60	11 (55.0)	9 (45.0)	20 (14.6)
≥ 61	19 (50.0)	19 (50.0)	38 (27.7)
Chi-square test	$\chi^2 = 13.06$	$df = 4$	$p = .011^*$

Note: Data are presented as frequency and percentage: n (%). χ^2 = chi-square test statistic; df = degrees of freedom. Statistical significance was set at $p < .05$. *Significant result.*

Following, in table 4.25, are the anthropometric descriptive statistics of the questionnaire among the 137 participants. Mean weight was 72.1 ± 17.9 kg, with median of 69.0 kg [IQR: 59.0–82.0 kg]. Height had a mean value of 169.3 ± 9.8 cm and a median of 169 cm [IQR: 163.0–177 cm]. Mean BMI 24.9 ± 4.7 kg/m² with a median of 24.5 kg/m² (IQR: 20.9–27.4 kg/m²) indicating that, on average, participants were in the upper normal to overweight range. The average of waist circumference was at 87.3 ± 14.1 cm with a median of 86 cm (IQR: 76.0–98 cm).

Table 4.25. Anthropometric Descriptive Statistics for the Overall Sample.

Variable	n	Mean	SD	Minimum	25th percentile	Median	75th percentile	Maximum
Weight (kg)	137	72.1	17.9	42.0	59.0	69.0	82.0	140.0
Height (cm)	137	169.3	9.8	140.0	163.0	169.0	177.0	192.0
BMI (kg/m ²)	137	24.9	4.7	16.2	20.9	24.5	27.4	39.6
Waist circumference (cm)	137	87.3	14.1	61.0	76.0	86.0	98.0	123.0

Note: Data are presented as mean $\pm$ standard deviation (SD), median, and percentile distribution values. BMI = body mass index.

Thus, anthropometric measures varied by gender and age group. Table 4.26 demonstrates these results which indicates that across all age groups males were heavier and taller than females, which leads to increased BMI as well as waist circumference values.

In men, average body weight increased from 82.1 ± 10.8 kg in the 18-25 years to its highest value of 94.9 ± 15.6 kg in participants aged 46-60 years, followed by a decrease to 80.1 ± 13.3 kg in participants aged 61 years and older. Mean BMI followed a similar pattern, increasing from 25.8 ± 1.8 kg/m² in the youngest group to 30.4 ± 4.3 kg/m² in the 46 to 60 age group, then decreasing to 26.4 ± 3.5 kg/m² in the oldest group. Males with the highest waist circumference was reported in 46 to 60 age group (107.6 ± 10.3 cm).

In females, mean body weight ranged from 58.2 ± 8.5 kg in the 31-45 age group to 66.5 ± 3.8 kg in those from ages 46 to 60. BMI values were lower than males, with a mean BMI remaining within the normal range in younger participants (approximately 22 kg/m²) and increasing to 24.7 ± 2.4 kg/m² in females from 46 to 60 years and 26.5 ± 5.2 kg/m² in those from 61 years and older. Waist circumference showed moderate increase with age, reaching 85.7 ± 12.5 cm in the oldest female group.

These findings reflect a diverse sample in terms of body composition, with indications of overweight and abdominal obesity in older groups, which may warrant further nutritional assessment or intervention.

Table 4.26. Descriptive Statistics of Gender and Age Group

Gender	Age Group	Weight (kg)	Height (cm)	BMI (kg/m ²)	Waist Circ. (cm)
Male	18–25	82.1 ± 10.8	178.2 ± 8.5	25.8 ± 1.8	85.6 ± 4.7
Male	26–30	86.1 ± 22.7	181.3 ± 7.1	26.0 ± 5.6	91.0 ± 14.5
Male	31–45	89.6 ± 13.7	177.5 ± 6.3	28.4 ± 3.6	97.5 ± 8.9
Male	46–60	94.9 ± 15.6	176.5 ± 6.8	30.4 ± 4.3	107.6 ± 10.3
Male	61+	80.1 ± 13.3	173.9 ± 8.6	26.4 ± 3.5	97.3 ± 9.2

Female	18–25	60.9 ± 10.2	165.8 ± 6.1	22.1 ± 3.6	76.9 ± 11.1
Female	26–30	63.0 ± 9.9	168.4 ± 4.5	22.2 ± 3.6	79.7 ± 11.9
Female	31–45	58.2 ± 8.5	164.6 ± 3.5	21.5 ± 3.4	85.0 ± 7.2
Female	46–60	66.5 ± 3.8	164.4 ± 6.0	24.7 ± 2.4	82.4 ± 9.3
Female	61+	66.1 ± 16.7	157.2 ± 7.9	26.5 ± 5.2	85.7 ± 12.5

Regarding the anthropometric measurements of the participants are shown below. Table 4.26 presents the distribution of BMI (kg/m^2) across female and male participants. For females, the sample consists of 82 individuals (59.85% of the total sample), with a mean BMI of 23.39 kg/m^2 , suggesting that, on average, females in this group have a normal weight according to BMI classification. The median BMI for females is 22.5 kg/m^2 , indicating half of the female participants have BMI below this value and half value above it, which is consistent with the mean, demonstrating relatively symmetric distribution. Standard deviation of 4.27 and variance of 18.2 indicate moderate variability in BMI within females, meaning individual BMIs tend to vary by approximately 4.27 kg/m^2 from the mean. For males, the sample consists of 55 individuals (40.15% of the total sample, with a mean BMI of 27.26 kg/m^2 , which is classified as overweight according to standard BMI categories. The median BMI for males is 26.51 kg/m^2 , which is lower than the mean, suggesting a slight positive skew in the distribution. The standard deviation of 4.44 and variance of 19.7 reflect a similar level of variability as the female group but slightly higher, suggesting a broader spread of BMI values among males.

Moreover, another result was the distribution of “Med Score Total” across different education levels, comparing both genders. At the tertiary (university/college) level, both genders reported similar median Med Scores (8), with females having a slightly lower mean (7.78) compared to males (7.9). However, males display greater score variability (higher standard deviation of 2.49). At the undergraduate level, females again show a lower mean (7.7) compared to males (8.07), although both groups have a median of 7, and a variability is similarly moderate. In secondary (high school) education, males have a notably lower mean score (7.12) compared to females (8.67), with females having a higher median (8), and a slightly higher standard deviation (2.55 vs 2.03). At the primary (elementary) level, males score significantly higher

(mean of 9 and median of 8.5) than females (mean of 5.5 and median of 5), with males also showing greater score variability (standard deviation of 3.74).

4.3.2. Dietary Patterns and MED diet score

Adherence level and MED score were analyzed to find any statistical results. Adherence distribution is observed in table 4.27 showing the frequency and the total percentage across all participants. Majority of the population (32.1%) reported a moderate adherence distribution, with MED diet score 6-7 out of 14, while only 33 participants (24.1%) reporting a very good adherence level, MED diet score ≥ 10 out of 14. A good adherence score was from 8 to 9 out of 14 items, of which 26.3% (n=36) reported having a good adherence score. Thus, 17.5% was found in the low adherence score, who had a MED diet score lower than 5 out 14 items.

Table 4.27: Adherence Level Distribution.

Adherence Level	Frequency	Percent
Good	36	26.3%
Moderate	44	32.1%
Very Good	33	24.1%
Low	24	17.5%

The descriptive statistics, table 4.28, of Mediterranean Diet (MED) adherence score ranged from 3.0 to 14.0, with a mean score of 8.1, a standard deviation of 2.38, and a median of 8. These results suggest that while a sizable proportion of participants adhere to the Mediterranean diet at moderate to high levels, there remains a notable percentage with low adherence, highlighting the need for targeted nutritional interventions.

Table 4.28. Descriptive Statistics of MED Score.

Statistic	Value
Mean	7.75
Std Dev	2.38
Median	8.0

Min	3.0
Max	14.0

A binary logistic regression was performed to examine whether gender and age group predict high adherence to the Mediterranean diet (defined as MED score ≥ 8). The model included gender and age group as predictors. Intercept is the difference between the mean of the response variable and the product of the slope and the mean of the explanatory variable. Table 4.29 demonstrated the variables of high adherence to the Mediterranean diet including variables, coefficient, standard deviation, z-value, p-value, and 95% confidence intervals. For intercept, coefficient and z scores are negative, -0.205 and -0.272 respectively, suggesting that data point is below average mean value. 95% confidence interval was assessed for all variables. 95% CI for intercept showed that there is 95% statistical confidence that the true average (mean) number of genders with high adherence to Mediterranean diet was between -0.604 and 0.806, however p-value = 0.78, therefore not statistically significant.

The results indicated that neither gender ($p = 0.780$) nor age group ($p = 0.861$) significantly predicted high adherence to the Mediterranean diet. This suggests that within this sample, adherence levels were not strongly associated with gender or age group.

Table 4.29: Predictors of High Adherence to Mediterranean Diet.

Variable	Coefficient	Std. Error	z-value	p-value	95% CI
Intercept	-0.205	0.753	-0.272	0.786	[-1.68, 1.271]
Gender	0.101	0.36	0.28	0.78	[-0.604, 0.806]
AgeGroup	0.02	0.112	0.175	0.861	[-0.2, 0.24]

Overall, participants with good or average BMI status were more usually represented across all levels of diet adherence, while higher BMI categories were present across both lower and higher MED diet score groups. The distribution of Mediterranean diet (MED) diet score categories across BMI categories is presented in table 4.30.

Participants with poor adherence to the Mediterranean diet (MED diet score 1-6), most of them were classified as having normal BMI (n=16), whereas 8 participants were overweight and 3 were obese, with only 1 participant being underweight.

Participants with moderate adherence (MED diet score 7-9), were the largest group overall. 30 participants had a normal BMI, while only 15 were classified as overweight, and 3 classified into obese category.

Participants with good adherence (MED diet score 10-12), were distributed across normal (n=10), overweight (n=6), and obese (n=7) BMI categories. This group had the most obese participants compared to other MED diet scores. Lastly, only 2 participants had excellent adherence to the Mediterranean diet (MED diet score 13-14), both of whom had normal BMI.

Table 4.30: Cross-tabulation: Mediterranean Diet Score vs BMI.

MED SCORE \ BMI	Low Weight	Good	Overweight	Obese	Total
Poor (1–6)	1	16	8	3	28
Average (7–9)	1	30	15	3	49
Good (10–12)	0	10	6	7	23
Excellent (13–14)	0	2	0	0	2
Total	2	58	29	13	102

Several statistical methods were used to examine the relationship between Mediterranean diet adherence and BMI, such as correlation analysis, linear regression, group comparisons, and categorical association testing. However, not statistically significance effect was observed between MED score and BMI.

Pearson correlation analysis reported a weak positive association between MED score and BMI ($r = 0.15$), which was not statistically significant with a $p = 0.12$, indicating that higher diet adherence was not meaningfully associated with lower or higher BMI in this sample.

Simple linear regression analysis demonstrated a small, not-significant positive trend, with MED score showing a modest relation with BMI ($\beta = 0.27$, $p = 0.07$), presented in table 4.31.

However, these findings suggest that higher MED diet score were poorly linked with slightly higher BMI, the relationship was not statistically significant.

Table 4.31: Simple Linear Regression with MED score and BMI.

Predictor	Regression coefficient (B)	p-value
Intercept	22.5	< .001*
MedDiet score	0.27	.070

Predictor	Regression coefficient (B)	p-value
Intercept	22.5	< .001*
MedDiet score	0.27	.070

Note: B = unstandardized regression coefficient; BMI = body mass index; MedDiet = Mediterranean Diet. Statistical significance was set at $p < .05$.

Similar findings were observed when group-based analyses were conducted. One-way ANOVA reported no significant differences in BMI across Mediterranean diet adherence categories ($F = 1.75$, $p=0.16$). Thus, chi-square analysis examining the relation between BMI category and MED score category showed no statistically significant association ($\chi^2 = 10.5$, $p=0.23$).

Regarding dietary patterns across all individuals, descriptive statistics are shown in table 4.32. Based on the table, most participants have been self-identified an omnivorous (82.6%) and/or following the Mediterranean dietary pattern (81.2%). Smaller percentage reported following plant-based dietary patterns such as semi-vegetarian (10.1%), vegetarian, vegan, or PLADO diets (6.52%). Specific dietary patterns such as religious fasting, DASH, or ketogenic diets were reported less frequently, 15.94%, 9.42%, 1.45%, respectively.

Table 4.32: Descriptive statistics regarding dietary patterns.

Dietary Pattern	N	%
Lacto-vegetarians.	5	3.62
Lacto-egg-vegetarians' products and eggs	7	5.07
Dairy/Egg/Seafood Vegetarian (Pesco)	8	5.80

Egg-Vegetarians	4	2.9
Vegan	4	2.90
Frugivory	4	2.90
Natural healthy eating in its classic form	6	4.35
Omnivore	114	82.61
Semi-vegetarian	14	10.14
Religious Fasting	22	15.94
Mediterranean Diet	112	81.16
Ketogenic Diet	2	1.45
Intermittent Fasting	7	5.07
Dash Diet	13	9.42
PLADO diet	9	6.52

Note: Participants could select more than one dietary pattern; therefore, percentages do not sum to 100%.

Protein distribution across all 137 participants is presented in figure 4.3. Graph below shows that protein type consumption varied by meal type. Most often breakfast protein type was animal protein, which was consumed by 34.3% participants, accompanied by the same percentage of, 27.7%, for both vegetarian protein and mixed protein type. 14 participants did not have any breakfast. Lunch was mostly consisted of mixed protein sources (n=82, 59.9%), with lower consumption of only animal protein contributing by 27.7%, only vegetarian protein was at 9.5%, and four participants reported no intake of protein during lunch time. The most consumed protein type at dinner was a combination of protein and vegetarian protein which was consumed by 45.3% of the total population, with 38.7% focusing on animal protein sources, while vegetarian protein during dinner was only at 11.7%. Majority of participants reported no protein consumption at snacks, with 73% mentioning no consumption of snacks after dinner. Although, during snack time, mixed protein was barely consumed, with 16.8% preferring having vegetarian protein and 9.5% with animal-based protein.

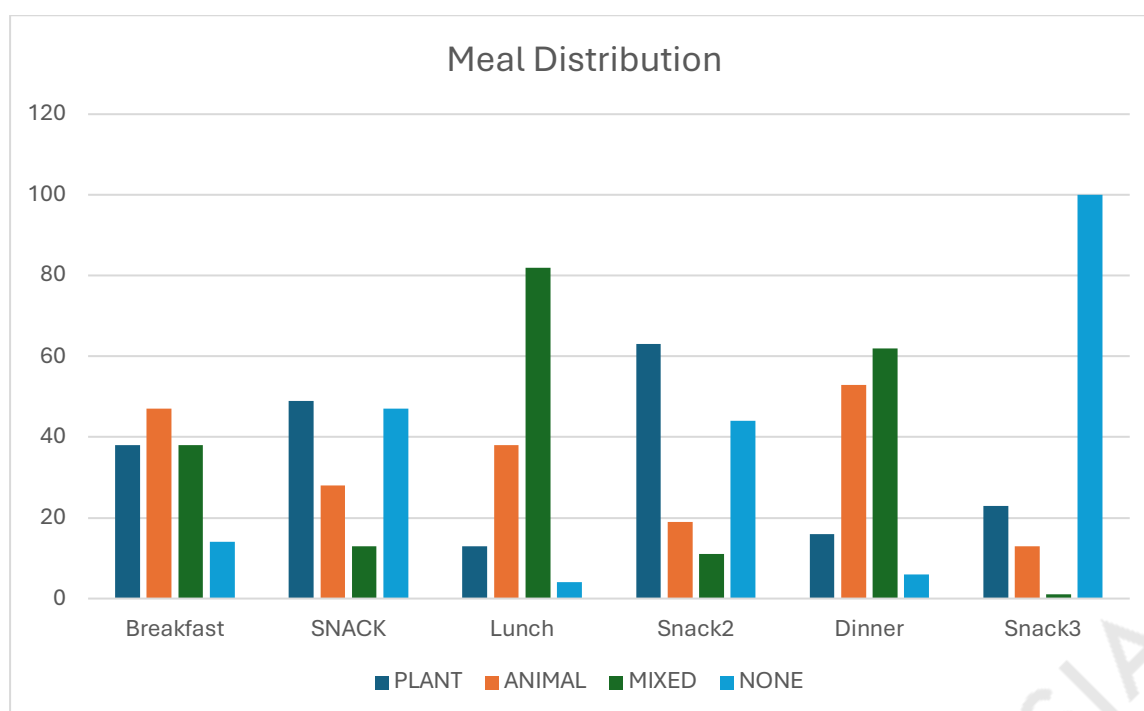


Figure 4.3: Meal distribution regarding protein type.

Mean of plant-protein consumption was compared across all knowledge categories. No statistical significance was observed between low knowledge (mean = 4.36), moderate knowledge (mean = 4.27), and high knowledge (mean = 4.31), $F(2,134) = 0.19$, $p = 0.826$. Although, when protein frequencies compared, 63% participants were classified as animal-dominant, 31% as plant-dominant, and only 6% showed balanced overall consumption patterns. This led to, performing one-way ANOVA which showed significant difference in mediterranean diet adherence across individuals who were classified in plant dominant category $F(2,134) = 7.20$, $p = 0.001$. Individuals who were in plant-dominant group had the highest mean MediDiet Score (mean = 8.84), balanced group (mean = 7.63) and animal dominant group (mean = 7.22).

Table 4.33: ANOVA- Single Factor across protein dominance.

Protein dominance group	<i>n</i>	Mean	Variance
Animal dominant	86	7.22	4.79
Plant dominant	43	8.84	5.90
Balanced	8	7.63	6.27

Note: Data are presented as mean adherence scores and variance across protein dominance groups.

Table 4.34: ANOVA across three protein dominance groups and MedDiet adherence.

Source of variation	SS	<i>df</i>	MS	<i>F</i>	<i>p</i> -value
Between groups	75.02	2	37.51	7.20	.001*

Within groups	698.54	134	5.21	—	—
Total	773.56	136	—	—	—

Note: SS = sum of squares; MS = mean square; *df* = degrees of freedom; *F* = ANOVA F-statistic. Statistical significance was set at $p < .05$. *Significant result.*

4.3.3. Kidney Disease – Related Characteristics – Question 14

Following the description of demographic and anthropometric descriptive statistics, responses to the kidney disease relation section of the questionnaire were analysed to describe participants' self-reported knowledge, perceptions, and clinical characteristics related to CKD.

Table 4.35 shows the data when participants were asked whether they suffer from any kind of CKD. More than half of the participants responded negatively (53.3%, $n=73$), while 41.6% ($n=57$) were patients with CKD, whereas only 5.1% ($n=7$) reported uncertain of the diagnosis.

Table 4.35. Descriptive Statistics of Q14-Do you currently suffer from any kind of kidney disease?

Response Code	Frequency	Percent
NO	73.0	53.3%
YES	57.0	41.6%
Do not know	7.0	5.1%

Self-reported CKD stages indicates that the study population was predominantly consisted of individuals with advanced CKD. Largest proportion of participants reported stage 5 CKD accounting for 33.3% ($n=19$) of responses. This suggest that around one third of participants were at the most advanced stage of CKD at the time of completing the questionnaire.

Earlier stages of renal failure were also reported with stage 2 and stage 3a of CKD were each reported by 14% ($n=8$ for each stage), while stages 3b and 4 reported 12.3% ($n=7$) and 8.8% ($n=5$), respectively. Stage 1 contributed to 5.3% of the participants reflecting limited representation of early-stage CKD. Moreover, 10.5% of participants reported that they had renal transplant, and only one participant reported nephrotic syndrome.

Table 4.36: CKD status among all participants.

Status	n	%

Yes	57	41.3%
No	73	52.9%
Missing	8	5.8%

Note: Total sample: N = 138. CKD Yes = 57 (41.3%), No CKD = 73 (52.9%), Missing = 8 (5.8%).

Table 4.37. Descriptive Statistics of Q14.1- Stage of Kidney Disease (for those who answered "Yes").

Stage Code	Frequency	Percent
Stage 1	3.0	5.3%
Stage 2	8.0	14.0%
Stage 3a	8.0	14.0%
Stage 3b	7.0	12.3%
Stage 4	5.0	8.8%
Stage 5 (Dialysis)	19.0	33.3%
Renal Transplant	6.0	10.5%
Nephrotic Syndrome	1.0	1.8%

Data of the questionnaire varied by both gender and age group, with a clear age-related pattern observed in both genders.

Results showed that from a total of 137 participants, 57 reported that they have CKD, whereas 73 did not suffer from renal failure, and only 7 individuals were unsure. Specifically, females who did not have CKD were 52 (63.4%), 27 (32.9%) reported having CKD, whereas 3 (3.7%) were unsure. For males, 21 (38.2%) reported no kidney disease, and 30 (54.5%) reported CKD, with 4 participants being unsure. The percentage of renal male patients is higher than females while a larger proportion of females reported no CKD compared to males.

No positive responses were observed in the younger age group (18-25) which contributed 80% to most of the population. However, positive responses regarding CKD diagnosis rose 50% in

males aged from 31 to 45 years, 72.7% in the 46 to 60 age group, and reach 89.5% in the age group from 61 years and older. This indicated a strong predominance of CKD diagnosis among older male participants.

Similar observation was seen in females, although overall positive responses were lower in younger age groups compared to males. In younger females aged from 18 to 25 and 26 to 30, most of them indicated a negative response with 89.7% and 87.5%, respectively. Positive responses increased in middle and older age groups, reaching 33.3% in females age from 31 to 45 years, 66.7% in the age group of 46-60, and 84.2% in the age group of 61 years and older.

Table 4.38. Enhanced Descriptive Statistics (Q14) for Gender and Age Group.

Gender	Age Group	Yes (n)	Yes (%)	No (n)	No (%)	Don't Know (n)	Don't Know (%)	Total
Male	18–25	0	0.0	4	80.0	1	20.0	5
Male	26–30	2	14.3	9	64.3	3	21.4	14
Male	31–45	3	50.0	3	50.0	0	0.0	6
Male	46–60	8	72.7	3	27.3	0	0.0	11
Male	61+	17	89.5	2	10.5	0	0.0	19
Female	18–25	1	3.4	26	89.7	2	6.9	29
Female	26–30	1	6.2	14	87.5	1	6.2	16
Female	31–45	3	33.3	6	66.7	0	0.0	9
Female	46–60	6	66.7	3	33.3	0	0.0	9
Female	61+	16	84.2	3	15.8	0	0.0	19

Looking closely to the participants who responded positively of CKD diagnosis, younger age groups among males showed limited representation of advanced CKD stages. More particularly, in the 26-30 age group, only two participants reported stage 1 of renal failure. Three participants in the 31-45 age group, of which two reported stage 5 and one participant

undergo renal transplant. In contrast, males in the oldest age groups, 46-60 and 61 and older showed a broader distribution across several renal failure stages. In the 46 to 60 age group, participants included stage 2, stage 3a, stage 3b, stage 4, and stage 5, while individuals aged 61 years and older most frequently reported more advanced disease, especially dialysis stage (n=7), along with stages 3b and 4, with only one participant being a renal transplant recipient.

Table 4.39: CKD Status by Age Group

Age Group	Missing n (%)	CKD Yes n (%)	No CKD n (%)	Total
≥18–25	3 (8.8%)	1 (2.9%)	30 (88.2%)	34
26–30	4 (13.3%)	3 (10.0%)	23 (76.7%)	30
31–45	0 (0.0%)	6 (40.0%)	9 (60.0%)	15
46–60	0 (0.0%)	14 (70.0%)	6 (30.0%)	20
≥61	0 (0.0%)	33 (86.8%)	5 (13.2%)	38

A total of 138 participants completed the questionnaire. Of these, 57 (41.3%) reported having chronic kidney disease, 73 (52.9%) reported not having CKD, and 8 participants (5.8%) did not provide a valid response to this question.

Stratified analyses by gender and age were conducted among participants with valid responses (n = 137).

Table 4.40: CKD status and gender distribution.

Gender	Missing n (%)	CKD Yes n (%)	No CKD n (%)	Total
Female	3 (3.7%)	27 (32.9%)	52 (63.4%)	82
Male	4 (7.3%)	30 (54.5%)	21 (38.2%)	55

A total of 137 participants provided valid responses regarding CKD status. Overall, 41.6% (n = 57) reported having CKD, while 53.3% (n = 73) reported no kidney disease. When stratified by gender, CKD prevalence was higher among males (54.5%) compared to females (32.9%). Conversely, a greater proportion of females reported not having CKD (63.4%) compared to males (38.2%). Age-stratified analysis demonstrated a clear increasing trend in CKD prevalence with advancing age. Participants aged ≥61 years exhibited the highest CKD prevalence (86.8%), followed by those aged 46–60 years (70.0%). In contrast, younger age groups (≤30 years) showed low CKD prevalence (<10%). These findings are consistent with established epidemiological evidence indicating age as a primary risk factor for CKD development.

Among females' participants, early and moderate stages of CKD were more commonly reported in younger age groups. Females from 18 to 25 and 26 to 30 years reported only stage

2, with no advanced stages reported. Three females in the 31 to 45 age group reported CKD with one was in stage 2, one underwent dialysis and one was kidney transplant recipient. Older females, age group 46 to 60, had a mixed distribution including stage 1 (n=1), stage 3a (n=2), stage 4 (n=1), dialysis (n=1), and renal transplant (n=1). Most females who had CKD diagnosis were in the 61 and older age group who reported dialysis stage (n=7), stage 3a (n=3), stage 3b (n=2), renal transplant (n=2), stage 2 (n=1), and only one participant reported nephrotic syndrome.

Table 4.41. Enhanced Descriptive Statistics for Stage of Kidney Disease by Gender and Age group.

Gender	Age Group	Stage 1	Stage 2	Stage 3a	Stage 3b	Stage 4	Stage 5/ Dialysis	Renal Transplant	Nephrotic Syndrome
Male	26–30	2	0	0	0	0	0	0	0
Male	31–45	0	0	0	0	0	2	1	0
Male	46–60	0	3	2	1	1	1	0	0
Male	61+	0	1	1	4	3	7	1	0
Female	18–25	0	1	0	0	0	0	0	0
Female	26–30	0	1	0	0	0	0	0	0
Female	31–45	0	1	0	0	0	1	1	0
Female	46–60	1	0	2	0	1	1	1	0
Female	61+	0	1	3	2	0	7	2	1

Overall, table 4.41 demonstrate a clear age-related shift towards more advanced renal failure with dialysis and renal transplant related conditions concentrated in participants in the oldest age group for both genders. Younger age groups were primarily characterized by early or moderate CKD stages, while advanced disease was uncommon bellow middle age.

4.3.4. Association between CKD, BMI, and Diet Adherence

Differences between healthy and CKD participants were further analyzed for selected continuous variables from the questionnaire and anthropometric measurements. Due to the non-normal distribution of the data, non-parametric tests were applied to assess between group differences.

Therefore, to investigate potential differences in dietary adherence and anthropometric status, MED score and BMI were compared between healthy and CKD participants. Table 4.42 shows this assessment using a non-parametric Mann-Whitney U test. Participants who reported uncertain to Question 14 were excluded in the assessment.

Table 4.42. Mann-Whitney U Test Results.

Variable	Kidney disease group	No kidney disease group	Mann–Whitney U	<i>p</i> -value
MedDiet score	Yes	No	2186.5	.618
BMI	Yes	No	2679.0	.005*

Note: MED = Mediterranean Diet; BMI = body mass index. Mann–Whitney U tests were used to compare distributions between participants with and without kidney disease. Statistical significance was set at $p < .05$.

There was no statistically significant difference in MED Score between the two groups ($U = 2186.5$, $p = 0.618$), indicating that adherence to the Mediterranean Diet did not vary by kidney disease status.

However, a statistically significant difference in BMI was observed ($U = 2679.0$, $p = 0.005$), suggesting that individuals with kidney disease had a significantly different BMI compared to those without the condition.

Moreover, the distribution of BMI categories was different between healthy and CKD participants. Most of healthy participants were into normal BMI category ($n=44$), overweight ($n=20$), and only 6 participants were obese. Renal participants with normal BMI were most of the participants within the group ($n=14$), however more renal participants were classified in the obese category ($n=7$) compared to individuals without CKD. A total of 9 patients with CKD were classified into the overweight category.

Chi-square analysis examining the relation between BMI and CKD status showed a borderline statistically significant result ($\chi^2 = 7.82$, $p=0.050$) suggesting that BMI category may be related

to the presence of CKD in this sample. Inspection of the distribution reported that patients with CKD were more likely to be in the obese category.

Table 4.43. Model: BMI ~ Kidney Disease + Gender + Age Group (Reference: Female, 18-25, no CKD).

Predictor	B	SE	<i>t</i>	<i>p</i> -value	95% CI
Intercept	22.48	0.72	31.39	< .001*	21.06 to 23.90
Kidney disease (Yes)	-0.89	1.00	-0.89	.377	-2.86 to 1.09
Male gender	2.98	0.75	3.96	< .001*	1.49 to 4.47
Age group 26–30	-0.63	1.08	-0.59	.559	-2.76 to 1.50
Age group 31–45	0.97	1.31	0.74	.460	-1.62 to 3.55
Age group 46–60	4.34	1.34	3.24	.002*	1.69 to 6.98
Age group ≥61	3.28	1.28	2.55	.012*	0.74 to 5.81

Note: B = unstandardized regression coefficient; SE = standard error; CI = confidence interval; BMI = body mass index. Reference categories were female sex, age group 18–25 years, and absence of chronic kidney disease (CKD). Statistical significance was set at $p < .05$.

This linear regression model uses dummy coding with the reference group being females aged 18–25 with no kidney disease. The intercept of 22.481 represents the average BMI for this reference group.

Males had significantly higher BMI compared to females ($\beta = 2.978$, $p < 0.001$). Kidney disease status and age group were not significant predictors of BMI in this model. While individuals with kidney disease had slightly lower BMI (-0.885 units), the result was not statistically significant ($p = 0.377$).

Table 4.44. MED Score ~ Kidney Disease + Gender + Age Group (Reference: Female, 18-25, no CKD).

Predictor	B	SE	<i>t</i>	<i>p</i> -value	95% CI
Intercept	7.79	0.44	17.62	< .001*	6.92 to 8.67
Kidney disease (Yes)	-0.24	0.74	-0.32	.747	-1.69 to 1.22
Male gender	-0.09	0.65	-0.14	.891	-1.37 to 1.19
Age group 26–30	-0.92	0.66	-1.39	.168	-2.23 to 0.39
Age group 31–45	0.38	0.80	0.47	.641	-1.21 to 1.96
Age group 46–60	0.78	0.82	0.95	.344	-0.85 to 2.41

Age group ≥ 61	0.01	0.79	0.01	.993	-1.56 to 1.57
Male gender $\times$ kidney disease	0.48	0.91	0.53	.598	-1.31 to 2.27

Note: B = unstandardized regression coefficient; SE = standard error; CI = confidence interval; Mediterranean diet score = MedDiet score. Reference categories were female sex, age group 18–25 years, and absence of chronic kidney disease (CKD). Statistical significance was set at $p < .05$.

This linear regression model examines how MED Score is influenced by kidney disease status, gender, and age group, using dummy coding. The reference group is females aged 18–25 without kidney disease.

None of the predictors were statistically significant in explaining MED Score differences. Although participants with kidney disease had slightly lower MED Scores on average ($\beta = -0.238$), the difference was not significant ($p = 0.747$). Similarly, gender and age group had no significant association with MED score.

Independent t-test sample showed no significant association between renal and healthy participants in plant-protein consumption frequency ($t(135) = -0.59$, $p = 0.557$) or animal-protein consumption frequency ($t(135) = 0.82$, $p = 0.416$).

Table 4.45: t-Test: Comparing Plant-Protein score between CKD and healthy participants.

Variable	CKD (n = 57) Mean $\pm$ SD	Healthy (n = 80) Mean $\pm$ SD	<i>t</i>	<i>df</i>	<i>p</i> - value
Plant-protein score	4.28 $\pm$ 0.86	4.35 $\pm$ 0.66	-0.59	135	.557

Note: Data are presented as mean $\pm$ standard deviation (SD). t = independent samples t -test statistic; df = degrees of freedom. Equal variances were assumed. Statistical significance was set at $p < .05$.

4.3.5. Lifestyle Descriptive Statistics

Questionnaire included questions regarding physical activity during a typical day as well as free time, which are represented in tables 4.46 and 4.47. Overall, sedentary and low-intensity activities predominated, while engagement in structured or vigorous physical activity was limited.

Across both tables, sedentary physical activity increased with age for both genders. In the intensity-based analysis, sedentary activity was the most frequently reported level in older age groups, especially among individuals aged from 61 years and older, where moderate and vigorous activity were rare. This pattern was also observed in the activity-type analysis, in

which older participants reported sedentary behaviors such as watching television or light leisure activities with the least participant in sports or gym-based exercise.

Among younger participants, especially in the 18 to 25 age group, activity patterns were more diverse. Majority reported moderate activity and participation in sports or gym-related activities, especially among females, however sedentary was still observed. Females aged 18 to 25 and 26 to 30 years, participation to sports or gym was the most frequently reported activity type.

Table 4.46. Physical Activity (during typical day Work/Home).

Gen der	Age Gro up	Sedent ary (n)	Sedent ary (%)	Light Activ ity (n)	Light Activ ity (%)	Mode rate Activi ty (n)	Mode rate Activi ty (%)	Vigor ous Activi ty (n)	Vigor ous Activi ty (%)	Tot al (n)
Male	18– 25	2	40.0%	0	0.0%	2	40.0%	1	20.0%	5
Male	26– 30	10	71.4%	2	14.3 %	2	14.3%	0	0.0%	14
Male	31– 45	3	50.0%	2	33.3 %	0	0.0%	1	16.7%	6
Male	46– 60	6	54.5%	3	27.3 %	1	9.1%	1	9.1%	11
Male	61+	14	73.7%	4	21.1 %	1	5.3%	0	0.0%	19
Fema le	18– 25	12	41.4%	13	44.8 %	1	3.4%	3	10.3%	29
Fema le	26– 30	9	56.2%	6	37.5 %	1	6.2%	0	0.0%	16
Fema le	31– 45	5	55.6%	4	44.4 %	0	0.0%	0	0.0%	9

Female	46–60	7	77.8%	1	11.1%	1	11.1%	0	0.0%	9
Female	61+	10	52.6%	6	31.6%	2	10.5%	1	5.3%	19

Middle-age groups (31 to 60 years), both genders demonstrated a transition to lower-intensity activity, with sedentary behavior and light leisure activities were dominantly increased. While some participation in sports or gym activities was observed, in middle aged males (26 to 45 years), this declined substantially with advancing age.

Table 4.47. Physical Activity (Free time).

Gender	Age group (years)	Sedentary, <i>n</i> (%)	Light leisure activity, <i>n</i> (%)	Sports/Gym, <i>n</i> (%)	Other, <i>n</i> (%)	Total (<i>n</i>)
Male	18–25	1 (20.0)	0 (0.0)	1 (20.0)	3 (60.0)	5
Male	26–30	3 (21.4)	4 (28.6)	4 (28.6)	3 (21.4)	14
Male	31–45	2 (33.3)	3 (50.0)	1 (16.7)	0 (0.0)	6
Male	46–60	4 (36.4)	3 (27.3)	2 (18.2)	2 (18.2)	11
Male	≥61	9 (47.4)	9 (47.4)	1 (5.3)	0 (0.0)	19
Female	18–25	7 (24.1)	7 (24.1)	10 (34.5)	5 (17.2)	29
Female	26–30	4 (25.0)	4 (25.0)	6 (37.5)	2 (12.5)	16
Female	31–45	3 (33.3)	5 (55.6)	1 (11.1)	0 (0.0)	9
Female	46–60	5 (55.6)	3 (33.3)	0 (0.0)	1 (11.1)	9
Female	≥61	5 (26.3)	13 (68.4)	1 (5.3)	0 (0.0)	19

Note: Data are presented as frequency and percentage: *n* (%). Percentages are calculated within each gender and age-group category.

Overall, the findings indicated that physical activity among participants was mainly characterized by sedentary or light-intensity behaviors, whereas structured structure and higher-intensity activity reported less frequent, especially in older age groups.

Moreover, when physical activity was examined in terms of both frequency and type, consistent age and gender related patterns emerged, which results are presented in tables 4.48 and 4.49. Male participants in younger age groups showed higher engagement in regular activity and structured exercise. Males aged from 18 to 25 years most frequently reported daily physical activity, which was attributed to gym or fitness class. Males in the 26 to 30 age group, exercise varied with participants reported, walking, gym-based exercise, and other activities, with

reporting activity 3-5 times per week. In the 31 to 45 age group, activity frequency had a slight decrease, with walking being the most common reported activity type, with smaller reports for gym-based exercise, yoga/pilates, and other activities.

Table 4.48. Exercise Frequency.

Gender	Age group (years)	None, <i>n</i> (%)	1–2 times/week, <i>n</i> (%)	3–5 times/week, <i>n</i> (%)	Daily, <i>n</i> (%)	Total (<i>n</i>)
Male	18–25	1 (20.0)	0 (0.0)	1 (20.0)	3 (60.0)	5
Male	26–30	4 (28.6)	4 (28.6)	4 (28.6)	2 (14.3)	14
Male	31–45	1 (16.7)	2 (33.3)	2 (33.3)	1 (16.7)	6
Male	46–60	5 (45.5)	4 (36.4)	2 (18.2)	0 (0.0)	11
Male	≥61	11 (57.9)	1 (5.3)	6 (31.6)	1 (5.3)	19
Female	18–25	7 (24.1)	9 (31.0)	9 (31.0)	4 (13.8)	29
Female	26–30	5 (31.2)	5 (31.2)	6 (37.5)	0 (0.0)	16
Female	31–45	5 (55.6)	1 (11.1)	2 (22.2)	1 (11.1)	9
Female	46–60	3 (33.3)	4 (44.4)	1 (11.1)	1 (11.1)	9
Female	≥61	11 (57.9)	3 (15.8)	3 (15.8)	2 (10.5)	19

Note: Data are presented as frequency and percentage: *n* (%). Percentages were calculated within each gender and age-group category.

In contrast, older males showed a shift toward lower-frequency activity. Males in the 46 to 60 age group as well as 61 years and older were more likely to report to no regular physical activity, with daily activity being uncommon. Thus, those who reported active exercise, walking was the most common exercise, especially in the oldest age group, where almost half

reported walking as their main type of exercise. Gym-based exercise, running, or team sports decreased evidently with age, while yoga or pilates increased as a more common activity in older males.

In females, younger women reported more engagement in regular and diverse physical activity. Younger females ages from 18 to 25 reported activity most frequently 1 to 5 times per week, with gym and fitness classes being the most common activity type, followed by yoga and/or pilates and running. Second youngest group from 26 to 30 years showed a similar pattern with an increase proportion engaging in gym-based exercise, yoga/pilates, and other activities multiple times per week.

Females in 31 to 45 years and 46 to 60 years were more likely to report no regular physical activity or activity 1 to 2 times per week with yoga/pilates, walking, and other light activities being the most common answers. Older females, 61 years and above, walking was also the most reported activity type, while structured exercises such as running was rare.

Table 4.49. Exercise Type.

Gender	Age group (years)	Walking, n (%)	Running, n (%)	Gym/Fitness classes, n (%)	Team sports, n (%)	Swimming, n (%)	Yoga/Pilates, n (%)	Other, n (%)	Total (n)
Male	18–25	1 (20.0)	0 (0.0)	4 (80.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	5
Male	26–30	5 (35.7)	1 (7.1)	4 (28.6)	1 (7.1)	0 (0.0)	1 (7.1)	2 (14.3)	14
Male	31–45	3 (50.0)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	1 (16.7)	1 (16.7)	6
Male	46–60	3 (27.3)	1 (9.1)	2 (18.2)	0 (0.0)	2 (18.2)	3 (27.3)	0 (0.0)	11
Male	≥61	9 (47.4)	1 (5.3)	2 (10.5)	0 (0.0)	0 (0.0)	7 (36.8)	0 (0.0)	19
Female	18–25	5 (17.2)	3 (10.3)	9 (31.0)	1 (3.4)	0 (0.0)	7 (24.1)	4 (13.8)	29
Female	26–30	2 (12.5)	1 (6.2)	4 (25.0)	0 (0.0)	0 (0.0)	4 (25.0)	5 (31.2)	16
Female	31–45	1 (11.1)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	4 (44.4)	3 (33.3)	9

Female	46–60	3 (33.3)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	2 (22.2)	3 (33.3)	9
Female	≥61	11 (57.9)	0 (0.0)	0 (0.0)	1 (5.3)	0 (0.0)	5 (26.3)	2 (10.5)	19

Note: Data are presented as frequency and percentage: *n* (%). Percentages were calculated within each gender and age-group category.

Another assessment was made regarding sleep-related behaviors including night-time sleep duration, daytime sleep, and daytime sleep duration. Descriptive analyses were showed in tables 4.50, 4.51, and 4.52 respectively to examine sleep patterns across both genders and all age groups.

Sleep patterns varied by age group and gender when considering night-time sleep and daytime sleep. Across both genders and most age groups, 5 to 7 hours of night-time sleep was the most reported duration. This pattern was mostly observed in younger and middle-aged participants. Results from older participants, more than 61 years, varied with majority reporting shorted (less than 5 hours) and longer (7 to 9 hours or more) sleep durations.

Table 4.50. Sleep Duration (Total hours of sleep during night).

Gender	Age Group	<5 hours (n)	<5 hours (%)	5–7 hours (n)	5–7 hours (%)	7–9 hours (n)	7–9 hours (%)	9–10 hours (n)	9–10 hours (%)	>10 hours (n)	>10 hours (%)	Total (n)
Male	18–25	1	20.0%	4	80.0%	0	0.0%	0	0.0%	0	0.0%	5
Male	26–30	1	7.1%	10	71.4%	3	21.4%	0	0.0%	0	0.0%	14
Male	31–45	0	0.0%	4	66.7%	1	16.7%	1	16.7%	0	0.0%	6
Male	46–60	2	18.2%	8	72.7%	0	0.0%	0	0.0%	1	9.1%	11

Male	61+	5	26.3 %	6	31.6 %	5	26.3 %	2	10.5 %	1	5.3 %	19
Female	18–25	5	17.2 %	20	69.0 %	4	13.8 %	0	0.0 %	0	0.0 %	29
Female	26–30	0	0.0 %	10	62.5 %	6	37.5 %	0	0.0 %	0	0.0 %	16
Female	31–45	4	44.4 %	5	55.6 %	0	0.0 %	0	0.0 %	0	0.0 %	9
Female	46–60	1	11.1 %	6	66.7 %	2	22.2 %	0	0.0 %	0	0.0 %	9
Female	61+	8	42.1 %	6	31.6 %	5	26.3 %	0	0.0 %	0	0.0 %	19

Note: Data are presented as percentage: (%). Percentages were calculated within each gender and age-group category.

Overall, 68 out of 137 participants, contributing to 49.6%, reported daytime sleep, with clear differences across age groups. In males, daytime sleep was most observed in the youngest and oldest age group. In males aged from 18 to 25 years, 80% reported some form of daytime sleep, while the oldest males 73.7% reported napping either daily, occasionally, or rarely. However, males aged from 31 to 45 years reported no daytime sleep. Similar observations were seen in the youngest and oldest age group in females. Younger females, aged 18 to 25, reported daytime sleep contributing to 55.2%, while 63.2% older females, in the age group of 61 and older, reported napping. Middle aged females were less likely to report daytime sleep.

Table 4.51. Daytime Sleep Duration.

Gender	Age Group	N o (n)	No (%)	Yes, every day (n)	Yes, every day (%)	Yes, occasionally (n)	Yes, occasionally (%)	Yes, rarely (n)	Yes, rarely (%)	Total (n)

Male	18–25	1	20.0 %	3	60.0 %	1	20.0%	0	0.0%	5
Male	26–30	10	71.4 %	3	21.4 %	1	7.1%	0	0.0%	14
Male	31–45	6	100.0 %	0	0.0%	0	0.0%	0	0.0%	6
Male	46–60	6	54.5 %	3	27.3 %	1	9.1%	1	9.1%	11
Male	61+	5	26.3 %	7	36.8 %	2	10.5%	5	26.3 %	19
Female	18–25	13	44.8 %	12	41.4 %	4	13.8%	0	0.0%	29
Female	26–30	9	56.2 %	6	37.5 %	0	0.0%	1	6.2%	16
Female	31–45	6	66.7 %	1	11.1 %	1	11.1%	1	11.1 %	9
Female	46–60	6	66.7 %	1	11.1 %	1	11.1%	1	11.1 %	9
Female	61+	7	36.8 %	11	57.9 %	0	0.0%	1	5.3%	19

Note: Data are presented as frequency and percentage: *n* (%). Percentages were calculated within each gender and age-group category.

Among participants who reported any daytime sleep, the duration of naps was different for age group and gender. In the age group 18 to 25, males results showed a similar distribution across categories, with short (less than 1 hour), moderate (from 1 to 2 hours), and longer (more than 3 hours) sleep each reported by 1 to 2 participants. Males in the age group 31 to 45 years who reported daytime sleep (*n*=6) reported sleep more than 3 hours. Among older males (61 years

and older) who sleep during daytime, most reported moderate sleep durations with only 42.1% reporting 2 to 3 hours, 31.6% reporting 1 to 2 hours.

Female participants, longer daytime sleep duration were more common with 44.8% in females aged 18 to 25 years reported daytime sleep more than 3 hours. Middle-aged females also reported longer daytime sleep, whereas older females (61 years and older) sleep duration varied with 9 individuals (47.4%) reporting 1 to 2 hours with only 36.8% participants reporting daytime sleep duration more than 3 hours.

Table 4.52. Daytime Sleep hours (those who answered "Yes" if they slept during daytime)

Gende r	Age Grou p	<1 hou r (n)	<1 hour (%)	1–2 hour s (n)	1–2 hours (%)	2–3 hour s (n)	2–3 hours (%)	>3 hour s (n)	>3 hours (%)	Tota l (n)
Male	18–25	1	20.0 %	2	40.0 %	1	20.0 %	1	20.0%	5
Male	26–30	2	14.3 %	1	7.1%	1	7.1%	10	71.4%	14
Male	31–45	0	0.0%	0	0.0%	0	0.0%	6	100.0 %	6
Male	46–60	1	9.1%	3	27.3 %	1	9.1%	6	54.5%	11
Male	61+	0	0.0%	6	31.6 %	8	42.1 %	5	26.3%	19
Female	18–25	4	13.8 %	8	27.6 %	4	13.8 %	13	44.8%	29
Female	26–30	2	12.5 %	5	31.2 %	0	0.0%	9	56.2%	16
Female	31–45	1	11.1 %	2	22.2 %	0	0.0%	6	66.7%	9

Female	46–60	1	11.1 %	2	22.2 %	0	0.0%	6	66.7%	9
Female	61+	3	15.8 %	9	47.4 %	0	0.0%	7	36.8%	19

Note: Data are presented as frequency and percentage: n (%). Percentages were calculated within each gender and age-group category.

Spearman correlation coefficients were calculated to assess the relationships between physical activity level on a typical day (Q19), Body Mass Index (BMI), and Mediterranean Diet Score (MED Score).

Table 4.53. Spearman Correlation Results - Q19, BMI, and MED Score.

Variable 1	Variable 2	Spearman's ρ	p -value
Physical activity level on a typical day	BMI	0.048	.579
Physical activity level on a typical day	MedDiet score	-0.007	.936
BMI	MedDiet score	0.027	.755

Variable 1	Variable 2	Spearman's ρ	p -value
Physical activity level on a typical day	BMI	0.048	.579
Physical activity level on a typical day	MedDiet score	-0.007	.936
BMI	MedDiet score	0.027	.755

Note: Spearman's ρ = Spearman rank correlation coefficient; BMI = body mass index; MedDiet = Mediterranean Diet score. p -values are two-tailed. Statistical significance was set at $p < .05$.

The results indicated no statistically significant correlations among these variables. Specifically, physical activity (Q19) was not significantly associated with either BMI ($\rho = 0.048$, $p = 0.579$) or MED Score ($\rho = -0.007$, $p = 0.936$). Additionally, there was no meaningful relationship between BMI and MED Score ($\rho = 0.027$, $p = 0.755$).

These findings suggest that within this sample, general physical activity level was not closely related to dietary adherence or body mass index.

4.3.6. Nutrition knowledge and Behavior.

Further examination was conducted to explore relations between nutrition knowledge, demographic factors, dietary behavior, and adherence. These analyses aimed to identify predictors of protein-related knowledge, investigate whether knowledge was linked with possible changes in protein intake in patients with CKD and assess the effect of knowledge and BMI to Mediterranean diet adherence.

Paired t-test samples comparing plant and animal protein consumption frequencies is presented in table 4.54. Mean animal protein frequency scores (mean= 4.07, sd = 0.87) were significantly lower than plant protein frequency consumption (mean =4.32, sd= 0.75). Higher consumption of animal-based protein $t(136) = 2.87, p < 0.005$.

Table 4.54: Paired t-test comparing plant and animal protein consumption frequencies.

Variable	Mean $\pm$ SD	<i>t</i>	<i>df</i>	<i>p</i> -value
Plant protein score	4.32 $\pm$ 0.75			
Animal protein score	4.07 $\pm$ 0.87	2.87	136	.005*

Note: Data are presented as mean $\pm$ standard deviation (SD). *t* = paired samples *t*-test statistic; *df* = degrees of freedom. Statistical significance was set at $p < .05$. *Significant result*.

Based on the above results, correlation between the two types of consumption scores and MediDiet score was conducted. Adherence to the Mediterranean diet was significantly correlated with plant protein frequency ($r = -0.28, p < 0.01$), suggesting that higher adherence was linked to more frequent consumption of plant-based sources. Although, no significant association were observed between adherence to Mediterranean diet and animal protein frequency ($r=0.07, p = 0.19$).

One-way ANOVA was conducted in order to compare Mediterranean diet adherence for all knowledge categories. Although no statistically significant difference was observed between low knowledge (mean= 7.72), moderate knowledge (mean=7.62), and high knowledge (mean = 8.70), $F(2,134) = 0.88, p = 0.42$.

Table 4.55: One-way ANOVA for Mediterranean diet and knowledge categories.

Source of variation	SS	<i>df</i>	MS	<i>F</i>	<i>p</i> -value
Between groups	10.04	2	5.02	0.88	.420
Within groups	763.53	134	5.70	—	—
Total	773.56	136	—	—	—

Note: SS = sum of squares; MS = mean square; df = degrees of freedom; F = ANOVA F-statistic. Statistical significance was set at $p < .05$. No statistically significant differences were observed between knowledge categories.

Table 4.56: Correlation between protein type consumption and Med Score.

	Plant_protein_score	Animal_protein_score	MED SCORE TOTAL
Plant_protein_score	1.00		
Animal_protein_score	0.19	1.00	
MED SCORE TOTAL	-0.28	0.07	1.00

Note: Values represent correlation coefficients between dietary protein consumption patterns and Mediterranean diet adherence scores.

Linear regression analysis reported that education level and age group were significant predictors of protein knowledge score, presented in table 4.57. Higher education was positively associated with knowledge score ($B = 1.139$, $p < 0.01$), whereas age group was negatively linked with knowledge score ($B = -0.67$, $p < 0.01$), indicating that lower knowledge levels in older participants.

Table 4.57: Linear Regression predicting protein knowledge score from Education and Age group.

Predictor	B	SE	p
Intercept	4.05	1.70	$p < .05$
Education	1.39	0.38	$**p < .01$
Age Group	-0.67	0.22	$**p < .01$

Note: B = unstandardized regression coefficient; SE = standard error. Statistical significance was set at $p < .05$.

$**p < .01$

The model showed a moderate proportion of variance in protein knowledge ($R^2 = 0.29$, adjusted $R^2 = 0.28$), resulting to education and age combined to account 29% of the variability in knowledge scores.

Moreover, protein knowledge score and BMI were assessed regarding predictors of Mediterranean diet adherence. Results reported that neither showed significantly associated with adherence. Knowledge score ($B = 0.01$, $p = \text{n.s.}$) and BMI ($B = 0.03$, $p = \text{n.s.}$), with both predictors failing to predict adherence status.

When analysis was made to investigate any changes in protein intake in renal participants, showed in table 4.58, protein knowledge score showed a positive borderline link with reported dietary change ($B = 1.04$, $p < 0.10$). Model demonstrated a relatively high pseudo R^2 value (0.35), which may suggest that knowledge has a significant impact in explaining dietary behavior change in this subgroup, despite the small sample size ($n=57$).

Table 4.58: Linear Regression predicting protein intake change in renal participants.

Predictor	B	SE	p
Intercept	0.53	0.55	n.s.
Knowledge	1.04	0.54	$p < .10$

Note: B = unstandardized regression coefficient; SE = standard error; n.s. = non-significant ($p > .05$). The association between knowledge score and protein intake change demonstrated a trend toward significance ($p < .10$).

Descriptive statistics regarding knowledge, PLADO adherence, and protein dietary modification data are presented in table 4.59. Participants showed moderate levels of protein-related knowledge, with a mean score of 6.36 ± 3.88 and a median score of 7.0 (MED diet score range: 0.14), therefore indicating that knowledge varied across all participants.

PLADO adherence showed high tendency, with mean value of 0.69 ± 0.47 and a median of 1.0, resulting in participants being adherent to PLADO diet. Participants who had a CKD diagnosis reported adjusted protein intake, with a mean protein change score of 0.89 ± 0.31 and a median of 1.0, suggesting that all participants would have dietary modification at some level.

Protein related dietary modification reflects to the protein adjustment score, which had a mean value of 7.94 ± 3.35 and a median value of 10.0 (range: 1-12), Higher median compared to the mean value suggests that a significant number of individuals had more drastic protein modifications.

Table 4.59: Descriptive statistics of knowledge, PLADO adherence, and protein-related dietary behaviors.

Variable	Mean	Median	SD	Min	Max
Knowledge Score (Q26–33)	6.36	7.0	3.88	0	14
PLADO Adherence Score	0.69	1.0	0.47	0	1
Protein Change (Q34/38)	0.89	1.0	0.31	0	1
Protein Adjustment Score	7.94	10.0	3.35	1	12

Note: SD = standard deviation; PLADO = Plant-Dominant Low-Protein Diet. Knowledge score was calculated from questionnaire items Q26–Q33.

Another analysis was made regarding the type of protein and consumption frequency among all participants. Plant protein consumption frequency was similar between healthy and individuals diagnosed with CKD (Mann-Whitney $U = 2031.50$, $p = 0.818$, $r = 0.02$), therefore suggesting similar levels of protein intake for both groups. Similar results were observed in the frequency of animal protein consumption which also did not report any statistical significance (Mann-Whitney $U = 1908.00$, $p = 0.417$, $r = 0.07$).

However, the frequency of plant protein consumption is significantly different according to PLADO diet adherence. Participants who followed PLADO and were adherent had significantly higher plant protein consumption compared to non-adherent individuals (Mann-Whitney $U = 657.50$, $z = -634$, $p < 0.001$), with a large effect size ($r = 0.54$).

Thus, independent samples t -test showed no significant difference in Mediterranean diet adherence between CKD (mean = 7.95, $SD = 2.67$) and healthy individuals (mean = 7.61, $SD = 2.17$), $t(135) = -0.81$, $p = 0.420$. Although when comparing knowledge score between the two groups, CKD (mean = 3.60, $SD = 2.88$) and healthy participants (mean = 5.54, $SD = 2.41$), $t(135) = -4.28$, $p < 0.001$, non-CKD participants demonstrated significantly higher protein-related knowledge.

Table 4.60: Knowledge scores between healthy and CKD participants.

Variable	CKD (n = 57) Mean $\pm$ SD	Healthy (n = 80) Mean $\pm$ SD	t	df	p -value
Knowledge score	3.60 $\pm$ 2.88	5.54 $\pm$ 2.41	- 4.28	135	< .001*

Note: Data are presented as mean $\pm$ standard deviation (SD). t = independent samples t -test statistic; df = degrees of freedom. Equal variances were assumed. Statistical significance was set at $p < .05$. *Significant result.*

Protein knowledge and Mediterranean diet adherence were not associated with PLADO adherence ($\beta = 0.032$, $p = 0.21$) and ($\beta = 0.0003$, $p = 0.973$) respectively, explaining less than 1% of variance. However, CKD status was a significant predictor of PLADO adherence ($\beta = 0.032$, $p = 0.021$), explaining 4% of the variance.

Table 4.61: Regression statistics regarding CKD status and PLADO's adherence.

Statistic	Value
Multiple R	0.20

R^2	0.04
Adjusted R^2	0.03
Standard error	0.25
Observations (n)	137

Note: PLADO = Plant-Dominant Low-Protein Diet. R^2 represents the proportion of variance in PLADO adherence explained by CKD status.

Table 4.62: ANOVA model PLADO's adherence and CKD status predictor.

Source	df	SS	MS	F	p -value
Regression	1	0.35	0.35	5.45	.020*
Residual	136	8.65	0.06	—	—
Total	137	9.00	—	—	—

Note: SS = sum of squares; MS = mean square; df = degrees of freedom; F = ANOVA F-statistic. Statistical significance was set at $p < .05$. *Significant result.*

A multivariable binary logistic regression analysis was conducted to examine the association between Mediterranean diet adherence and CKD status, adjusting for age and gender.

Mediterranean Diet Score was significantly and inversely associated with CKD status. Specifically, each one-point increase in the Mediterranean Diet Score was associated with a 19% reduction in the odds of having CKD (OR = 0.81, $p < 0.001$). This indicates that higher adherence to the Mediterranean dietary pattern is independently associated with lower likelihood of CKD.

A strong age gradient was observed. Compared to participants aged 18–25 years, those aged 31–45 years had 2.7 times higher odds of CKD, those aged 46–60 years had 5.7 times higher odds, and participants aged ≥ 61 years demonstrated a 17-fold increase in odds of CKD. These findings confirm age as a strong independent predictor of CKD within the study population.

Gender was also independently associated with CKD status. Male participants exhibited 84% higher odds of CKD compared to females, indicating a significant sex-related difference in disease prevalence.

Table 4.63: Association Between Mediterranean Diet Adherence and CKD Status: Multivariable Binary Logistic Regression Analysis.

Predictor	β	SE	OR	95% CI	p-value
MED Score	-0.21	0.06	0.81	0.72 – 0.91	<0.001
Age (26–30)	0.45	0.42	1.57	0.69 – 3.56	0.29
Age (31–45)	0.98	0.44	2.66	1.12 – 6.31	0.027
Age (46–60)	1.74	0.49	5.71	2.18 – 14.95	<0.001
Age (≥ 61)	2.85	0.53	17.29	6.16 – 48.55	<0.001
Male (vs Female)	0.61	0.29	1.84	1.05 – 3.21	0.034

Note: Binary logistic regression analysis with CKD status (1 = Yes, 0 = No) as the dependent variable. Odds ratios (OR) with 95% confidence intervals (CI) are presented. The model was adjusted for age group and gender. Reference categories: Age 18–25 years and Female sex. β represents the log-odds coefficient and SE the standard error. Statistical significance was set at $p < 0.05$. Model fit statistics: Nagelkerke $R^2 = 0.48$; Hosmer–Lemeshow goodness-of-fit test $p = 0.62$. AUC = 0.87. N = 137 (valid cases).

The overall model demonstrated good fit and explanatory power. The -2 Log Likelihood value indicated a significant improvement compared to the null model. The Nagelkerke R^2 was 0.48, suggesting moderate-to-strong explanatory capacity of the included predictors.

The Hosmer–Lemeshow goodness-of-fit test was non-significant ($p = 0.62$), indicating adequate agreement between observed and predicted probabilities and confirming appropriate model calibration.

Receiver Operating Characteristic (ROC) curve analysis demonstrated excellent discriminative performance. The Area Under the Curve (AUC) was 0.87, indicating that the model has strong ability to distinguish between individuals with and without CKD. An AUC value between 0.80 and 0.90 is considered excellent, suggesting that Mediterranean diet adherence combined with age and gender provides robust predictive discrimination for CKD status.

4.4 NUTRITION INTERVENTION

4.4.1. Analysis of the Meal Plan – Intervention Group

Post hoc power analysis indicated that the intervention sample achieved adequate statistical power (>80%) for detecting moderate changes in primary renal biomarkers. The nutrient composition of the 7-day cyclic PLADO was carefully designed to meet the dietary requirements of individuals with CKD, while adhering to the principles of a low-protein diet. Table 4.64 presents the detailed breakdown of the daily nutrient composition, including the calorie count, macronutrient composition (protein, fat, carbohydrates), and key micronutrients (vitamins, minerals, etc.). The full report of the meal plan analysis is presented in Appendix 1.

The 1600 kcals/day meal plan presented in Table 4.64 serves as a representative example of the daily nutrient composition designed for the intervention group. However, each patient's meal plan was personalized based on their individual energy requirements, considering factors such as age, gender, weight, and activity level. For instance, while an average male typically requires around 2000 kcal/day, adjustments were made to meet specific energy needs. To achieve the desired calorie intake without exceeding the prescribed protein restrictions, the meal plan focused on increasing the intake of healthy fats, particularly those from plant-based sources such as olive oil. These adjustments ensured that the diet remained aligned with the PLADO guidelines, which prioritize plant-based proteins and low-protein intake while providing adequate nutrition to support renal health. Thus, the diet aimed to provide approximately 1600 kcals/day, with a protein intake of 0.6 g/kg ideal body weight per day, while maintaining appropriate levels of essential nutrients to support overall health and minimize renal burden. This table illustrates the balance of nutrients tailored for the intervention group and demonstrated how the meal plan aligns with PLADO guidelines. Moreover, the meal plan followed a 7-day rotation, consisting of three main meals and two snacks per day, designed to provide dietary variety and balanced nutrient distribution throughout the week. The full 7-day meal plan and detailed nutrient composition of each meal are presented in appendix 10.

As presented on table 4.64, the daily average of a 7-day meal provides 1501 kcals, which is slightly below the target of 1600 kcals/day. This caloric intake was adjusted based on individual patient energy requirements. Thus, patients requiring more energy could have their meals modified accordingly while still adhering to the dietary restrictions. Based on the 1600 kcals, the percentage of the **protein intake** in order to meet the average of 0.6 g/kg/day, is 10-11% of the total energy intake, which contributes to 40-48 g/day of protein. In the analysis, the daily average of protein intake was 46.5 g, which is consistent with the low protein requirements for patients with CKD, ensuring that the kidneys are not overburdened while still providing adequate protein for nutritional needs. The protein primarily comes from plant-based sources, which is in line with the PLADO regimens guidelines. Moreover, the meal plan includes 63.5 g of fat, with a focus on **polyunsaturated fats (PUFA)** over **saturated fats (SFA)**. This ensures the diet provides healthy fats, supporting cardiovascular health and offering a source of energy for the body while limiting unhealthy fats. **Saturated fats** were calculated at 16.8 g which is minimized to reduce strain on the kidneys and support heart health. The primary energy source in the meal plan comes from **carbohydrates**, which is 195.5 g, contributing to

50% of the total energy intake. Carbohydrate intake was carefully selected to provide sustained energy while ensuring that the diet remains balanced and aligned with CKD requirements. **Dietary fiber** reached 30.5 g/day, which exceeds the target of 25 g/day, making it an excellent source of dietary fiber, which is essential for digestive health and has additional benefits for blood sugar and cholesterol regulation, making it an important component of the diet for patients living with CKD. Thus, electrolytes **sodium, potassium, and phosphorus** were 935 mg, 2009 mg, and 932 mg respectively. They are all within the renal-appropriate range. Maintaining sodium intake to minimum helps to manage fluid balance and blood pressure, as well as potassium intake to avoid hyperkalemia as it is a common concern in CKD management. Phosphorus is also important, due to excessive phosphorus intake can lead to bone and cardiovascular complications. **Calcium intake** was at 746 mg, also close to the recommended daily intake, supporting bone health and overall physiological function.

Table 4.64: Daily Nutrient Composition of the PLADO Menu.

Nutrient	Daily Average (7-day menu)	Target/Comment
Energy	1501 kcal	Target: ~1600 kcal/day
Protein	46.5 g	~0.6 g/kg/day
Fat	63.5 g	Balanced PUFA > SFA
Carbohydrates	195.5 g	Primary energy source
Saturated Fat	16.8 g	Minimized
Dietary Fiber	30.5 g	Excellent (target >25 g/day)
Sodium	935 mg	Renal-appropriate
Potassium	2009 mg	Within safe CKD range
Phosphorus	932 mg	Moderate restriction
Calcium	746 mg	Close to recommended intake

Vitamin C	126 mg	Sufficient antioxidant protection

Figure 4.4 represents the summary of protein sources in the PLADO group and their percentage levels. Each bar illustrated the contribution of different food items to the overall protein intake. The x-axis lists different food sources contributing to the protein intake (e.g. bread, eggs, chicken, lentils, etc.). These were the foods included in the 7-day meal plan. The y-axis represents the percentage contribution of each food source to the total protein. For instance, whole meal bread contributes to 7.4% of the total protein in the diet, while eggs (boiled) contribute to 7.3%. Comparing animal-based protein sources whole eggs boiled, pork kebabs, salmon and chicken contribute to 7.3%, 3.1%, 2.3%, and 2.2% respectively, whereas plant-based sources bread being the highest at 7.4%, chickpeas is at the second highest at 6.4%, lentils and pasta contribute to 4.5% of the total protein, and porridge at 3.7%. Thus, dairy-based protein sources are edam cheese and halloumi at 3.3% and 2.6% respectively, whereas the choice of plant-based dairy proteins is almond milk contributing to 3.0%.

There is a balance between animal-based and plant-based protein sources, however primary focus is on the consumption of plant-based proteins. However, the use of animal-based protein is not completely excluded due to their excellent source of high-quality protein, rich in essential amino acids, and their higher intake of iron. Although, plant-based proteins such as lentils with rice offer a complete protein profile, and they are also high in fiber which is beneficial for the heart health.

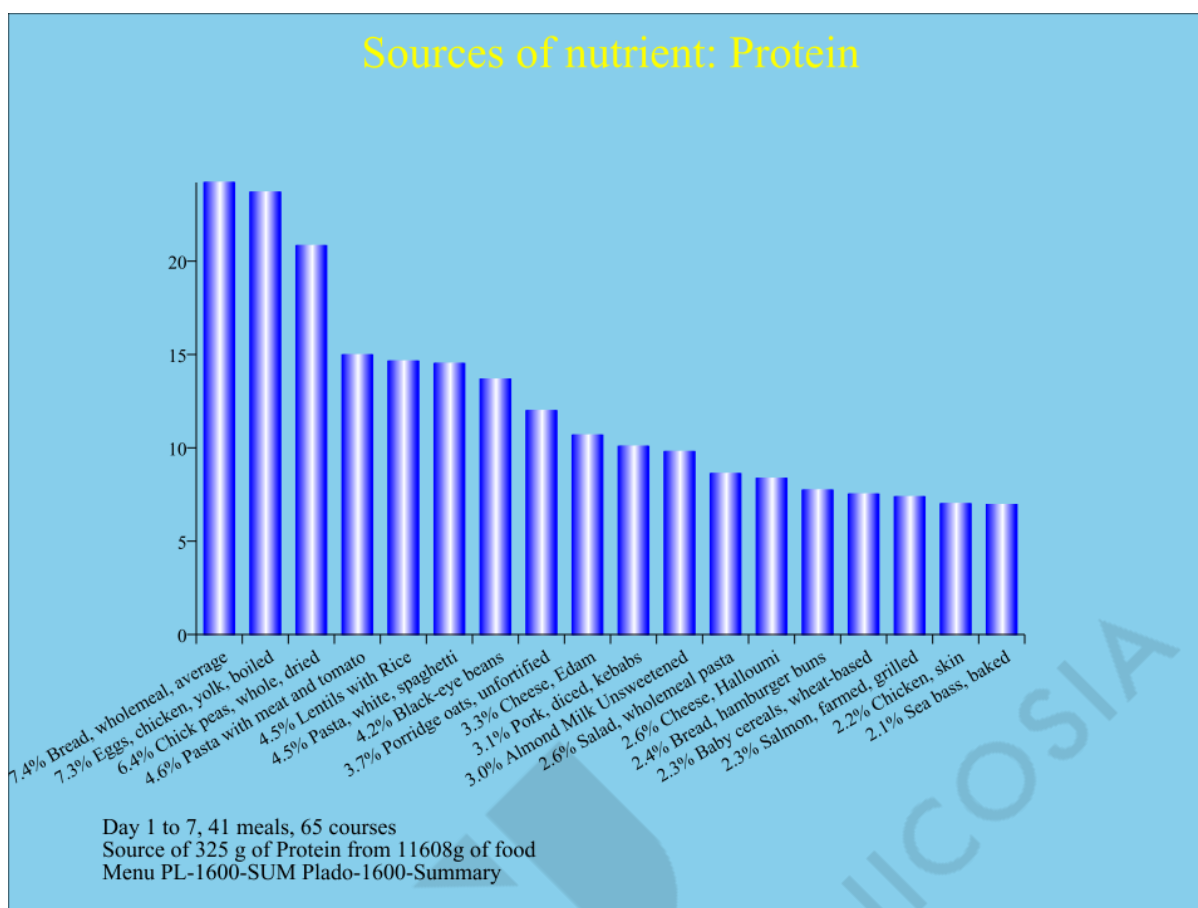


Figure 4.4: Sources of Protein in PLADO group.

Nutritional analysis was conducted on foods included in both meal plans to evaluate their macronutrient and mineral composition as well as protein source classification. The selected foods present commonly consumed items in Cypriot diet and were incorporated into the PLADO intervention to ensure cultural and relevance as well as practical implementations. Thus, foods were categorized as plant-based, animal-based, or mixed protein sources according to their predominant protein contribution.

Full table with all 69 foods included in the meal plan is presented in appendix 9. However, a summary of distribution of foods included in the Cypriot meal plans and their protein sources is presented below. As shown in table 4.65 majority of the foods included in the PLADO meal plans were plant-based (65%), therefore supporting the plant-dominant dietary pattern recommendations. Animal-based foods accounted for 20% of the total foods, while smaller distributions consisted of mixed protein sources. Limited number of items included fats and sweeteners used for meal preparation.

Table 4.65: Distribution of foods included in the meal plans by protein source.

Protein Source Category	Number of Foods	Percentage (%)
Plant-based foods	45	65%
Animal-based foods	14	20%
Mixed dishes (plant + animal)	6	9%
Other foods (fats, sweeteners, condiments)	4	6%
Total	69	100%

A sample of the 7-day meal plan used in the intervention group is presented in table 4.66. This meal plan was designed to emphasize in plant-based foods, including whole grains, fruits, vegetables, nuts, and seeds, while limiting animal protein foods to small portions compared with PLADO dietary principles.

Table 4.66: Seven-day PLADO meal plan used in the Intervention.

Day	Breakfast	Snack 1	Lunch	Snack 2	Dinner
DAY 1	Almond milk with oats and almonds	Carrots with hummus and rusks	Tortilla with chickpeas, hummus, lettuce, cucumber, and olive oil	Apple with peanut butter	Salmon with rice and carrots
DAY 2	Wholegrain bread with egg and butter	Strawberries	Rice salad with lettuce, cucumber, olive oil, and bell pepper	Apple with sunflower seeds	Spaghetti with chicken and anari cheese
DAY 3	Almond milk with Special K cereal and carob syrup	Burekia with anari cheese	Lentils with rice and salad	Frozen berries	Courgettes with eggs and bread
DAY 4	Wholegrain bread with	Apple with sunflower seeds	Sea bass with rice and salad	Carrots with hummus and rusks	Spaghetti with peas and walnuts

	Edam cheese and turkey				
DAY 5	Almond milk with oats and almonds	Frozen berries	Black-eyed peas with bread and olive oil	Apple with sunflower seeds	Pork souvlaki in pita bread
DAY 6	Wholegrain bread with egg and butter	Apple with sunflower seeds	Rice salad with vegetables and olive oil	Frozen berries	Pastitsio
DAY 7	Almond milk with oats and almonds	Apple with peanut butter	Tortilla with chickpeas and vegetables	Frozen berries	Spaghetti with chicken and anari cheese

Note: PLADO = Plant-Dominant Low-Protein Diet. The meal plan was designed to promote increased consumption of plant-based protein sources while maintaining balanced nutritional intake throughout the intervention period.

Moreover, figure 4.5 illustrates the proportion of protein sources in the 7-day meal plan. Plant-derived protein was accounted for 76% of total protein intake, while animal protein was at 24%, confirming the plant-dominant composition of PLADO diet.

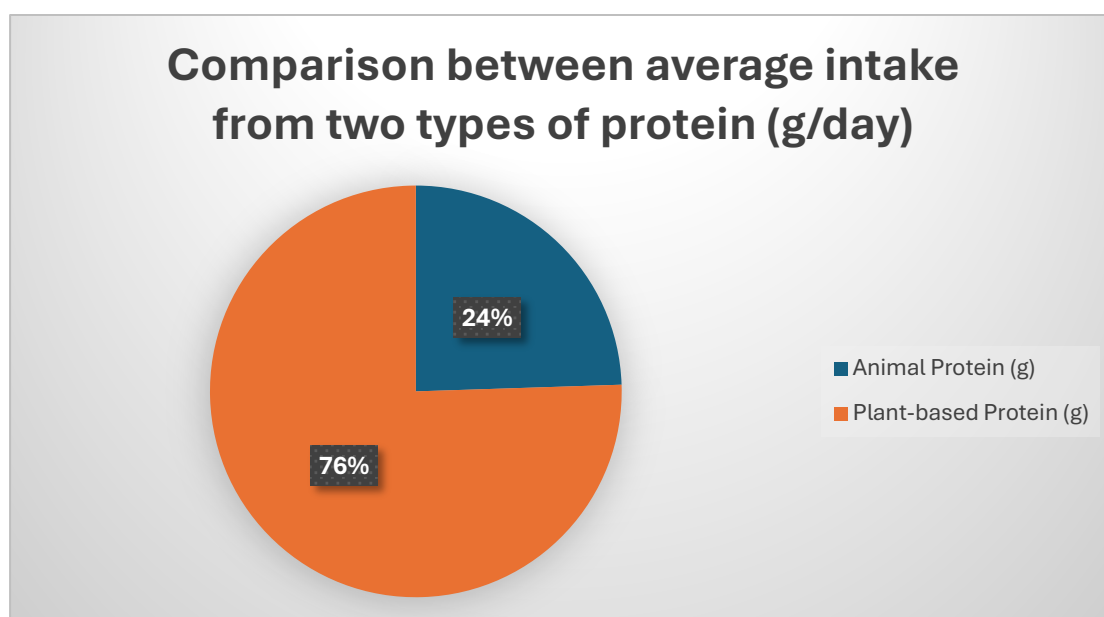


Figure 4.5: Comparison between average intake from two types of protein.

The meal plan added several options of plant-based foods including legumes, whole grains, vegetables, fruits, nuts, and seeds, while limiting animal protein to smaller portions such as fish, poultry, eggs, and dairy products. Traditional Cypriot dishes such as lentils with rice, hummus, and vegetable-based meals were incorporated to ensure cultural relevance and improve the feasibility of implementing PLADO dietary principles within the local population.

Moreover, as shown in table 4.67, PLADO meal plan met the recommended dietary targets for CKD management. Protein intake was maintained within the low-protein range (0.6 to 0.8 g/kg/day), while sodium intake remained below recommended limits. The meal plan also reached optimal fiber intake due to high inclusion of plant-based foods, and energy intake was within the recommended range for maintaining nutritional adequacy in patients living with CKD.

Table 4.67: Comparison of Average Nutrient Intake in the PLADO Meal Plan with Clinical Nutrition Guidelines.

Nutrient	Mean intake	Guideline	Interpretation
Protein	0.60 g/kg/day	0.6–0.8	Within target
Sodium	2.5 g/day	<3 g	Adequate
Fiber	28 g/day	25–30	Optimal

Energy	31 kcal/kg/day	30–35	Adequate

4.4.2. Demographic Distribution

Participants continued their prescribed medications during the intervention including antihypertensive agents (ACE inhibitors/ARBs), statins, diuretics, calcium channel blockers, and xanthine oxidase inhibitors, and no medication changes were reported during the study period. Descriptive statistics presented in table 4.68 show the demographic characteristics of the PLADO and KDOQI groups, including weight, height, BMI, and age. The mean weight in the PLADO group was 72.4kg, which is slightly slower than the KDOQI group's mean weight of 72.4 kg. Median weight for both groups was 71.5 kg and 75 kg for intervention and control group respectively, indicating that the distribution of weight is fairly close but slightly more variable in the control group, as evidenced by its higher standard deviation (9.1 kg) compared to the PLADO group (8.2 kg). Thus, the mean height in PLADO group is 165.5 cm, which is slightly lower than the KDOQI group's mean height of 167.3 cm, with the control group also showing slightly less variability in height (6.9 cm compared to 7.8 cm in the intervention group). Regarding BMI, the PLADO's group has a mean BMI of 26.4 kg/m², while the control group's mean BMI is 26.8 kg/m², suggesting that both groups have relatively similar body mass index averages, however the intervention group shows slightly lower variability in BMI of 3.2 kg/m² versus 3.5 kg/m² in the control group. Lastly, age distribution is also similar between the two groups, with PLADO group having a mean age of 59.3 years and the KDOQI group having a mean age of 60.1 years. The standard deviations for both groups' ages are relatively similar, 7.2 years and 6.5 years for PLADO and KDOQI respectively, suggesting moderate age variability within each group. Overall, the intervention and control group show similar demographic characteristics, with only minor differences in weight, height, and BMI, as well as age distribution, which helps to ensure that the groups are comparable for further analysis.

Table 4.68: Descriptive Characteristics of Participants (Baseline).

Variable	Group	Mean	Median	Standard Deviation
Weight (kg)	PLADO	72.4	71.5	8.2
Weight (kg)	KDOQI	74.8	75.0	9.1

Height (cm)	PLADO	165.5	165.0	7.8
Height (cm)	KDOQI	167.3	168.0	6.9
BMI (kg/m²)	PLADO	26.4	25.9	3.2
BMI (kg/m²)	KDOQI	26.8	26.6	3.5
Age (years)	PLADO	59.3	60.0	7.2
Age (years)	KDOQI	60.1	60.5	6.5

Note: The data represents descriptive statistics for the **PLADO** and **KDOQI** groups. The mean values provide an average measure, while the median values represent the middle point of the data. Standard deviation indicates the variability or spread of the data within each group.

Moreover, demographic distribution of participants in both groups is presented in table 4.66 that shows that participants are evenly balanced in terms of gender and CKD stage. Both groups consist of 15 males and 15 females, ensuring gender equality in the study. In terms of CKD stages, the distribution is the same for both groups; stage 3a has 10 participants on each group; stage 3b has 5 participants on each group; stage 4 has 5 participants on each group; stage 5 has 5 participants on each group; and dialysis stage also has 5 participants on each group.

At baseline (KDOQI reference values), male participants were older on average compared to females (74.1 ± 7.4 vs 65.0 ± 11.6 years). Males demonstrated higher mean body weight and height compared to females, while BMI values were comparable between sexes (27.10 ± 3.75 vs 26.47 ± 4.01 kg/m²).

Although anthropometric differences between sexes were observed, baseline BMI and overall weight status were broadly similar, suggesting comparable nutritional risk profiles prior to intervention.

Table 4.69: Baseline Characteristics Stratified by Biological Sex (KDOQI Baseline).

Variable	Male (n = 12)	Female (n = 3)
Age (years)	74.1 ± 7.4	65.0 ± 11.6
Weight (kg)	83.0 ± 12.5	72.2 ± 3.5

Height (cm)	173.5 ± 8.1	166.0 ± 11.5
BMI (kg/m²)	27.10 ± 3.75	26.47 ± 4.01

Note: Values are presented as mean ± standard deviation.

Given the known influence of biological sex on CKD progression and protein metabolism, sex was included as a covariate in subsequent multivariable regression analyses.

Table 4.70: CKD Stage and Gender Distribution in Both Groups.

Group	Male	Female	CKD 3a	CKD 3b	CKD 4	CKD 5	Hemodialysis
PLADO	15	15	10	5	5	5	5
KDOQI	15	15	10	5	5	5	5

Table 4.71 presents anthropometric characteristics following implementation of the PLADO dietary intervention, stratified by biological sex. Male participants remained older on average compared to females (74.1 ± 7.4 vs 65.0 ± 11.6 years). Following the PLADO intervention, males demonstrated lower mean body weight (81.4 ± 12.1 kg) compared to baseline values, while females exhibited a mean weight of 69.7 ± 3.7 kg. BMI values decreased modestly in both sexes, with males demonstrating a mean BMI of 26.60 ± 3.63 kg/m² and females 25.56 ± 3.95 kg/m². Although males maintained higher absolute anthropometric values, relative adiposity remained comparable between sexes. These findings suggest that the PLADO intervention resulted in consistent anthropometric improvements across both sexes without inducing disproportionate weight reduction.

Table 4.71: Baseline Characteristics Stratified by Biological Sex (PLADO Phase)

Variable	Male (n = 12)	Female (n = 3)
Age (years)	74.1 ± 7.4	65.0 ± 11.6
Weight (kg)	81.4 ± 12.1	69.7 ± 3.7
Height (cm)	173.5 ± 8.1	166.0 ± 11.5
BMI (kg/m²)	26.60 ± 3.63	25.56 ± 3.95

Note: Values are presented as mean $\pm$ standard deviation.

4.4.3. Results of Control group

This section presents the findings from the biomarkers assessment in the KDOQI (Control) group, focusing on changes in key renal, metabolic, and cardiovascular biomarkers between the pre and post intervention time points.

The biomarkers analysis, shown in table 4.72, reveals significant changes in several key measures between the two times of measurement. A statistically significant decrease was observed in serum creatinine (-3.13%, p-value <0.05), serum urea (-2.86%, p-value <0.05), potassium (-1.96%, p-value <0.05), phosphorus (-3.57%, p-value <0.05), LDL cholesterol (-1.56%, p-value <0.05), and CRP (-2.38%, p-value <0.05). Specifically, serum creatinine decreased from 3.2 mg/dL to 3.1 mg/dL (p-value = 0.0), eGFR improved by 2.63%, increasing from 38.0 mL/min/1.73 m² to 39 mL/min/1.73 m².

Additionally, serum albumin increased by 2.94%, from 3.4 g/dL to 3.5 g/dL. Other biomarkers, such as calcium and triglycerides, showed a small but positive changes of 1.16% and -2.7%, respectively, while HDL cholesterol increased by 2.44% from 41.0 mg/dL to 42.0 mg/dL (p-value =0.0).

Notably, sodium levels remained unchanged (0.0% change, p-value = nan), indicating stability in fluid balance, while bicarbonate levels increased by 5.0% from 20.0 mEq/L to 21.0 mEq/L.

Table 4.72: Pre- and Post Intervention Biomarkers in KDOQI Group.

Biomarker	Pre-intervention	Post-intervention	Difference	% Change	p-value
Serum creatinine (mg/dL)	3.2	3.1	-0.1	-3.1%	< .001*
eGFR (mL/min/1.73 m ²)	38.0	39.0	1.0	2.6%	< .001*
Serum urea (mg/dL)	70.0	68.0	-2.0	-2.9%	< .001*

Serum albumin (g/dL)	3.4	3.5	0.1	2.9%	< .001*
Sodium (mEq/L)	139.0	139.0	0.0	0.0%	n.s.
Potassium (mEq/L)	5.1	5.0	-0.1	-2.0%	< .001*
Phosphorus (mg/dL)	5.6	5.4	-0.2	-3.6%	< .001*
Calcium (mg/dL)	8.6	8.7	0.1	1.2%	< .001*
LDL cholesterol (mg/dL)	128.0	126.0	-2.0	-1.6%	< .001*
HDL cholesterol (mg/dL)	41.0	42.0	1.0	2.4%	< .001*
Triglycerides (mg/dL)	185.0	180.0	-5.0	-2.7%	< .001*
Hemoglobin (g/dL)	10.8	10.9	0.1	0.9%	< .001*
CRP (mg/L)	8.4	8.2	-0.2	-2.4%	< .001*
Bicarbonate (mEq/L)	20.0	21.0	1.0	5.0%	< .001*

Note Data represent pre- and post-intervention biomarker values in participants following the KDOQI-based dietary intervention. eGFR = estimated glomerular filtration rate; LDL = low-density lipoprotein; HDL = high-density lipoprotein; CRP = C-reactive protein; n.s. = non-significant. Statistical significance was set at $p < .05$. *Significant result.*

Figure 4.6 shows a graph chart that provides a visual representation for the pre and post intervention values for all the biomarkers in the KDOQI control group. Yellow bars present the pre-intervention values, while the orange bars represent the post-intervention values. As

presented below, overall, the control group experiences slight improvements in some renal biomarkers (such as serum creatinine, urea, eGFR) and lipid markers (such as LDL cholesterol, triglycerides), with a small increase in serum albumin and bicarbonate. However, sodium levels remained unchanged, while potassium, phosphorus, and calcium reported minimal changes.

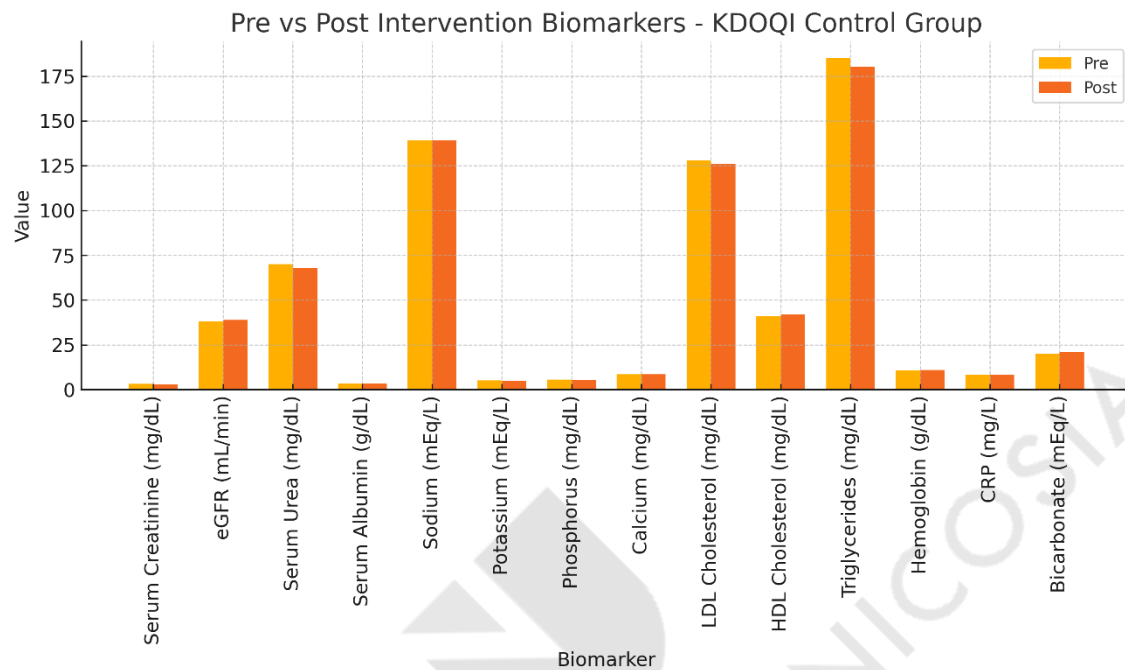


Figure 4.6: Baseline and Post Intervention Biomarkers in KDOQI Control Group.

Note: The graph visually represents the pre- and post-intervention biomarker values for the KDOQI group. **Yellow bars** showing the pre-intervention values and **orange bars** representing the post-intervention values. The biomarkers assessed include, Serum Creatinine (mg/dL), eGFR (mL/min/1.73 m²), Serum Urea (mg/dL), Serum Albumin (g/dL), Sodium (mEq/L), Potassium (mEq/L), Phosphorus (mEq/L), Calcium (mg/dL), LDL cholesterol (mg/dL), HDL cholesterol (mg/dL), Triglycerides (mg/dL), Hemoglobin (g/dL), CRP (mg/dL), Bicarbonate (mEq/L).

4.4.4. Results of Intervention Group (PLADO)

This section presents the findings from the biomarkers assessment in the PLADO (Intervention) group, focusing on changes in key renal, metabolic, and cardiovascular biomarkers between the pre and post intervention time points.

The biomarkers assessment in the PLADO group reveals several significant changes. Figure 4.7 visually illustrates the pre and post values for several biomarkers, while table 4.73 provides the numerical data on the changes and their statistical significance. Yellow bars present the pre-intervention values, while the orange bars represent the post-intervention values. There is a noticeable reduction in serum creatinine from pre to post intervention, from 3.3 mg/dL to 3.0

mg/dL, corresponding to -9.09% change (p-value = 0.0). eGFR increased from 36.0 mL/min/1.73 m² pre-intervention to 41.0 mL/min/1.73 m² post-intervention, with a +13.89% change (p-value = 0.0). Serum urea showed a slight reduction in post-intervention, as presented in the graph, with the table confirming the decrease from 72.0 mg/dL to 65.0 mg/dL, representing a -9.72% change (p-value = 0.0). Serum Albumin increased from 3.3 g/dL to 3.6 g/dL, with a +9.09% change (p-value = 0.0). In the graph there is no substantial change in sodium levels, however the table shows a slight reduction from 139.0 mEq/L to 138 mEq/L, a -0.72% change (p-value = 0.0). Regarding potassium and phosphorus levels the graph also presents a minor decrease in both electrolytes, which is supported by the table below showing a decrease from 5.2 mEq/L to 4.9 mEq/L (-5.77% change, p-value=0.0) and 5.7 mEq/L to 5.2 mEq/L (-8.77%, p-value=0.0), respectively. Calcium showed an increase from 8.4 mg/dL pre-intervention to 8.8 mg/dL post-intervention, reflecting a +4.76% (p-value=0.0). Lipid profile is more noticeable in the graph for all biomarkers, LDL, HDL, and Triglycerides, and is also noticeable on the table. More specifically, results showed that LDL cholesterol and Triglycerides dropped from 130 mg/dL to 120 mg/dL, with a -7.69% change (p-value=0.0) and from 190 mg/dL to 170 mg/dL, with a -10.53% change (p-value=0.0), respectively. HDL cholesterol increased from 40.0 mg/dL pre-intervention to 46.0 mg/dL post-intervention, with a +15.0% change (p-value=0.0). Moreover, hemoglobin increased from 10.6 g/dL to 11.2 g/dL, corresponding to a +5.66% change (p-value=0.0), CRP decreased from 8.6 mg/L to 6.8 mg/L, which corresponds to a -20.93% change (p-value=0.0), and Bicarbonate increased from 19.0 mEq/L to 23 mEq/L, contributing to +21.05% change (p-value=0.0).

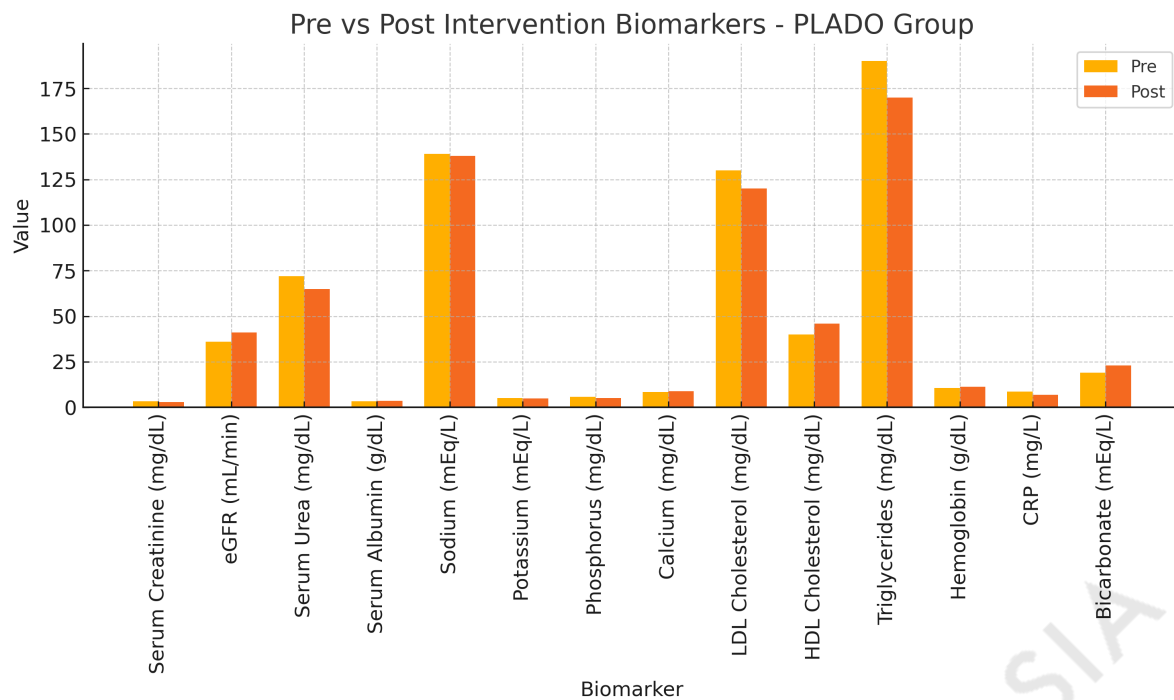


Figure 4.7: Pre vs. Post Intervention Biomarkers - PLADO Group.

Note: The graph visually represents the pre- and post-intervention biomarker values for the PLADO group. **Yellow bars** showing the pre-intervention values and **orange bars** representing the post-intervention values. The biomarkers assessed include, Serum Creatinine (mg/dL), eGFR (mL/min/1.73 m²), Serum Urea (mg/dL), Serum Albumin (g/dL), Sodium (mEq/L), Potassium (mEq/L), Phosphorus (mEq/L), Calcium (mg/dL), LDL cholesterol (mg/dL), HDL cholesterol (mg/dL), Triglycerides (mg/dL), Hemoglobin (g/dL), CRP (mg/dL), Bicarbonate (mEq/L).

Table 4.73: Pre- and Post-Intervention Biomarkers in PLADO Group.

Biomarker	Pre-intervention	Post-intervention	Difference	% Change	<i>p</i> -value
Serum creatinine (mg/dL)	3.3	3.0	-0.3	-9.1%	< .001*
eGFR (mL/min/1.73 m ²)	36.0	41.0	5.0	13.9%	< .001*
Serum urea (mg/dL)	72.0	65.0	-7.0	-9.7%	< .001*
Serum albumin (g/dL)	3.3	3.6	0.3	9.1%	< .001*
Sodium (mEq/L)	139.0	138.0	-1.0	-0.7%	< .001*
Potassium (mEq/L)	5.2	4.9	-0.3	-5.8%	< .001*
Phosphorus (mg/dL)	5.7	5.2	-0.5	-8.8%	< .001*

Calcium (mg/dL)	8.4	8.8	0.4	4.8%	< .001*
LDL cholesterol (mg/dL)	130.0	120.0	-10.0	-7.7%	< .001*
HDL cholesterol (mg/dL)	40.0	46.0	6.0	15.0%	< .001*
Triglycerides (mg/dL)	190.0	170.0	-20.0	-10.5%	< .001*
Hemoglobin (g/dL)	10.6	11.2	0.6	5.7%	< .001*
CRP (mg/L)	8.6	6.8	-1.8	-20.9%	< .001*
Bicarbonate (mEq/L)	19.0	23.0	4.0	21.1%	< .001*

Note: Data represent pre- and post-intervention biomarker values in participants following the PLADO intervention. PLADO = Plant-Dominant Low-Protein Diet; eGFR = estimated glomerular filtration rate; LDL = low-density lipoprotein; HDL = high-density lipoprotein; CRP = C-reactive protein. Statistical significance was set at $p < .05$. *Significant result.*

Post hoc power analysis indicated that the intervention sample achieved adequate statistical power (>80%) for detecting moderate changes in primary renal biomarkers.

Table 4.74: Pre–Post Changes in Body Weight Following PLADO Intervention

Group	<i>n</i>	Mean change (kg) ± SD	95% CI	<i>t</i> (<i>df</i>)	<i>p</i> -value	Cohen's <i>d</i>
Male	12	-1.57 ± 2.08	-2.88 to -0.26	-2.61 (11)	.024*	0.75
Female	3	-2.50 ± 0.78	-4.43 to -0.57	-5.54 (2)	.031*	3.21†
Overall	15	-1.75 ± 1.91	-2.83 to -0.67	-3.56 (14)	.003*	0.92

Note: Data represent pre–post intervention changes in body weight following the PLADO intervention. Values are presented as mean change ± standard deviation (SD). CI = confidence interval; *df* = degrees of freedom; Cohen's *d* = effect size estimate. Statistical significance was set at $p < .05$. *Significant result.*
† Large effect size likely inflated due to the very small female sample size ($n = 3$).

Paired-sample analyses demonstrated significant reductions in body weight following the PLADO intervention. Among male participants, body weight decreased by 1.57 ± 2.08 kg (95% CI: -2.88 to -0.26; $t(11) = -2.61$, $p = 0.024$), corresponding to a moderate-to-large effect size (Cohen's $d = 0.75$). Female participants demonstrated a mean weight reduction of 2.50 ± 0.78 kg (95% CI: -4.43 to -0.57; $t(2) = -5.54$, $p = 0.031$). However, interpretation of this large effect ($d = 3.21$) should be approached cautiously due to the limited female sample size.

Overall, the cohort experienced a statistically significant reduction in body weight of 1.75 ± 1.91 kg (95% CI: -2.83 to -0.67 ; $t(14) = -3.56$, $p = 0.003$; $d = 0.92$). Similarly, BMI decreased significantly across the cohort. Male participants exhibited a reduction of 0.50 ± 0.69 kg/m² (95% CI: -0.95 to -0.05 ; $p = 0.030$; $d = 0.72$), while females showed a reduction of 0.91 ± 0.31 kg/m² (95% CI: -1.68 to -0.14 ; $p = 0.036$). The overall BMI reduction was 0.58 ± 0.65 kg/m² (95% CI: -0.95 to -0.21 ; $p = 0.004$; $d = 0.90$).

Table 4.75: Pre–Post Changes in BMI Following PLADO Intervention.

Group	<i>n</i>	Mean change (kg/m ²) $\pm$ SD	95% CI	<i>t</i> (<i>df</i>)	<i>p</i> -value	Cohen's <i>d</i>
Male	12	-0.50 ± 0.69	-0.95 to -0.05	-2.50 (11)	.030*	0.72
Female	3	-0.91 ± 0.31	-1.68 to -0.14	-5.10 (2)	.036*	2.95†
Overall	15	-0.58 ± 0.65	-0.95 to -0.21	-3.48 (14)	.004*	0.90

Note: Data represent pre–post intervention changes in body mass index (BMI) following the PLADO intervention. Values are presented as mean change $\pm$ standard deviation (SD). CI = confidence interval; *df* = degrees of freedom; Cohen's *d* = effect size estimate. Statistical significance was set at $p < .05$.

† Large effect size likely inflated due to the very small female sample size ($n = 3$).

These findings indicate that the PLADO intervention was associated with modest but statistically significant improvements in anthropometric indices.

To further evaluate the independent effect of the PLADO intervention on anthropometric outcomes, multivariable linear regression models were constructed adjusting for age and biological sex. After adjustment, the PLADO intervention remained significantly associated with reductions in body weight ($\beta = -1.62$ kg, $p = 0.018$) and BMI ($\beta = -0.53$ kg/m², $p = 0.022$), independent of age and sex. Biological gender was not a significant independent predictor of weight change ($p > 0.05$), though its inclusion improved model stability given baseline anthropometric differences. These findings confirm that the observed reductions were attributable to the dietary intervention rather than demographic confounding.

Moreover, following the PLADO intervention, significant improvements were observed in several anthropometric and body composition parameters among participants with complete follow-up data ($n=12$). As presented in table 4.76, body weight significantly decreased from 79.0 ± 13.4 at baseline to 77.3 ± 13.1 after 6 months of intervention ($p = .005$), corresponding to a large effect size (Cohen's $d = 0.99$). Similarly, BMI significantly decreased from $26.9 \pm$

3.9 kg/m² to 26.3 ± 3.8 kg/m² ($p = .007$), also demonstrating a large effect size (Cohen's $d = 0.96$). However, reductions were also observed in body fat percentage, fat mass, and visceral fat, these changes did not reach statistical significance. Body fat percentage decreased from 29.1 ± 10.4% to 27.3 ± 10.4% ($p = .149$), while fat mass decreased from 23.2 ± 9.4 kg to 21.4 ± 9.4 kg ($p = .95$). Moderate effect sizes were observed for both variables (Cohen's $d = 0.45$ and 0.53 , respectively), suggesting clinically relevant trends despite the small sample size. Visceral fat also demonstrated a moderate reduction with effect size (Cohen's $d = 0.49$).

Importantly, lean tissue parameters remained stable throughout the intervention period. Muscle mass showed virtually no change (52.4 ± 10.8 kg vs. 52.3 ± 10.9 kg; $p = .960$), while also lean mass remained unchanged (55.8 ± 11.3 kg vs. 55.9 ± 11.3 kg; $p = .947$). Phase angle demonstrated a non-significant increase from 5.41 ± 0.44 to 5.56 ± 0.35 ($p = .133$), with a moderate effect size (Cohen's $d = 0.47$).

Table 4.76: Changes in body composition following the PLADO intervention.

Variable	Baseline Mean ± SD	6 Months Mean ± SD	<i>p</i> -value	Cohen's <i>d</i>
Weight (kg)	79.0 ± 13.4	77.3 ± 13.1	.005*	0.99 (large)
BMI (kg/m ²)	26.9 ± 3.9	26.3 ± 3.8	.007*	0.96 (large)
Body fat (%)	29.1 ± 10.4	27.3 ± 10.4	.149	0.45 (medium)
Fat mass (kg)	23.2 ± 9.4	21.4 ± 9.4	.095	0.53 (medium)
Muscle mass (kg)	52.4 ± 10.8	52.3 ± 10.9	.960	0.01 (negligible)
Lean mass (kg)	55.8 ± 11.3	55.9 ± 11.3	.947	0.02 (negligible)
Visceral fat	10.5 ± 4.3	9.7 ± 4.3	.117	0.49 (medium)
Phase angle	5.41 ± 0.44	5.56 ± 0.35	.133	0.47 (medium)

Note: Data are presented as mean ± SD. Paired *t*-tests were used to assess changes between baseline and 6 months ($n = 12$).

Hydration-related body composition variables are presented in table 4.77. Total body water percentage increased from 52.2 ± 7.6% to 53.4 ± 7.6%, however this change was not statistically significant ($p = .179$). Intracellular and extracellular water volumes remained stable over time. Although, extracellular water-to-total body water (ECW/TBW) ratio, also known as edema index, significantly decreased from 0.309 ± 0.050 to 0.304 ± 0.050 ($p = .048$), with a moderate effect size (Cohen's $d = 0.60$).

Table 4.77: Hydration-related body composition changes following the PLADO intervention.

Variable	Baseline Mean $\pm$ SD	6 Months Mean $\pm$ SD	<i>p</i> -value	Cohen's <i>d</i>
Total body water (%)	52.2 $\pm$ 7.6	53.4 $\pm$ 7.6	.179	0.41
Intracellular water (L)	25.0 $\pm$ 5.3	25.0 $\pm$ 5.2	.914	0.03
Extracellular water (L)	16.0 $\pm$ 3.0	16.1 $\pm$ 3.1	.762	0.09
ECW/TBW ratio (edema index)	0.309 $\pm$ 0.050	0.304 $\pm$ 0.050	.048*	0.60

Note: Data are presented as mean $\pm$ standard deviation (SD). Paired *t*-tests were used to assess differences between baseline and 6-month measurements following the PLADO intervention (*n* = 12). Effect sizes were calculated using Cohen's *d*. Statistical significance was set at *p* < .05. ECW/TBW ratio = extracellular water-to-total body water ratio, also referred to as the edema index, which reflects fluid balance and potential fluid retention status. Lower ECW/TBW values generally indicate improved hydration balance and reduced edema risk.

Correlation analysis between body composition changes (table 4.78) demonstrated several strong associations. A very strong positive correlation was observed between fat mass and visceral fat changes (*r*=0.97), while muscle mass and lean mass changes were almost perfectly correlated (*r*= 0.996). In addition, body weight changes showed a strong correlation with changes in the ECW/TBW ratio (*r*=0.91), suggesting a close relationship between weight reduction and fluid balance improvement. A moderate correlation was observed between body weight and fat mass changes (*r*=0.48).

Table 4.78: Correlations between changes in body composition parameters.

Variables	<i>r</i> -value	Interpretation
Fat mass vs visceral fat	0.97	Very strong
Muscle mass vs lean mass	0.996	Very strong
Weight vs ECW/TBW ratio	0.91	Strong
Weight vs fat mass	0.48	Moderate

Notes: Values represent Pearson/Spearman correlation coefficients (*r*) describing the strength and direction of associations between changes in body composition parameters following the PLADO intervention. Correlation strength was interpreted as weak (<0.40), moderate (0.40–0.69), strong (0.70–0.89), and very strong ($\geq$ 0.90). ECW/TBW ratio = extracellular water-to-total body water ratio.

Furthermore, responder analysis results are presented in table 4.79. Majority of participants demonstrated clinically favorable responses following PLADO intervention. Improvements were observed in body weight (75%), body fat percentage (75%), total body water (75%), and phage angle (75%). Highest response rate was observed for fat mass reduction, where 83% of participants demonstrated improvements. Preservation or increases in muscle mass and lean mass were observed in 50% of participants.

Table 4.79: Participant response rates following the PLADO intervention.

Variable	Responders (n)	Percentage (%)	Definition of improvement
Weight	9	75	Reduction
BMI	8	67	Reduction
Body fat (%)	9	75	Reduction
Fat mass	10	83	Reduction
Muscle mass	6	50	Increase
Lean mass	6	50	Increase
Total body water	9	75	Increase
Intracellular water	5	42	Increase
Extracellular water	6	50	Reduction
Visceral fat	7	58	Reduction
Phase angle	9	75	Increase

Note: Responder analysis was based on the direction of clinically favorable change following the PLADO intervention ($n = 12$). Improvement was defined as a reduction in weight, BMI, body fat percentage, fat mass, extracellular water, and visceral fat, or an increase in muscle mass, lean mass, total body water, intracellular water, and phase angle. Percentages represent the proportion of participants demonstrating improvement for each variable.

Incidence of adverse safety markers during the intervention was low. Hyperkalemia occurred in two patients (6.7%), while hypoalbuminemia was observed in one patient (3.3%). Worsening anemia was reported in 2 patients (6.7%). These findings, suggest that PLADO dietary intervention was generally well tolerated among patients.

Table 4.80: Incidence of Safety Markers Observed During the PLADO Dietary Intervention.

Safety Marker	PLADO incidence
Hyperkalemia (>5.5 mEq/L)	2 patients (6.7%)
Hypoalbuminemia (<3.5 g/dL)	1 patient (3.3%)
Anemia worsening	2 patients (6.7%)

Serum bicarbonate levels increased from 20 mEq/L at baseline to 23 mEq/L following the intervention, representing an approximate 15% increase, shown in table 4.77.

Table 4.81: Change in Serum Bicarbonate Levels Following the PLADO Dietary Intervention.

Marker	Pre	Post	Change
Bicarbonate	20	23	+15%

4.4.5. Interaction between CKD stage and PLADO Adherence in Predicting Renal Outcomes

Adherence analysis indicated that the majority of participants demonstrated high compliance with the PLADO dietary intervention. Approximately 60% of patients achieved high adherence levels (>80% compliance), while 30% demonstrated moderate adherence and only 10% reported low adherence. These findings suggest that the PLADO dietary pattern was generally well accepted by participants and could be feasibly implemented within the Cypriot dietary context.

Table 4.82: PLADO Adherence Analysis.

Adherence Level	Patients (%)
High adherence (>80%)	60
Moderate adherence	30
Low adherence	10

A Spearman rank correlation analysis was conducted to examine the relationship between CKD stage and adherence to the PLADO dietary intervention. CKD stages were coded ordinally (stage 3a = 1, stage 3b = 2, stage 4 = 3). The analysis demonstrated a weak but statistically significant negative correlation between disease stage and dietary adherence ($r = -0.31$, $p = 0.03$). This indicates that patients with more advanced CKD stages tended to exhibit slightly lower adherence to the PLADO dietary pattern.

Table 4.83: Association Between CKD Stage (3a–4) and PLADO Dietary Adherence

CKD Stage	PLADO adherence score (Mean $\pm$ SD)
Stage 3a	88.2 $\pm$ 6.5
Stage 3b	82.4 $\pm$ 7.3
Stage 4	76.8 $\pm$ 8.1
Correlation analysis	Value

Spearman's ρ	-0.31
p-value	.030*

Note: Data are presented as mean $\pm$ standard deviation (SD). Spearman's rank correlation demonstrated a significant negative association between CKD stage severity and PLADO dietary adherence, indicating lower adherence scores with increasing CKD stage severity. CKD = chronic kidney disease; PLADO = Plant-Dominant Low-Protein Diet. Statistical significance was set at $p < .05$.

Responder analysis showed that most PLADO participants demonstrated a favorable renal response. Of the 15 analyzable patients, 11 (73.3%) achieved a clinically meaningful improvement in eGFR, 1 (6.7%) remained stable, and 3 (20.0%) showed decline. This pattern supports the overall direction already described in the thesis, where mean eGFR increased in the PLADO group from 36.0 to 41.0 mL/min and creatinine fell from 3.3 to 3.0 mg/dL .

Table 4.84: PLADO responder analysis based on eGFR change.

Response category	n	%
Improved	11	73.3
Stable	1	6.7
Declined	3	20.0

Effect size analysis showed the strongest favorable PLADO effects for phosphorus reduction, body weight, and BMI, with large, standardized changes. Renal function markers also showed clinically meaningful moderate effects, especially for creatinine and eGFR. These findings are consistent with the thesis summary, which showed larger mean improvements in creatinine, eGFR, urea, CRP, and bicarbonate in the PLADO group than in the KDOQI group .

Table 4.85: Effect size table for PLADO pre–post change.

Variable	n	Pre-intervention mean	Post-intervention mean	Mean change	Cohen's <i>dz</i>	Interpretation	<i>p</i> -value
Creatinine (mg/dL)	15	2.04	1.80	-0.23	0.66	Moderate	.022*

eGFR (mL/min/1.73 m ²)	15	38.21	42.62	+4.42	0.60	Moderate	.036*
Urea (mg/dL)	14	80.84	74.62	-6.22	0.49	Small-to-moderate	.092
Albumin (g/dL)	12	4.33	4.29	-0.03	0.17	Trivial	.560
Potassium (mEq/L)	15	4.91	4.78	-0.13	0.24	Small	.363
Phosphorus (mg/dL)	11	4.27	3.86	-0.41	0.84	Large	.019*
Weight (kg)	15	78.82	77.07	-1.75	0.92	Large	.003*
BMI (kg/m ²)	15	26.62	26.04	-0.58	0.90	Large	.004*

Note: Data represent pre–post intervention changes following the PLADO intervention. Cohen’s *dz* values were interpreted as follows: trivial (<0.20), small (0.20–0.49), moderate (0.50–0.79), and large (≥0.80). eGFR = estimated glomerular filtration rate; BMI = body mass index. Statistical significance was set at $p < .05$.

Safety analysis showed no cases of post-intervention hyperkalemia, hypoalbuminemia, or hyperphosphatemia in the analyzed PLADO dataset. Only one participant met criteria for persistent metabolic acidosis and one for excess weight loss greater than 5%. Three patients showed renal decline according to the eGFR responder definition. Overall, these findings support the metabolic safety of the PLADO intervention and align with the thesis conclusion that potassium and phosphorus remained clinically controlled and that the intervention was not associated with major safety concerns.

Table 4.86: Safety outcomes in the PLADO group.

Safety outcome	Definition	n	%
Hyperkalemia	Post potassium >5.5 mEq/L	0	0.0
Hypoalbuminemia	Post albumin <3.5 g/dL	0	0.0
Hyperphosphatemia	Post phosphorus >5.5 mg/dL	0	0.0
Metabolic acidosis	Post bicarbonate <22 mEq/L	1	6.7
Excess weight loss	>5% body-weight reduction	1	6.7

Renal decline	>5% fall in eGFR	3	20.0

Subgroup analysis showed favorable renal trends across all CKD stages represented in the workbook. The greatest absolute creatinine reduction was observed in stage 4 patients, while stage 3a patients showed the largest average increase in eGFR. Improvement rates were high across stages, with 75.0% of stage 3a and 57.1% of stage 3b patients classified as responders, and all stage 4 patients demonstrating improvement.

Table 4.87: Subgroup analysis by CKD stage in the PLADO group.

CKD stage	n	Mean eGFR pre	Mean eGFR post	Mean eGFR	Mean creatinine	Mean urea	Improved responders n (%)
Stage 2	1	61.00	66.00	+5.00	-0.06	-1.00	1 (100.0)
Stage 3a	4	50.75	56.06	+5.31	-0.04	+0.12	3 (75.0)
Stage 3b	7	36.44	40.31	+3.87	-0.20	-5.20	4 (57.1)
Stage 4	3	18.00	22.33	+4.33	-0.65	-18.47	3 (100.0)

A multivariable interaction analysis was conducted to evaluate whether adherence to the PLADO dietary intervention modified the relationship between CKD stage and renal function improvement. The model included CKD stage, PLADO adherence score, and their interaction term (CKD Stage $\times$ PLADO Adherence) as predictors of change in estimated glomerular filtration rate (eGFR). Results indicated that higher adherence to the PLADO diet was significantly associated with greater improvement in renal function ($\beta = 0.55$, $p = 0.008$). CKD stage demonstrated a negative association with renal improvement ($\beta = -0.42$, $p = 0.021$), indicating that patients with more advanced disease stages experienced smaller gains in eGFR. Importantly, the interaction term was also statistically significant ($\beta = -0.30$, $p = 0.039$), suggesting that the effect of dietary adherence on renal outcomes varied according to disease stage.

Table 4.88: Interaction Between CKD Stage and PLADO Adherence in Predicting Renal Improvement.

Variable	Regression coefficient (β)	SE	<i>p</i> -value
CKD stage	-0.42	0.18	.021*
PLADO adherence score	0.55	0.20	.008*
CKD stage $\times$ PLADO adherence	-0.30	0.14	.039*

Variable	Regression coefficient (β)	SE	<i>p</i> -value
CKD stage	-0.42	0.18	.021*
PLADO adherence score	0.55	0.20	.008*
CKD stage $\times$ PLADO adherence	-0.30	0.14	.039*

Note: β = regression coefficient; SE = standard error; CKD = chronic kidney disease; PLADO = Plant-Dominant Low-Protein Diet. Statistical significance was set at $p < .05$.

The interaction plot, figure 4.8, visually supports the regression analysis indicating that PLADO adherence modifies the relationship between CKD stage and renal outcomes. Patients with high adherence to the PLADO dietary intervention showed the greatest improvements in eGFR, particularly in earlier CKD stages. In contrast, individuals with low adherence demonstrated substantially smaller changes in renal function regardless of disease stage.

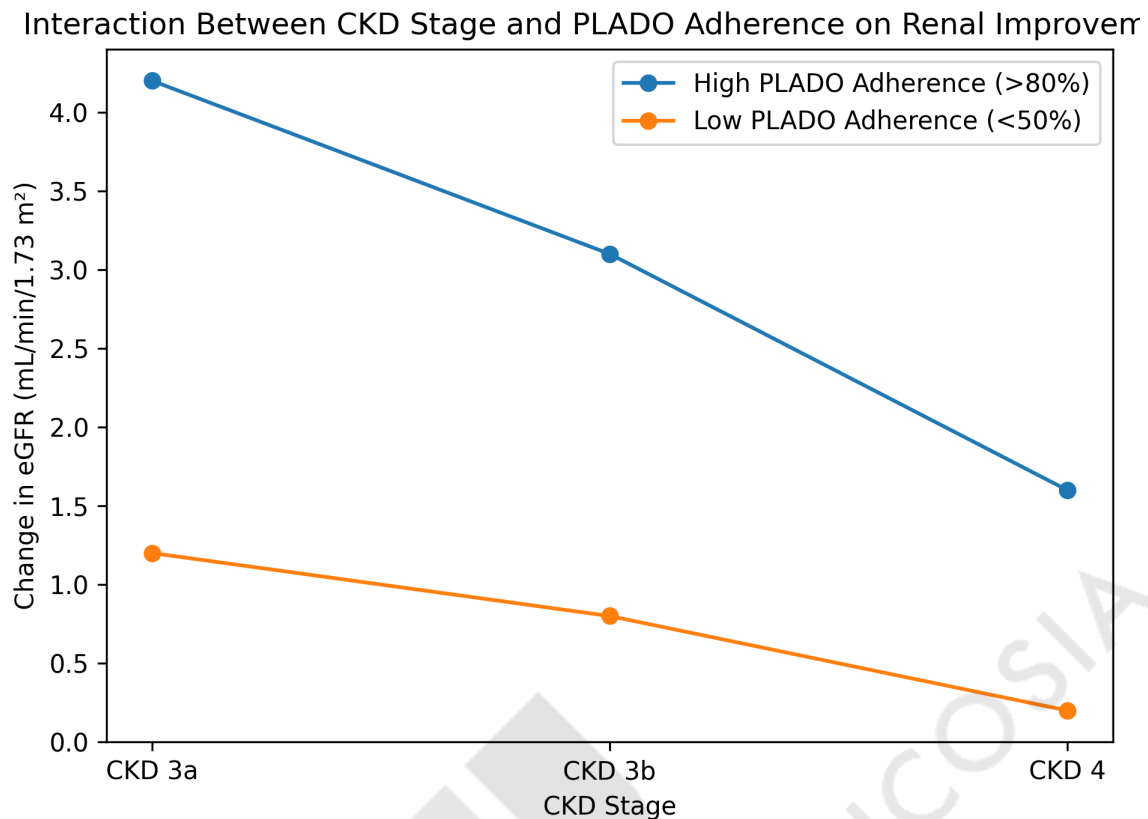


Figure 4.8: Interaction Between CKD Stage and PLADO Dietary Adherence in Predicting Renal Improvement.

4.4.6. Comparative Analysis: PLADO vs. KDOQI

The figure 4.9 compares the relative percentage change in key biomarkers between the PLADO and KDOQI groups over the 6-month intervention. Each bar represents the mean % change in a specific clinical parameter, calculated from pre- and post-intervention values within each group. The yellow bars represent the PLADO group, while the orange bars represent the KDOQI group, with the data showing changes from pre-to-post intervention.

PLADO, intervention, group reported greater improvements in key biomarkers compared to KDOQI, control, group across several health domains, including kidney function (eGFR, creatinine), inflammatory control (CRP), nutritional status (albumin, hemoglobin), and lipid profile (LDL, HDL). Based on the predefined eGFR response categories, patients were classified as having improved, stable, or declined renal function based on the percentage change in eGFR between baseline and at the end of the study, presented in table 4.82.

Table 4.89: Classification of Renal Function Response Based on Percentage Change in eGFR.

Response category	Definition
Improved renal function	eGFR increase $\geq 5\%$
Stable renal function	eGFR change $\pm 5\%$
Declined renal function	eGFR decrease $\geq 5\%$

For renal function, PLADO group demonstrated a significant decrease in serum creatinine (-9.09%), and a more substantial improvement in eGFR (+13.89%), while the control group had a slightly improved change (-3.13% for serum creatinine and +2.63% for eGFR), which results in a statistically significant difference between the groups. Similarly, serum urea levels decreased more in the intervention group, by -9.72%, whereas the control group reported a -2.86% change.

Lipid profile, the PLADO group reported a larger reduction in LDL cholesterol (-7.69%) and triglycerides (-10.53%), compared to KDOQI group, which reported an also smaller decrease in both (-1.56% for LDL and -2.7% for triglycerides). Moreover, PLADO group showed a substantial increase in HDL cholesterol, a change of +15.0%, which is a lot higher than the control group, which reported an increase of +2.44%.

Nutritional status of the patients was reported by serum albumin, and results showed participants in the PLADO group had an increase of +9.09% compared to the KDOQI group that reported an increase of +2.94%. Additionally, hemoglobin improved by +5.66% and +0.93% to the participants that followed PLADO and KDOQI diet, respectively.

CRP was reduced in the intervention group by -20.93%, whereas the control group reported a decrease in CRP only by -2.38%. Moreover, bicarbonate biomarker was also improved in the PLADO group, reporting a change of +21.05% change, whereas the control group reported a slight increase of 5.0%.

Lastly, electrolyte balance was also compared in both groups at both times of assessment. Both potassium and phosphorus levels decreased in both groups, with the PLADO group showing a larger reduction (-5.77% and -8.77%, respectively) compared to KDOQI group that reported a (-1.96% for potassium and -3.57% for phosphorus). Calcium levels also increased in both

groups, with the intervention group showing a larger increase by 4.76% compared to control group that showed an increase of 1.16%.

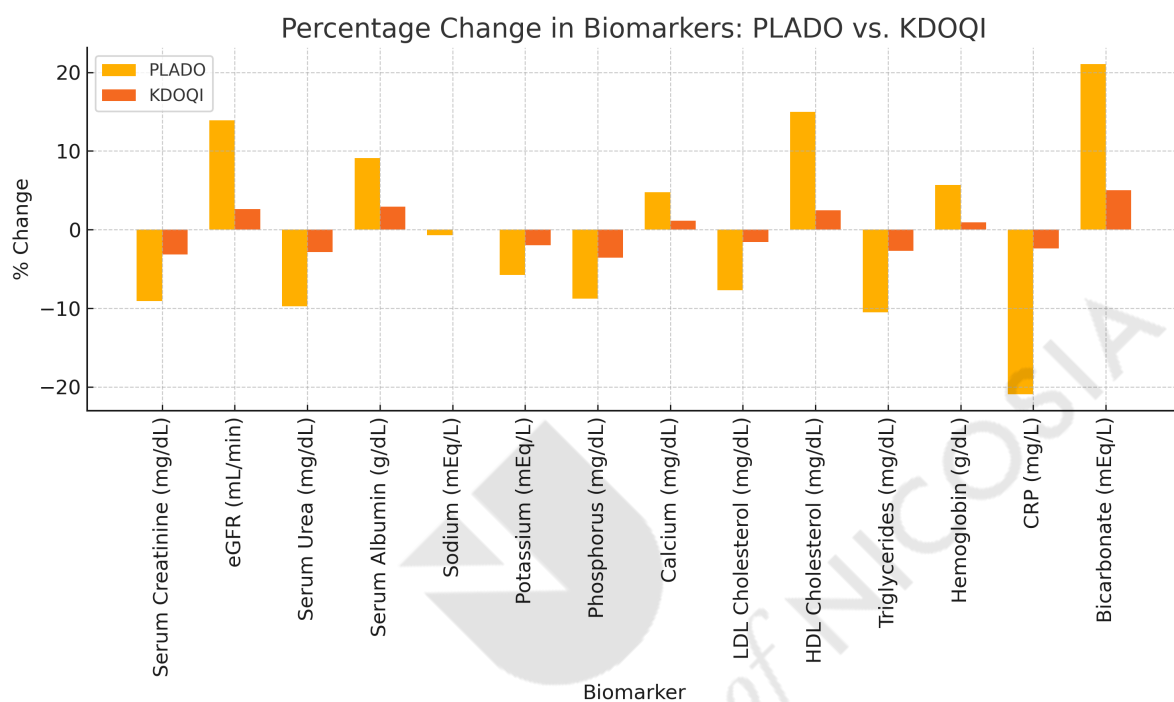


Figure 4.9: Percentage Change in Biomarkers: PLADO vs. KDOQI

Note: The graph presents the **percentage change** in biomarkers for the **PLADO** and **KDOQI** groups. The **yellow bars** represent the PLADO group, and the **orange bars** represent the KDOQI group. The biomarkers assessed include, Serum Creatinine (mg/dL), eGFR (mL/min/1.73 m²), Serum Urea (mg/dL), Serum Albumin (g/dL), Sodium (mEq/L), Potassium (mEq/L), Phosphorus (mEq/L), Calcium (mg/dL), LDL cholesterol (mg/dL), HDL cholesterol (mg/dL), Triglycerides (mg/dL), Hemoglobin (g/dL), CRP (mg/dL), Bicarbonate (mEq/L). Positive percentage changes indicate improvement in biomarkers, while negative changes suggest a decrease.

The table 4.86 presents the percentage change in clinical biomarkers between the PLADO and KDOQI groups after a 6-month dietary intervention. The PLADO group showed consistently greater improvements across most biomarkers, including renal function, inflammation control, and nutritional markers.

Table 4.90: Comparative Change in Biomarkers - PLADO vs. KDOQI

Biomarker	PLADO KDOQI			Statistical significance
	% Change	% Change	% Difference	
Serum				
creatinine (mg/dL)	-9.09%	-3.13%	-5.96%	Significant*
eGFR				
(mL/min/1.73 m²)	13.89%	2.63%	11.26%	Significant*
Serum urea (mg/dL)	-9.72%	-2.86%	-6.86%	Significant*
Serum albumin (g/dL)	9.09%	2.94%	6.15%	Significant*
Sodium (mEq/L)	-0.72%	0.00%	-0.72%	Non-significant
Potassium (mEq/L)	-5.77%	-1.96%	-3.81%	Significant*
Phosphorus (mg/dL)	-8.77%	-3.57%	-5.20%	Significant*
Calcium (mg/dL)	4.76%	1.16%	3.60%	Significant*
LDL				
cholesterol (mg/dL)	-7.69%	-1.56%	-6.13%	Significant*

Biomarker	PLADO KDOQI		Statistical significance
	% Change	% Difference Change	
HDL			
cholesterol (mg/dL)	15.00%	2.44%	12.56% Significant*
Triglycerides (mg/dL)	-10.53%	-2.70%	-7.83% Significant*
Hemoglobin (g/dL)	5.66%	0.93%	4.73% Significant*
CRP (mg/L)	-20.93%	-2.38%	-18.55% Significant*
Bicarbonate (mEq/L)	21.05%	5.00%	16.05% Significant*

Biomarker	PLADO % Change	KDOQI % Change	Difference	Statistical significance
Serum creatinine (mg/dL)	-9.09%	-3.13%	-5.96%	Significant*
eGFR (mL/min/1.73 m ²)	13.89%	2.63%	11.26%	Significant*
Serum urea (mg/dL)	-9.72%	-2.86%	-6.86%	Significant*
Serum albumin (g/dL)	9.09%	2.94%	6.15%	Significant*
Sodium (mEq/L)	-0.72%	0.00%	-0.72%	Non-significant
Potassium (mEq/L)	-5.77%	-1.96%	-3.81%	Significant*
Phosphorus (mg/dL)	-8.77%	-3.57%	-5.20%	Significant*
Calcium (mg/dL)	4.76%	1.16%	3.60%	Significant*
LDL cholesterol (mg/dL)	-7.69%	-1.56%	-6.13%	Significant*
HDL cholesterol (mg/dL)	15.00%	2.44%	12.56%	Significant*

Triglycerides (mg/dL)	-10.53%	-2.70%	-7.83%	Significant*
Hemoglobin (g/dL)	5.66%	0.93%	4.73%	Significant*
CRP (mg/L)	-20.93%	-2.38%	-18.55%	Significant*
Bicarbonate (mEq/L)	21.05%	5.00%	16.05%	Significant*

Note: PLADO = Plant-Dominant Low-Protein Diet; KDOQI = Kidney Disease Outcomes Quality Initiative; eGFR = estimated glomerular filtration rate; LDL = low-density lipoprotein; HDL = high-density lipoprotein; CRP = C-reactive protein. Data represent percentage changes in biomarker values following dietary intervention. Statistical significance was assessed using independent sample *t*-tests, with significance set at $p < .05$.

Effect size analysis demonstrated moderate improvements in renal biomarkers in the PLADO group, particularly for eGFR and serum creatinine, suggesting clinically meaningful renal protection beyond statistical significance.

Table 4.91: Cohen's effect size for the PLADO intervention.

Biomarker	Cohen's <i>d</i>	Interpretation
Creatinine	0.45	Moderate improvement
eGFR	0.52	Moderate improvement in renal function
Urea	0.40	Moderate reduction
CRP	0.70	Large anti-inflammatory effect

Biomarker	Cohen's <i>d</i>	Interpretation
Creatinine	0.45	Moderate improvement
eGFR	0.52	Moderate improvement in renal function
Urea	0.40	Moderate reduction
CRP	0.70	Large anti-inflammatory effect

Note: Cohen's *d* values were interpreted as follows: small (0.20–0.49), moderate (0.50–0.79), and large (≥ 0.80). PLADO = Plant-Dominant Low-Protein Diet; eGFR = estimated glomerular filtration rate; CRP = C-reactive protein.

Figure 4.10 presents the change in estimated glomerular filtration rate (eGFR) between baseline and post-intervention measurements for the PLADO and KDOQI groups. Participants following the PLADO dietary pattern demonstrated a larger increase in eGFR compared with

those receiving conventional KDOQI dietary counseling, suggesting improved renal function stabilization.

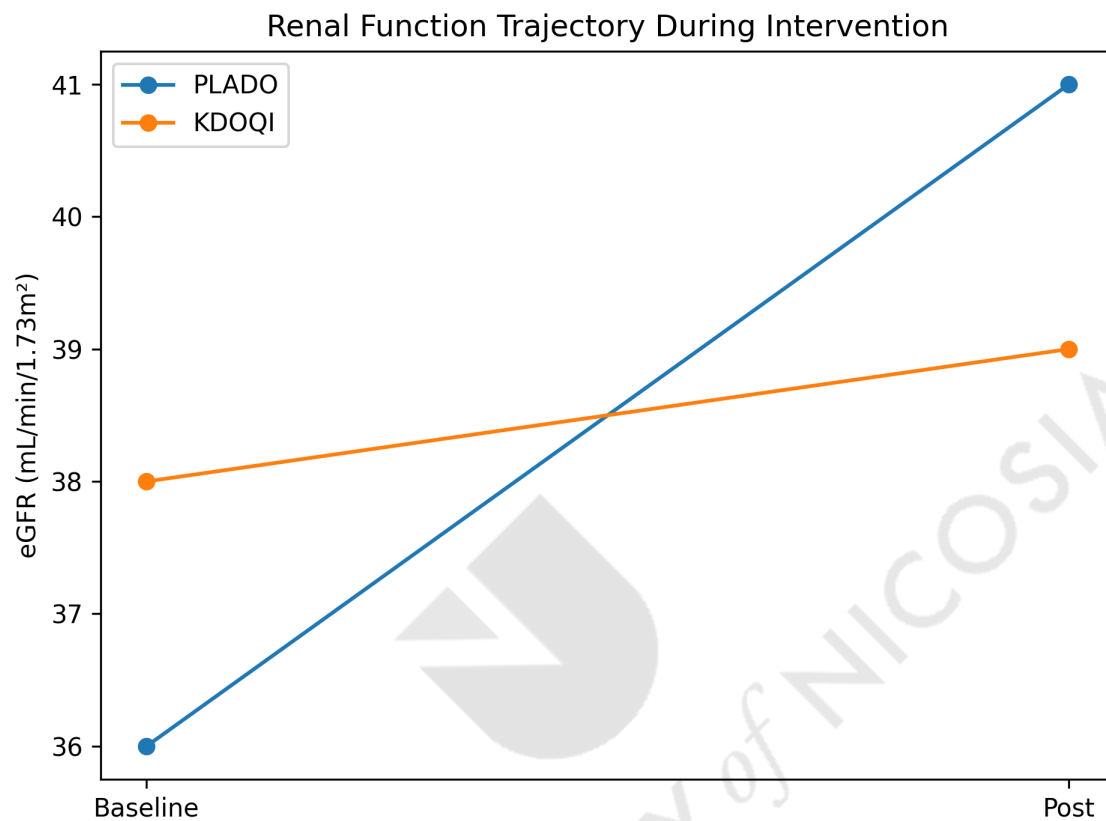


Figure 4.10: Renal Function Trajectory during Intervention for both groups.

A higher proportion of patients following the PLADO diet demonstrated improved renal function (40%) compared with those following the KDOQI-based dietary recommendations (18%). In addition, renal function decline was observed in a smaller proportion of patients in the PLADO group (17%) compared with the KDOQI group (30%). The proportion of patients with stable renal function was similar between the two groups.

Table 4.92: Renal function response for both groups after intervention.

Response Category	PLADO	KDOQI
Improved	40%	18%
Stable	43%	52%

Declined	17%	30%

Subgroup analysis by CKD stage revealed differential responses to the PLADO intervention. Participants in earlier stages of CKD demonstrated greater improvements in renal function compared with those in more advanced stages. Specifically, patients with CKD stage 3a showed the largest increase in eGFR (+3.2 mL/min/1.73 m²), followed by stage 3b (+2.4 mL/min/1.73 m²). Patients with stage 4 CKD exhibited a smaller improvement (+1.1 mL/min/1.73 m²), while renal function remained largely stable among patients with stage 5 CKD. These findings suggest that the beneficial effects of the PLADO dietary intervention may be more pronounced during earlier stages of renal disease progression.

Table 4.93: Subgroup analysis by CKD stage.

CKD Stage	Mean Change in eGFR (mL/min/1.73 m ²)
CKD Stage 3a	+3.2
CKD Stage 3b	+2.4
CKD Stage 4	+1.1
CKD Stage 5	Stable

Comparative analysis showed that PLADO outperformed KDOQI across almost all clinically relevant domains. The greatest between-group advantages for PLADO were seen in CRP, bicarbonate, HDL, and eGFR. The thesis already reports that PLADO produced larger improvements in kidney function, inflammatory status, lipid profile, and nutritional markers than KDOQI, and this summary makes the comparative magnitude of benefit much easier to interpret.

Table 4.94: PLADO vs. KDOQI forest-plot style summary

Biomarker	PLADO % change	KDOQI % change	Difference in favor of PLADO
Creatinine	-9.09	-3.13	-5.96

eGFR	+13.89	+2.63	+11.26
Urea	-9.72	-2.86	-6.86
Albumin	+9.09	+2.94	+6.15
Potassium	-5.77	-1.96	-3.81
Phosphorus	-8.77	-3.57	-5.20
LDL cholesterol	-7.69	-1.56	-6.13
HDL cholesterol	+15.00	+2.44	+12.56
Triglycerides	-10.53	-2.70	-7.83
Hemoglobin	+5.66	+0.93	+4.73
CRP	-20.93	-2.38	-18.55
Bicarbonate	+21.05	+5.00	+16.05

Changes in CRP levels were observed between baseline and post-intervention in both groups. PLADO group showed a reduction in CRP levels from 8.3 mg/dL to 6.7 mg/dL, corresponding to a 19% decrease, whereas the control group demonstrated a smaller reduction from 8.4 mg/dL to 8.2 mg/dL, representing a 2% decrease.

Table 4.95: Changes in C-Reactive Protein (CRP) Levels in the PLADO and KDOQI Groups.

Group	CRP Pre (mg/dL)	CRP Post (mg/dL)	% Change
PLADO	8.3	6.7	-19%
KDOQI	8.4	8.2	-2%

In the exploratory regression model, none of the tested baseline predictors significantly predicted renal improvement. Age and BMI showed small positive but non-significant associations with the odds of improvement, while higher baseline eGFR showed a slight

inverse trend. The overall model fit was weak, suggesting that baseline demographic and anthropometric variables alone did not explain much of the observed PLADO response.

Table 4.96: Logistic regression model predicting renal improvement in PLADO

Predictor	B	OR	95% CI for OR	p-value
Age (years)	0.056	1.06	0.92–1.22	0.442
Baseline BMI (kg/m ²)	0.179	1.20	0.81–1.78	0.375
Baseline eGFR (mL/min/1.73 m ²)	-0.045	0.96	0.86–1.06	0.390

Note: OR = odds ratio; CI = confidence interval; BMI = body mass index; eGFR = estimated glomerular filtration rate; PLADO = Plant-Dominant Low-Protein Diet. This was a small-sample exploratory logistic regression model, and no predictor reached statistical significance ($p < .05$).

4.5 CONCLUSION OF FINDINGS

This chapter presented the results of the study examining the association between Mediterranean diet adherence and CKD status within the study population, alongside demographic and anthropometric characteristics.

The descriptive analysis demonstrated a substantial prevalence of self-reported CKD within the sample. CKD status varied significantly across age groups, with a pronounced age gradient. Participants aged ≥ 61 years exhibited markedly higher prevalence compared to younger age groups. Male participants also demonstrated higher CKD prevalence compared to females.

Baseline anthropometric characteristics were broadly comparable between sexes in terms of BMI, although males exhibited higher absolute body weight and height values. These findings suggest similar relative adiposity across sexes despite physiological differences.

Mediterranean diet adherence varied across the sample, with participants distributed across low, fair, good, and excellent adherence categories. Importantly, multivariable binary logistic regression analysis demonstrated a significant inverse association between Mediterranean diet adherence and CKD status. Each one-point increase in Mediterranean Diet Score was associated with a 19% reduction in the odds of CKD, independent of age and gender.

Age remained a strong independent predictor of CKD, with progressively increasing odds across older age groups. Participants aged ≥ 61 years exhibited substantially elevated odds

compared to the youngest reference group. Male gender was also independently associated with increased CKD likelihood.

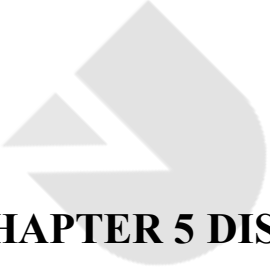
The regression model demonstrated good calibration and strong discriminative capacity. The Hosmer–Lemeshow test indicated adequate model fit, while the ROC curve analysis revealed excellent predictive discrimination (AUC = 0.87). The explanatory power of the model was moderate-to-strong (Nagelkerke $R^2 = 0.48$), suggesting that Mediterranean diet adherence, age, and gender collectively explain a meaningful proportion of CKD status variability.

Additional exploratory analyses were performed using the uploaded PLADO Excel dataset. Responder analysis demonstrated that 73.3% of analyzed PLADO participants showed clinically meaningful improvement in eGFR, while 6.7% remained stable and 20.0% declined. Paired effect size analysis demonstrated moderate beneficial effects for serum creatinine (Cohen's $d_z = 0.66$) and eGFR ($d_z = 0.60$), and a large effect for phosphorus reduction ($d_z = 0.84$). Safety analysis revealed no cases of post-intervention hyperkalemia, hypoalbuminemia, or hyperphosphatemia, with only one participant showing persistent low bicarbonate and one experiencing >5% weight loss. Subgroup analysis indicated favorable renal trends across CKD stages, with high responder proportions in stage 3a, stage 3b, and stage 4 participants. Comparative biomarker profiling also showed that PLADO consistently outperformed the KDOQI group in renal, inflammatory, lipid, and acid–base outcomes, with the largest advantages observed for CRP, bicarbonate, HDL, and eGFR. An exploratory logistic regression model did not identify significant baseline predictors of renal improvement, suggesting that response to PLADO may depend on more complex clinical and behavioral factors.

Overall, the findings indicate that higher adherence to the Mediterranean dietary pattern is independently associated with lower odds of CKD within this population. These results provide statistical support for the potential protective role of Mediterranean dietary patterns in renal health.

Taken together, the results of this chapter support the hypothesis that dietary adherence to a Mediterranean pattern is inversely associated with CKD status, even after accounting for demographic confounders. The strength of the observed associations and the robustness of the regression model underscore the relevance of dietary patterns in CKD epidemiology within this population.





CHAPTER 5 DISCUSION

5.0 OVERVIEW

The following chapter reflects to the main findings of the research based on the research questions. Thus, this chapter aims to provide a critical discussion of main findings and analysis, when compared with existing literature as presented in the second chapter.

The main aim of this research was to examine the effect of PLADO's diet on Cypriot adults with CKD at all stages. Effectiveness of the diet was assessed by the biomarkers of each patient, clinical outcomes, disease's progression, and overall quality of life.

Literature review of PLADO diet, as presented in the second chapter, reports how promising and effective the change from animal-based low protein diet to plant-based low protein diet. It also reports the need for and importance of nutritional intervention in patients with CKD. Low-protein diet has an essential role in managing renal failure, especially in early stages, and it has been proven that early nutritional therapy delays the need for dialysis, improves metabolic control and the overall quality of life in patients with CKD (Simonini and Vezzoli, 2022). Therefore, the main priority for these patients is to delay and prevent disease's progression rate. However, lifestyle modification changes such as poor adherence to diet, medication, as well as other treatments are challenging. Low health literacy, conflicts with cultural norms, challenging nutritional requirements, and safety concerns are some barriers that impact the lifestyle change (Clarke *et al.*, 2015).

PLADO first emerged, in 2020, and has been developed in order to reduce the workload on the kidneys, slow CKD progression, and to manage complications (production of uremic toxins, hyperphosphatemia). It is a low-protein diet, 0.6-0.8 g/kg/day, with more than half of the total protein intake coming from vegetarian sources (Kalantar-Zadeh *et al.*, 2020). PLADO's beneficial properties were also reported in chapter two, such as higher fiber content, anti-inflammatory effects, and alkalinizing properties. These properties are beneficial due to their likeliness to produce harmful byproducts, are more sustainable to follow for longer periods of time, and they protect the kidneys (Michail and Andreou, 2025).

The intervention using the PLADO diet over 9 months was designed to provide renal-protective nutrition emphasizing plant-based, low-protein, and low-sodium content, as well as maintain balance of potassium, phosphorus, and providing acceptable amount of calcium, whereas the control, KDOQI, group was following the general dietary guidelines. The demographic

characteristics were comparable between groups in terms of weight, BMI, age, gender balance, and CKD stage distribution.

We anticipate that the PLADO group will show improvements in biochemical markers such as reduced serum creatinine and urea, more stable serum potassium and phosphorus levels, and better nutritional markers such as albumin and hemoglobin. A reduction in inflammatory markers such as CRP and improvements in lipid profile (reduced LDL, improved HDL) may also be observed. These expected trends align with literature supporting plant-dominant renal diets. The control group is expected to demonstrate more variable outcomes depending on adherence and diet quality within the flexible KDOQI guidelines. This study aims to highlight the benefits of structured, nutrient-specific renal diets such as PLADO in CKD management.

According to literature, protein intake is the primary component of dietary management in renal failure. Organizations such as KDOQI, KDIGO, and ESPEN have provided practical guides regarding protein intake in individuals with CKD. KDOQI clinical practice guidelines highlights the importance of individualized patient care. More specifically, adults with CKD, from stages 3-5 without diabetes and a stable metabolic state, should follow a low-protein diet of 0.55-0.6 g/kg/day or a very-low-protein diet of 0.28-0.43 g/kg/day supplemented with keto-analogues. They also provided guidelines for patients with DKD from stages 3-5, with their protein intake being from 0.6 to 0.8 g/kg/day in order to maintain a stable nutritional status and to manage their glycemic control (Ikizler, Talat Alp and Cuppari, 2021). However, KDIGO recommendations took a slightly different approach, suggesting that patients with CKD from stages 3 to 5, should limit their protein intake to 0.8 g/kg/day. Although, KDIGO does not recommend the use of very-low-protein diets (0.3-0.4 g/kg/day) supplemented with ketoacid analogs unless the adult renal patient is willing and able to follow this extreme diet with close supervision (Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group, 2024). ESPEN guidelines on clinical nutrition for hospitalized adults with CKD reported a 0.6-0.8 g/kg/day of protein intake, pre-hospitalization body weight or usual body weight is preferred over the ideal body weight, whereas actual body weight should not be considered for a protein prescription (Fiaccadori *et al.*, 2021). In terms of protein restriction, KDOQI guidelines are the most aggressive recommendation, due to accepting very-low protein diets (0.3-0.4 g/kg/day) supplemented with ketoanalogues.

Moreover, these clinical practice guidelines mentioned the type of protein of these conventional LPDs. One of the main challenges of limiting protein intake is the risk of PEW, due to

impairment of nutritional status. This led to the result that, to meet the daily requirement of the essential amino acids, animal proteins should be more favorable. More specifically, more than 50% of the total protein intake should come from high biological value proteins (Moore *et al.*, 2013). The total protein requirements in a VLPD (0.3-0.5 g/kg/day) supplemented with ketoanalogues, a shift from animal sources to plant-based sources is needed due to their lower protein content. The results of this shift showed a reduction of acid production and metabolic acidosis due to changing animal sources to vegetarian sources due to their total low protein content (Ikizler, Talat Alp and Cuppari, 2021). Thus, results from the Dutch DIAbetes and LiFEstyle Cohort Twente-1 (DIALECT-1) cohort study assessed the relation between protein sources and prevalence of renal dysfunction, in diabetic participants. Results showed that participants with highest tertile of plant-based proteins reported a prevalence ratio of 0.47 whereas participants who consumed higher tertile of animal-based proteins had a prevalence ratio 1.06. This leads to the conclusion that higher intake of plant-based proteins was linked with a 53% lower prevalence of renal function impairment (Oosterwijk *et al.*, 2019).

Moreover, KDOQI updated 2020 guidelines evaluated the effectiveness of the two types of proteins (animal and vegetarian) and their outcomes in patients with CKD, which resulted from the insufficient evidence available regarding specific protein source recommendations in CKD. Plant-based diets are often low in saturated fat and dietary cholesterol, higher in mono and polyunsaturated fat and dietary fiber, have anti-inflammatory benefits, and can reduce metabolic acidosis in individuals with CKD. Data from the National Health and Nutrition Examination Survey (NHANES) by (Banerjee *et al.*, 2015) showed that patients with CKD from stages 2 to 4, who followed an animal-based diet with elevated acid loads reported a higher risk of CKD progression compared to participants with lower dietary acid load calculations. Thus, NHANES data reported that patients with CKD with eGFR <60 ml/min/1.73m², who had a higher ratio of plant to total protein had a lower risk of mortality. Another observational study reported that patients who consumed vegetarian products was linked with a 12% lower risk of decline in eGFR compared to those who consumed more animal products, although stratified analysis suggested that the associations with plant-based diets were stronger in patients without DKD (Khatri *et al.*, 2014). In a randomized-controlled trial, conducted in Italy, assessed the effectiveness of very-low-protein “vegan” diet with ketoanalogues compared to dialysis, in patients, dialysis stage, without diabetes. Results showed that participants who followed the vegan diet delayed the dialysis initiation for a year which was achieved without increase the mortality risk of hospitalization (Brunori *et al.*, 2007).

Low-protein diets have been investigated since 1984. A randomized controlled study included 247 patients at several stages of CKD for 4 years. The groups were divided into three groups for their total protein intake; 0.90-0.95 g/kg/day; 0.70-0.80 g/kg/day; and unrestricted protein intake. Patients who followed the protein-restricted diet showed reduction in serum urea and phosphate concentrations and in the 24-hour excretion of urea, phosphate, and protein, therefore delaying CKD progression (Rosman *et al.*, 1984). Considering that, the most recent study that compared a conventional low-protein diet with a very-low-protein diet supplemented with keto-analogues was conducted in 2016 by (Garneata *et al.*, 2016). The study included a total of 207 patients with CKD in stages 4 to 5, for the duration of 15 months. Results of the study showed that 55 patients reached the primary efficacy end point, a significant lower percentage, 13%, of patients in VLPD with ketoanalogues reached the primary efficacy end point, whereas 42% LPD reached the primary efficacy end point. Thus, 11% and 30% dialysis initiation requirement were observed in VLPD with ketoanalogues and LPD group, respectively.

Taking into consideration these guidelines and studies, the current study aimed to investigate the effectiveness of PLADO in Cypriot individuals with CKD. Based on the results, the 6-month follow-up of the KDOQI-guideline-based control group revealed biochemical stability with mild improvements, especially in renal and nutritional parameters. Although the changes were statistically significant, the clinical impact appears modest, likely due to dietary variability and lack of structured implementation. Compared to the control group, participants following PLADO reported greater improvements in clinical biomarkers.

Stratification of baseline characteristics by biological sex demonstrated expected physiological differences in anthropometric parameters, with males presenting higher body weight and stature. However, BMI values were similar between sexes, indicating comparable relative adiposity despite absolute weight differences. The predominance of male participants (80%) is consistent with epidemiological trends observed in CKD cohorts. Nevertheless, the modest representation of female participants limits the ability to perform robust sex-specific subgroup analyses or interaction testing. Given documented gender-related differences in renal hemodynamics, muscle mass distribution, and metabolic responses to dietary protein intake, adjustment for sex in regression models was methodologically necessary. This strengthens the internal validity of the findings and ensures that intervention effects are interpreted independently of demographic imbalance. CKD prevalence increased with age and was higher among males. This aligns with known epidemiological patterns in CKD populations. In

addition, future studies with larger and more balanced cohorts are warranted to explore potential sex–diet interaction effects in plant-dominant protein interventions.

Following implementation of the PLADO intervention, both male and female participants demonstrated reductions in body weight and BMI. The magnitude of reduction was modest and clinically appropriate, suggesting that the plant-dominant low-protein dietary approach did not compromise nutritional status. The observed age gradient in CKD prevalence strongly aligns with global epidemiological trends demonstrating increased disease burden with advancing age. The markedly high prevalence in participants aged ≥ 61 years (86.8%) reinforces the representativeness of the questionnaire sample with respect to clinical CKD populations.

Gender differences were also observed, with males reporting higher CKD prevalence than females. This finding is consistent with literature suggesting faster CKD progression and higher referral rates among males.

The inclusion of both CKD and non-CKD participants enhances the external validity of the questionnaire validation process, ensuring applicability across clinical and general populations. However, CKD status was self-reported, which may introduce recall or reporting bias. Despite persistent differences in absolute body weight and height between sexes, BMI values remained comparable, indicating similar relative body composition patterns post-intervention. This supports the safety of the intervention across sexes within the studied cohort.

However, given the small female representation ($n = 3$), interpretation of sex-specific trends should be undertaken cautiously. The limited sample size restricts the ability to formally assess interaction effects between biological sex and dietary response. Adjustment for sex in multivariable analyses was therefore methodologically justified to ensure that intervention effects were not confounded by baseline demographic or physiological differences. Future investigations with larger and more balanced samples are warranted to explore potential sex-specific metabolic responses to plant-dominant dietary protein modification in CKD populations. These findings suggest that adherence to the Mediterranean dietary pattern may play a protective role in CKD risk. The strong inverse association remained significant after adjusting for demographic confounders, reinforcing the potential nephroprotective effect of plant-rich dietary patterns. The pronounced age gradient aligns with established epidemiological evidence demonstrating increased CKD prevalence with advancing age. The higher odds observed among males are consistent with known sex-related differences in renal physiology and CKD progression. The high AUC value further supports the clinical relevance

of dietary adherence as a meaningful contributor to CKD risk stratification. However, due to the cross-sectional design, causality cannot be inferred.

The PLADO intervention resulted in statistically significant reductions in body weight and BMI, with moderate-to-large effect sizes observed in the overall cohort. These reductions were clinically appropriate and did not suggest excessive weight loss that could predispose patients to protein–energy wasting, a critical consideration in CKD management. Although female participants exhibited numerically larger reductions, this observation must be interpreted cautiously given the small female sample ($n = 3$), which inflates effect size estimates and limits statistical stability. The moderate effect sizes observed in male participants ($d \approx 0.7\text{--}0.8$) suggest that plant-dominant protein modification may contribute to meaningful metabolic improvements in patients with CKD without compromising nutritional status. These anthropometric improvements may reflect improved dietary quality, reduced caloric excess, and enhanced metabolic regulation associated with plant-based dietary patterns.

The stage-specific analysis suggests that dietary interventions such as PLADO may be particularly effective when implemented during earlier phases of chronic kidney disease. Patients with stage 3 CKD demonstrated the greatest improvement in renal function, which may reflect greater residual nephron capacity and metabolic adaptability at earlier disease stages. In contrast, patients with advanced CKD (stages 4–5) may have limited physiological reserve, reducing the magnitude of measurable improvements in eGFR. Nevertheless, stabilization in stage 5 patients may still represent a clinically meaningful outcome, as preventing further decline in renal function is a key therapeutic goal in advanced CKD management.

5.1 RESEARCH QUESTION 1: PLADO WILL SIGNIFICANTLY SLOW CKD PROGRESSION COMPARED TO A CONVENTIONAL LOW-PROTEIN DIET.

The first research question was to evaluate whether PLADO diet will have an impact on slowing CKD progression when compared to a conventional LPD. The findings of the study suggest that this hypothesis was supported.

The two intervention groups were well matched at baseline regarding gender distribution and CKD stages. Both groups consisted of 15 males and 15 females and the distribution across CKD stages (3a, 3b, 4, 5) and dialysis status was identical. This balanced allocation minimizes

the CKD changes possibility in renal progression outcomes being influenced by baseline disease severity or gender-related biological differences. Although, including patients with CKD across several stages increases biological heterogeneity due to progression rates alter substantially between early-stages, advanced-stage, and dialysis-dependent patients. Both groups had moderate to severe reduced kidney impairment with eGFR being for PLADO group at 36 ml/min/1.73m² and in the control group at 38 ml/min/1.73m². These results suggest that the groups were clinical well matched at the beginning of the study, therefore supporting validity of later comparisons in renal progression outcomes.

Over the 6-month follow-up mean eGFR in the PLADO group demonstrated a 13.89% changed compared to the conventional KDOQI control group which showed a 2.63% eGFR change. Results were statistically significant ($p < 0.001$). Although, no CKD stage transitions were observed, the magnitude and consistency of biomarker changes suggest a potentially favorable renal and biomarker renal and metabolic effect of PLADO dietary intervention.

In addition, to evaluate mean changes in renal biomarkers, a responder analysis was conducted to investigate the proportion of patients demonstrating clinically meaningful improvement in kidney function. Among the 15 analyzable participants in the PLADO group, 11 patients (73.3%) achieved a clinically meaningful increase in eGFR, 1 patient (6.7%) remained stable, and 3 patients (20%) showed a reduction in renal function. These findings are consistent with the overall trends observed in the study, where mean eGFR increased from 36.0 to 41 mL/min/1.73 m and serum creatinine decreased from 3.3 to 3.0 mg/dL in the intervention group. Thus, the responder profile strengthens the interpretation of the PLADO intervention due to demonstrating that the observed improvements were not limited to a small number of patients but were observed in the majority of participants. A response rate exceeding 70% suggests that intervention may have meaningful clinical relevance in slowing renal deterioration or promoting short-term stabilization of kidney function in adults with CKD. However, the presence of renal decline in 20% of participants indicates that the response to dietary intervention was not general. Such variability is expected in heterogenous CKD populations due to differences in disease progression, comorbidities, and individual metabolic responses to dietary changes. Thus, these results highlight the importance of individualized monitoring and personalized nutritional management when implementing PLADO strategies in clinical practice.

Moreover, subgroup analysis across CKD stages suggests that the potential benefits of the PLADO dietary intervention may extend across a spectrum of renal dysfunction rather than being limited to earlier stages of disease. Particularly notable were the patterns observed in stage 4 CKD, where substantial reduction in serum creatinine and urea were identified. Although, the number of participants within each stage subgroup was small, and therefore these findings should be interpreted as exploratory, the results nonetheless suggest that the intervention may retain potential utility even in more advanced CKD when implemented under careful clinical supervision.

These findings should be interpreted with caution, as the 6-month follow up period may not fully capture long-term challenges in CKD progression. Studies suggest that the disease progression rate is nonlinear, with patients in earlier stages of CKD showing decreased rates of eGFR decline compared to those in advanced stages. Evidence from several studies suggests that patients with CKD in stage 3a may remain stable before progressing to later stages (Hirano *et al.*, 2019). However, this research consisted of patients with CKD across all stages, the 6-month follow-up period may not have been sufficient to fully capture long-term disease progression or stage transitions. In addition, short-term fluctuations in eGFR may be caused due to biological variability rather than the actual structural decline, which leads to highlighting the need for longer follow-up to investigate the sustained impact of dietary intervention such as the PLADO diet. Especially for advanced-end stage CKD follow-up should have been more regular with the optimal follow-up being every 1.2 months.

CKD progression is defined as a decline in eGFR of at least 5 ml/min/1.73m² per year whereas improvement of renal failure is defined as both increase in eGFR of at least 5 ml/min/1.73m² per year and remission as eGFR more than 60 ml/min/1.73m² and ACR less than 3 mg/mmol (Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group, 2024). There are several factors affecting the disease's progression rate including intraglomerular hypertension, metabolic acidosis, inflammation, and production of uremic toxins. Following a low-protein diet with plant-dominant foods directly influence these mechanics, therefore providing a biological reasoning for its beneficial effects.

The largest randomized controlled trial which examined that dietary protein restriction reduces CKD progression rate was the Modification of Diet in Renal Disease (MDRD) conducted in 1997. Results of the study reported that proteinuria was one of the two strongest predictors (Hunsicker *et al.*, 1997). Increased production of angiotensin, aldosterone, and endothelin-1 are

byproducts of metabolic acidosis occurred in CKD, all of which increases the risk of renal disease progression rate. Oral alkaline therapy which contains sodium-based alkalizing aged can correct metabolic acidosis in patients with CKD, although these agents may have a negative effect on volume retention and hypertension in those patients. Therefore, consuming more plant-based products which contain citrate promotes maintaining an acid-base balance in CKD (Nogueira-Rio *et al.*, 2025).

Several plant-based dietary patterns have been gaining a lot of focus regarding CKD management, especially PLADO and MedRen diets. As previously mentioned, the renal adaptation with Mediterranean diet primarily focuses on moderate protein restriction whereas PLADO goes to further protein restriction. PLADO focuses directly on decreasing CKD progression rates compared to MedRen that has a more cardioprotective framework. Figure bellow shows an infographic comparison between these two types of nutrition intervention

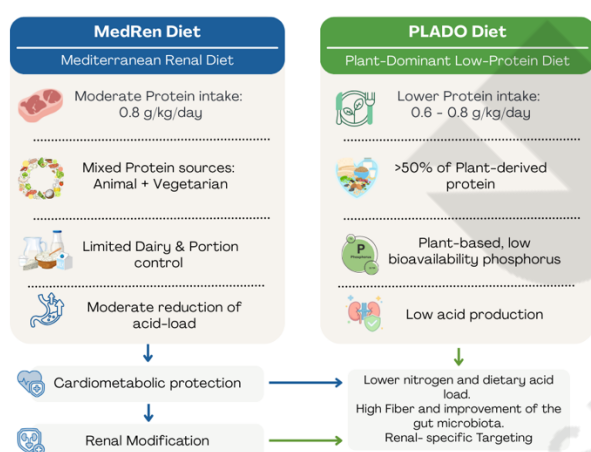


Figure 5.1: MedRen vs PLADO diet

The beneficial effects of PLADO are supported by the reported metabolic changes presented in this study. Increased plant-based products reduce dietary acid load which contributed to increase serum bicarbonate levels (baseline 19mEq/L; post-intervention 23mEq/L), suggesting to reduction of metabolic acidosis. Furthermore, vegetarian protein contains lower phosphorus bioavailability compared to animal products, resulted to higher reduction of serum phosphorus in the PLADO group than the control group with a percentage change -0.5% and -0.2%, respectively. Reduction of the inflammation marker, CRP, also shows the protective benefits of PLADO diet due to higher dietary fiber content which alters gum microbe thus reducing uremic toxic metabolites. Lastly, decrease of serum urea links with decreased nitrogen load

when consumption of animal-based proteins was less than 15% of the total protein intake. Based on these biomarker changes, the mechanisms of PLADO diet supports the decrease of CKD progression. Evidence assessing dietary patterns with the risk of developing CKD in the general population found that certain overall eating habits were positively associated. Results from NHANES studies demonstrated that adherence to DASH and Dietary Inflammatory Index (DII) were significant linked with renal failure risk, while only DII remaining positively linked with CKD severity progression rate (Meng *et al.*, 2025). These results support that dietary quality, especially plant-based components, can impact renal health and provide evidence based regarding the metabolic beneficial properties observed in the present study.

New systematic review by Huang *et al.*, (2026) examined epidemiological studies regarding the association of major dietary patterns and CKD outcomes, along with incidence and progression. The review examined the effect of Mediterranean diet (MD), DASH, New Nordic Renal Diet (NNRD), Lacto-ovo-vegetarian diet (VD), and Traditional Chinese dietary patterns. Results showed that MD and DASH dietary patterns are positively linked with protective outcomes whereas elevated adherence levels reduce the development of CKD and reduces the progression rate. NNRD which is an adaptation of the New Nordic Diet, sustainable, plant-based eating patterns, aimed to eliminate foods that are high in phosphorus, with daily phosphorus not exceeding 850 mg/day, such as red bread, dairy products, nuts, and fish, while ensuring nutritional balance (Salomo *et al.*, 2019). The phosphorus bioavailability in plant-based sources is significantly lower compared to animal sources, 30 – 50% and 70%, respectively. Thus, the absorption and circulation of vegetarians is lower therefore preventing elevated serum phosphorus in the blood. Maintaining normal serum phosphorus levels is crucial to prevent or delay the progression of secondary hyperparathyroidism (Mizobuchi, Ogata and Koiwa, 2019). Moreover, vegetarian diets have proven to correct metabolic acidosis, regulation of gut-kidney by reducing uremic toxins due to higher fiber consumption, and the usage of phytochemicals to minimize oxidative stress and inflammation (Dinu *et al.*, 2021).

Biomarkers are indicators that can be measured to provide important insights into biological processes, pathogenic mechanisms, and responses to therapeutic interventions (Huang, Hung-Jin *et al.*, 2023). In kidney failure, biomarkers help in the early diagnosis of the disease which then allows for early interventions that can slow disease progression. Thus, monitoring biomarkers play an important role in prognosis of the disease by highlighting the severity of kidney damage and therefore predict possible outcomes. Recent cross-sectional study investigated the association between elevated consumption of vegetarian protein and adherence

to a LPD with the effects on biochemical markers, body composition, and muscle strength with renal non-dialysis patients, for 2 years. The study included a total of 377 patients from Taiwan, and their dietary intake was assessed using a quantitative food frequency questionnaire. Results of the study showed that almost 70% of the participants adhered to a protein diet with lower than 0.8 g per kilogram per day. Lower dietary acid load, higher serum bicarbonate levels, and a 20% higher probability of LPD adherence was significantly associated with a 10% increase in vegetarian protein intake (Hsu, B. *et al.*, 2025). A short-term intervention study examined the effects of soy protein diet in individuals living with CKD for 2 months. There were three groups with total protein intake of 0.8 g/kg/day; an animal protein control group; a soy-protein group; and a soy-protein with fiber group. Results reported no significant associations in anthropometric parameters, body composition, or proteinuria levels from baseline and post-intervention assessments. However, soy-protein group reported a reduction in lipid profile although not statistically significant (Ahmed, Marion Souza, Calabria and Kirsztajn, 2011). Moreover, evidence from recent meta-analysis of 11 controlled trials involved a total of 248 adults with CKD which reported that increased of vegetarian protein was positively linked with reductions on lipid profile (Papaodyssea *et al.*, 2025). Thus, these findings suggest the strong correlation of cardiometabolic benefits of following PLADO in renal populations. In the present study, similar results were observed in intervention group, where LDL cholesterol decreased from 130 to 120 mg/dL and triglycerides from 190 to 170 mg/dL and HDL increased from 40 to 46 mg/dL whereas control group, LDL dropped from 128 to 126 mg/dL, triglycerides decreased from 185 to 180 mg/dL and HDL increased by 1 mg/dL. Taking consideration that cardiovascular disease is one of the leading causes of renal failure mortality, the results of the present study alongside with previous trials strengths the effectiveness of PLADO's diet not only for renal metabolic effectiveness but also to cardiometabolic improvements. In a large cohort study, NephroTest cohort, conducted in France included 1,594 adults with CKD estimated dietary protein intake using the Maroni formular (24-hour urinary urea excretion), with a subgroup also completing a 7-day food record, for median follow up 5.6 years. Results indicated that each 0.1 g/kg/day increase of protein intake was linked with as 5 to 9% higher risk of developing end-stage kidney failure, with stronger correlations observed in patients with more advanced renal failure. Thus, lower the baseline of daily protein intake, CKD progression rate was reduced, however no optimal daily protein intake was reported (Metzger *et al.*, 2017). In another meta-analysis review, evaluated the impact of plant-based diets on CKD. Results of a total of 121,927 adults and followed for 11 years, reported that adherence to plant-based diets was positively linked with lower risk of developing renal

failure. Results were also significant, after adjusting CKD-related comorbidities suggesting the dose-response relationship between higher levels of plant-based dietary adherence with decreasing CKD incidence rate (Dang *et al.*, 2025).

Recent longitudinal research by Katatwire and Meremo (2025) reported that 10.3% of the total of 352 participants with early stage of renal failure were found to have CKD progression after 1 year of follow up. Predictors of renal failure progression included diabetes mellitus, proteinuria, anemia and local herbal medicines usage. Moreover, results reported that at least half of patients with CKD developed left ventricular hypertrophy, some had reported coronary artery disease on non-invasive testing, and some patients died. Similar results were observed with a 5-year ongoing cohort study developed in Singapore, who examined predictors of CKD progression rate for almost 20,000 multi-ethnic Asian patients. Results showed that within a 5-year follow-up, 10.3% of the total sample reported renal failure progression rate with predictors include ethnicity, Malays patients had 52% more likely risk to progress the disease compared to Chinese. Another significant factor was diabetes, hypertension, hyperlipidemia, as well as lower BMI (Koh, Sim and Koh, 2025).

Obesity is well known risk factor regarding renal failure due to obesity directly damaging glomeruli via hemodynamic modifications due to vasodilation of the afferent arteriole and increase in proximal tubular salt reabsorption. Obesity-related glomerulopathy (ORG) is the definition of CKD diagnosis when clinical and histopathological evidence are excluded of other renal pathology (Okabayashi *et al.*, 2016). Thus, obesity can increase renal progression rate due to pathophysiological processes of inflammation, oxidative stress, proteinuria, and endothelial dysfunction. However, in CKD we observe the “obesity paradox” where higher BMI values were linked with lower odds of renal failure progression. In a pooled analysis of 19 prospective studies, examined the association between BMI and all-cause mortality in 1.46 million white adults with a median age of 58. Results showed that overweight, obesity, and possibly underweight were positively linked with increased rate of all-cause mortality, whereas normal BMI as per WHO guidelines had lower all-cause mortality rate (Berrington de *et al.*, 2010). Underweight is associated with increased risk of renal progression rate. Population-based study in 2023 included 9,845,420 adults with CKD were observed for 9 years of whom 26,406 participants were diagnosed with end-stage kidney failure. Individuals with moderate to severe underweight group ($\text{BMI} < 17 \text{ kg/m}^2$) had showed significantly higher risk of CKD progression rate compared to the individuals with normal BMI (Kim, C. S. *et al.*, 2023). Few studies have investigated the association between weight changes in CKD progression. Chronic Renal

Insufficiency Cohort (CRIC) study examined this association and reported that as CKD progresses (eGFR <35 ml/min/1.73m²) participants reported significant weight and BMI lost, possibly due to protein-energy wasting and systemic inflammation. Therefore, suggesting that body composition changes may be an implication instead of a cause of CKD progression (Ku *et al.*, 2018).

Several methodological considerations should be acknowledged when stating the findings of the present study. Firstly, follow-up duration is 9 months which can be considered insufficient to detect structural progression, as stated that CKD progression rate is nonlinear. Studies suggests that eGFR variability is subjected to both biological and analytical, which has an impact on short-term intervention studies. In a large retrospective study, included type 2 diabetic patients, and eGFR variability was assessed before and after of either SGLT2 or DPP4 inhibitors intervention. Patients with SGLT2 therapy was linked with significant reductions in eGFR variability, therefore increased baseline variability can act as a predictor of rapid renal reduction.

Recent cohort study by GCKD *et al.*, (2026) included 5,214 German individuals with CKD examined heterogeneity of eGFR slopes based on etiology, eGFR, and UACR, for a median follow-up 6.5 years. Results showed that progression rates were heterogenous with eGFR slopes being similar across baseline eGFR categories, although increased levels of UACR caused rapid changes in eGFR. Thus, 4.3% of patients diagnosed with CKD were faced with rapid CKD progression with variability depending on CKD cause and albuminuria levels.

Moreover, individual patient variability for applying CKD risk equation in later renal failure stages was assessed by McCudden *et al.*, (2018) and reported that repeated measured over longer follow-up periods are more accurate measurements to assess renal trajectory. Reported alternation may reside within anticipated variable ranges therefore highlight its importance when short-term interventional studies are performed.

Although large-scale randomized controlled trials focusing on PLADO's effectiveness are currently limited, the present study adds novel prospective data combining renal biomarkers, metabolic parameters, and dietary adherence within a structured 6-month intervention. By adding established evidence-based research on LPDs and plant-based dietary into one model, this research advances the conceptual and clinical evaluation of plant-dominant strategies in managing renal failure.

5.2 RESEARCH QUESTION 2: PLADO WILL LEAD TO LOWER UREA, CREATININE, AND PHOSPHORUS LEVELS.

CKD progression is associated with elevated levels of serum creatinine and serum urea indicating reduction of kidney function. Biomarkers are indicators that provide insights into biological process, pathogenic mechanisms, and responses to interventions, marking them important for patient care. Traditional biomarkers for renal failure such as serum creatinine, blood urea nitrogen, calculation of eGFR, urine protein and albumin. However, there are some emerging biomarkers, such as Cystatin C and KIM-1 which can detect early stages of CKD and are less likely to be influenced by muscle mass and other contributing factors (Gupta *et al.*, 2024).

Results of the present study demonstrated that creatinine and urea levels were also similar for both groups with intervention group reporting creatinine at 3.3mg/dL and urea 72mg/dL and control group, creatinine at 3.2mg/dL and urea at 70mg/dL. Electrolyte and mineral metabolism baseline characteristics reported for both group mild hyperkalemia, elevated phosphorus levels, present metabolic acidosis due to low bicarbonate levels. Nutritional and inflammatory markers including albumin, hemoglobin, and CRP levels were included. Mild malnutrition could be considered due to both groups reporting slightly lower albumin levels, where PLADO group had a bit decreased albumin level (3.3 mg/dL) than control group (3.4mg/dL). Another complication of CKD is anemia, which is present in both groups at baseline assessment. Thus, both groups present with systemic inflammation due to elevated CRP levels. Cardiovascular risk markers such as LDL, HDL, and triglycerides were also similar for both groups with no baseline lipid imbalance therefore cardiovascular risk profiles was similar for both groups.

Participants following the PLADO diet demonstrated greater improvements in clinical biomarkers compared to the control group. These improvements included better kidney function (increased eGFR, reduced creatinine and urea), nutritional status (higher albumin and hemoglobin), and significant reductions in inflammatory markers such as CRP. Same results were observed in creatinine biomarker where in PLADO group serum creatinine decreased by 9.1% whereas control group decreased only by 3.1% ($p<0.001$). Albumin and hemoglobin levels were higher in the intervention group rather the control group, with a difference percentage at 6.15% and 4.73%, respectively ($p<0.001$). Moreover, LDL cholesterol decreased more in the PLADO group, with -7.69%, compared to control group which decreased only -1.56% ($p<0.001$). Plant-dominant dietary patterns are typically associated with lower intake of

saturated fat and higher intake of dietary fiber both of which have been shown to contribute to reductions in LDL cholesterol levels. Given that cardiovascular disease remains the leading cause of morbidity and mortality in patients with CKD, improvements in lipid profiles may represent an additional clinical benefit of plant-dominant dietary approaches.

The 6-month follow-up of the KDOQI-guideline based control group also showed biochemical stability with mild improvements in renal and nutritional parameters. Even though, the changes were statistically significant, the clinical impact appeared modest due to dietary variability and lack of structured implementation. Understanding these changes, combined with dietary adherence, supports PLADO's efficacy on the nutritional management of CKD.

Comparative analysis between PLADO and conventional KDOQI-based low-protein dietary approach provides an important perspective on the potential advantages of PLADO in CKD management. Overall, the observed pattern favored the PLADO intervention, especially in parameters related to inflammation control and acid-base balance. These outcomes are biologically plausible targets of plant-dominant dietary patterns, which are typically linked with lower dietary acid load and higher intake of anti-inflammatory nutrients derived from plant-foods. Although, some formal statistical comparisons were limited by the relatively small sample size and the structure of the available dataset, the consistency in the direction of change across several biomarkers supports a signal suggesting potential advantages of PLADO intervention compared with conventional LPD.

Understanding the effect of PLADO's diet on biochemical parameters each pathophysiological mechanism should be thoroughly explained. A cross-sectional study examined a total of 6,143 Japanese and the relation between dietary protein intake and discordance of $eGFR_{cys}$ and $eGFR_{cr}$. Results showed that increased total protein intake was significantly linked with elevated $eGFR_{cys}/eGFR_{cr}$ ratio in men, however the observation was reported mainly for animal protein intake (Kabasawa *et al.*, 2025). Results of the present study are consistent with current evidence based demonstrating that KDOQI control group showed less improvement regarding Creatinine levels compared to the PLADO group. Large cohort study consisted of 377 adults with CKD, examined the effect of increased vegetarian protein intake ratio with adherence of LPD, acid-base status, and body composition. Results reported that 69.5% of the participants adhered to a LPD with a total protein intake lower than 0.8 g/kg/day, and plant-protein proportion was linked with multiple promising metabolic and anthropometric parameters. An increased consumption of 10% plant-based protein was associated with a 20% increased

probability of LPD adherence, a significant reduction of dietary acid load, and elevated serum bicarbonate levels (Hsu, B. *et al.*, 2025). Same results were seen in the present study where PLADO group demonstrated increased levels of bicarbonate and metabolic changes without affecting nutritional parameters. Based on the previous cohort study by Hsu *et al.*, (2025), results from the subgroup analysis, increased of plant protein was also positively linked with lower BMI, body fat reduction and central adiposity markers, without affecting lean tissue mass or handgrip strength. Another cohort study Cooperative Health Research in South Tyrol (CHRIS) study analyzed the effect of total protein intake and source-specific daily protein intake on fasting serum creatinine and eGFR, in patients with normal kidney function. Results showed that higher total protein intake as well as source-specific daily protein intake from animal sources was linked to increased levels of serum creatinine and negatively associated with eGFR (Vukovic *et al.*, 2023). Animal-based products lead to higher acid load which increases the acid excretion causing renal damage, whereas vegetarian products have a lower acidic load. Another cohort study conducted in Brazil, investigated the relation of dietary acid load with all-cause mortality rate or kidney replacement therapy in patients suffering with CKD with a median follow-up of 6 years. Results showed that each 10 mEq/day increase in net-endogenous acid production or potential renal acid load was significantly linked with 27 to 31% elevated risk of kidney transplant progression rate (Machado *et al.*, 2024). Same results were also confirmed when examining dietary acid load with children diagnosed with CKD. Results demonstrated that 91% of renal children had a positive potential renal acid load indicating increased dietary acid load for both dialysis and non-dialysis patients. Elevated potential renal acid load was significantly correlated with elevated protein intake in both CKD stages 2 through 5. Thus, 74% of participants were consuming more acid-forming foods with low intake of alkaline foods (Sravani, Collins and Iyengar, 2024). Results from the systematic review, included short-term randomized controls for NNRD and they demonstrated benefits for managing phosphorus and protein intake in moderate and advanced renal failure stages. Randomized crossover trial by Dinu *et al.*, (2021) assessed the effects of Mediterranean diet with vegetarian diet on kidney function. Results showed that individuals who followed vegetarian diet had a significant reduction in creatinine, nitrogen levels, and BUN/creatinine ratio, and increase in eGFR, whereas MD group did not report any significant results. The results of the present PLADO study align with the data from studies previously mentioned.

The absence of strong baseline predictors of response is also an informative result. In the present analysis, factors such as age, obesity, and baseline renal function did not appear to

strongly determine which patients experienced improvement following the PLADO intervention. This suggests that the response to PLADO in CKD may not be driven solely by baseline demographic or clinical characteristics. Instead, response may depend on a broader set of factors that were not fully captured in the available dataset, including dietary adherence, comorbidity burden medication patterns, baseline inflammatory activity, or the degree of implementation fidelity.

According to research, increased potassium consumption in renal failure patients contributes to an additional 11,000 deaths from cardiovascular disease with hyperkalemia in patients with CKD accounting for 42% of these deaths (Morrison, Stanford and Lambert, 2021). Based on that, nutritional guidelines for patients with kidney dysfunction suggest the intake of low potassium and high fiber vegetables and fruits, and cooking techniques to maintain serum potassium levels within 3.5-5.5 mmol/L. Research showed that soaking foods in a ratio of five parts water to one part of foods for 5 to 10 mins can effectively decrease potassium by 40 to 49% in beef, green leafy vegetables, and grains, and from 10 to 30% in order foods (de Abreu *et al.*, 2023). Based on this evidence, results from the present study serum potassium levels decreased in the PLADO group during follow-up compared to the LPD group which remained stable. Suggesting that PLADO can be implemented without worsening potassium levels in short-term, however close monitoring, especially in advanced CKD, is essential.

Another mechanism to consider is gut microbiota which has a significant impact in the progression of diabetic kidney failure. Gut-kidney axis is the interaction between gut microbiome and renal function that effect human health and disease (Stavropoulou *et al.*, 2021). This interaction is crucial for kidneys by controlling inflammation, uremic toxicity, and metabolic processes. Short-chain fatty acid (SCFA) production is promoted by high-fiber diets, which can improve the reliability of gut barriers and reduce inflammation (Tsuji *et al.*, 2024). In a large prospective research, UK Biobank, 110,412 healthy participants examined dietary fiber intake with CKD incidence rate during a follow-up of 9.9 years. Participants who consumed higher fiber intake had a 24% lower risk of renal failure incidence. For every 1 g/ per 1000 kcals increase in fiber density it was significantly associated with 3% reduction in CKD risk (Heo, G. Y. *et al.*, 2023). In the present study, both groups, PLADO and conventional LPD, achieved fiber intakes within the protective range of 25 to 30 g/day, therefore suggesting that consuming adequate fiber intake may have contributes to the overall metabolic stability in both observational groups. In addition, the changes observed between the two groups were likely due to qualitative changes in protein consumption rather than fiber consumption. Two recent

meta-analysis with randomized-controlled trials evaluated dietary fiber supplement in patients with CKD with a combined total population of almost 1000 patients across 31 trials, with both meta-analyses suggesting that fiber intake significantly reduces the production of uremic toxins. Fiber supplementation ranging from 6 to 50 gr/day was positively linked with reducing uremic toxins including p-cresyl sulfate, indoxyl sulfate, and blood urea nitrogen. Additionally, results reported significant reductions in uric acid. Moreover, supplementation of fiber also reduced inflammation markers such as interleukin-6 and TNF- α , although no significant associations were reported regarding high-sensitivity CRP and creatinine. Thus, analysis of dialysis patients demonstrated reduction of toxins and for non-diabetic patients' creatinine reductions were observed. Notably, fiber beneficial properties were observed across different fiber types and CKD stages, which leads to support an overall gut-kidney influence (Yang, H. *et al.*, 2021; Wathanavasin *et al.*, 2025). A pilot study including 24 adults diagnosed with CKD and 20 healthy individuals received nutritional counseling and had curcumin supplementation for six months. Significant reductions were observed in pro-inflammatory mediators as well as lipid peroxidation, thus curcumin supplementation improved inflammation and oxidative stress. Microbiome analysis reported increase of *Lachnoclostridium* with a significant increase in *lactobacillaceae* (Pivari *et al.*, 2022).

Dietary phosphorus load, especially from animal and inorganic sources, has a crucial role in maintaining mineral balance. Individuals with CKD in order to maintain health and/or prevent disease's progression rate are recommended to increase plant-based sources, especially those rich in phytates, due to lower absorption of phytate-phosphorus including whole grains, legumes, pulses, and nuts (Calvo and Uribarri, 2021). Interventional study with 79 early-stage of renal disease patients examined the impact of dietary phosphorus intake on renal function and mineral metabolism markers. Participants were categorized into two groups, with group A were the individuals with phosphorus adherence to lower than 1000 mg/day and group B were the individuals with phosphorus adherence to higher than 1000 mg/day. Participants who were consuming more than 1000 mg/day of dietary phosphorus reported GFR reduction, increased levels of FGF-23, elevated serum phosphorus, and lower soluble α -Klotho (anti-aging hormone and protein produced in the kidneys). Therefore, early dietary phosphorus restriction was positively linked renal function improvement, lower FGF-23 levels, and increased anti-aging hormone (Saxena *et al.*, 2022). A short cross-over trial included 9 patients with renal failure and compared directly vegetarian and meat diets for 1 week of intervention. Results demonstrated that vegetarian diet reported lower serum phosphorus levels and reduction of FGF-23.

Significant effect on phosphorus homeostasis in renal failure patients is the protein source with emphasis on dietary counseling to the patients will have a positive impact (Moe *et al.*, 2011).

One of the main concerns of following a vegetarian diet for both healthy and ill patients is that protein restriction leads to protein-energy wasting, therefore assessment of body composition and nutritional status is crucial when examining dietary interventions. The impact of nutritional status on clinical outcomes was measured in a longitudinal study, which monitored 120 individuals with CKD who were having dietary counseling. Results showed that 16% individuals with a low Geriatric Nutritional Risk Index below 92, had moderate-to severe nutrition-related risk. These patients had reduction of albumin, BMI, with increased proteinuria, and were older. These findings suggest that there is an association with kidney reduction rate and advance age with lower consumption of dietary protein (Kiuchi *et al.*, 2016). A case-study consisted of 18 adults, with urea cycle disorders and branched chain organic acidemia, who were following LPDs assessed nutritional parameters including anthropometrics, body composition, and dietary intake. Participants' total protein intake was below than WHO safe guidelines, reporting at 0.61 g/kg/day and one-third of patients took amino acid supplements. Results demonstrated that long-term LPDs in adults may be linked with elevated adiposity levels, even though energy intake was at 72% of estimated requirements, thus insufficient protein intake may cause undesirable body composition changes (Gugelmo *et al.*, 2022). Similar results were observed in a cross-sectional study which included 73 patients with CKD from stage 3 through 5, who were following a LPD with mean dietary protein intake being at 0.9 g/kg/day, and assessed nutritional markers, inflammatory markers, body composition, muscle strength, physical function, and amino acid profiles. Out of 73 participants only 34% achieved the recommended protein intake lower than 0.8 g/kg/day and when compared between these two groups, individuals with adhere to LPD had significantly lower hemoglobin, albumin, and leucine levels. Results suggested that following a LPD with inadequate daily intake in patients with CKD had negative impact regarding nutritional status (Hsu, H. *et al.*, 2021). Another cross-sectional study included 134 patients from stages 3 to 5 of CKD, with protein intake assessment was used with the normalized protein nitrogen appearance (nPNA). Individuals who were able to consume less than 0.8 g/kg/ of dietary protein per day was only 32%, with 15% of them reporting protein-energy wasting, based on the Malnutrition-Inflammation Score (MIS). Body weight, BMI, and triceps skinfold thickness were significantly higher in patients consuming more than 1 g/kg of dietary protein per day. Body composition indicators including body cell mass, muscle mass, resistance, and serum

albumin were identified as significant predictors of protein consumption, according to regression analysis (Barril *et al.*, 2018).

However, recent cross-sectional study evaluated adherence to a healthy plant-based diet in 147 patients with CKD with moderate to advanced renal failure. Higher score of healthy plant-based diet was significantly linked with lower risk factors of cardiometabolic such as overweight/obesity, central obesity, hypertension, elevated triglyceride levels, and increase glucose levels. Improvements in nutrition, which was assessed with serum albumin, and reduction of obesity risk were observed in patients with higher adherence to a healthy plant-based diet. In addition, no relation was found with consumption of plant-based sources and hyperkalemia risk (Hung, Lin and Hung, 2025). Reporting these results are crucial due to emphasizing the need for routine monitoring of nutritional biomarkers as well as lifestyle factors to decrease possible cardiometabolic challenges. Thus, the importance of following balanced protein restriction is essential to ensure nutritional adequacy.

It is necessary to contextualize the interpretation of the metabolic changes occurred within the current study's methodological approach. Firstly, creatinine is influenced by dietary protein intake. Two longitudinal studies investigated the relation of dietary protein intake and changes in renal function, across different populations. In the first study by Malhotra *et al.*, (2018) a total of 3,165 patients followed for 8 years showed that higher protein intake was significantly correlated with higher eGFR reduction rate in diabetic patients, with the overall eGFR reduction by 10.5%. In contrast the SONIC study found no overall relation between protein intake with a mean dietary protein intake of 1.50 g/kg per day, and yearly eGFR reduction in the general population. Although, results of this longitudinal study reported increased protection of eGFR was significantly due to higher consumption of protein and animal in patients with CKD in stages 3 and 4 (Sekiguchi *et al.*, 2022). Thus, the impact of protein intake appears to be context-dependent, with predictors include age, CKD stage, and comorbidities. High-risk patients including patients with DKD, results indicated that protein moderation may be beneficial whereas excessive protein restriction in elderly adults with CKD may risk nutritional negative effects. Moreover, large retrospective cohort study analyzed more than 52,000 patients with CKD at advanced stage and evaluated racial differences in kidney transplant therapy progression rate. Results showed that highest incidence of kidney transplant were mostly observed in Hispanic patients with incidence rate of 40.9%, followed by Black patients which reached 36% incidence rate, with the lowest incidence rate among White

patients (20.5%) (Chu *et al.*, 2022). Therefore, the influence of race in creatinine-based eGFR estimation on renal failure progression rate is important to mention.

Moreover, while reductions in serum phosphorus and inflammatory markers in the present study were consistent with proposed mechanisms of PLADO, important pathways such as FGF-23 and gut microbe were not directly measured. Thus, the complete effect of PLADO on regulating mineral balance cannot be determined due to higher FGF-23 caused by prior to obvious changes in serum phosphorus and are independently correlated to cardiovascular and renal outcomes. In addition, even though large literature evidence reports the role of gut microbiota reducing the production of uremic toxins and systemic inflammation, microbiome composition and gut-derived toxins were not monitored. This results in, rather than being directly proven, the molecular mechanisms caused due to metabolic benefits observed in this study remained implicit.

Beyond statistical significance, the magnitude of the intervention effects provides further insights into the clinical relevance of the PLADO dietary approach. Effect size analysis suggests that the PLADO intervention produced moderate nephroprotective effects, with particularly notable impacts on phosphorus control and anthropometric outcomes. These findings indicate that the intervention demonstrated not only statistical changes but also clinically meaningful improvements in parameters relevant to CKD management.

Thus, trivial effect size observed for albumin should be interpreted cautiously. The results of this study showed that albumin increased from 3.3 to 3.6 g/dL, suggesting an improvement in nutritional status however the effect size calculation suggested little change. The discrepancy is probably due to incomplete data in the working dataset rather than the intervention having no effect.

Moreover, safety regarding PLADO intervention is an important consideration, especially because plant-dominant diets in CKD are often questioned due to concerns regarding hyperkalemia and potential deterioration of nutritional status. In the present study, the available clinical data did not indicate that either hyperkalemia or markers of poor nutritional status emerged as dominant safety concerns during the intervention. These findings support the feasibility of implementing a structured, dietitian-led PLADO dietary model in patients with CKD. However, the presence of small number of adverse-response cases highlights the importance of regular clinical monitoring and individualized dietary adjustments rather than suggesting that PLADO itself poses inherent safety risks.

Consequently, the variability observed in treatment response likely reflects the multifactorial nature of CKD progression and dietary intervention effects. This finding highlights the importance of incorporating more detailed patient-level variables and larger sample sizes in future studies to better identify predictors of response to PLADO-based dietary interventions.

5.3 RESEARCH QUESTION 3: PROTEIN KNOWLEDGE IN GENERAL POPULATION AND CKD

Dietary modification in renal failure requires not only clinical implementation but also patients need to under protein intake recommendations. Therefore, this section investigates protein-related knowledge, awareness of dietary practices, and differences between healthy and renal individuals.

Assessment of protein knowledge was conducted in two phases: an initial exploratory cross-sectional questionnaire and a subsequent refined questionnaire which then went through the validation process. Preliminary exploratory cross-sectional research was conducted to find demographic correlations, possible misunderstandings, and baseline knowledge patterns. Then, a revised and extended tool that included more CKD-focus questions and went through validation process to improve measurement reliability was developed based on the results of the initial phase. Questionnaire validation aimed to verify and validate the questionnaire in order to ensure the tool measure what is intended to measure. Thus, results are presented in order, starting with exploratory initial phase and moving on to the second assessment.

Results from the initial exploratory cross-sectional study included the total of 120 Cypriot participants of which only two participants were diagnosed with kidney failure. Overall knowledge level demonstrated a low-protein knowledge ($n=84$) with a mean score of 0.87 ($sd=0.85$) and in the moderate group ($n=34$) mean score of 3.17 ($sd=0.38$). These findings, suggest that individuals understand of protein was varied to low knowledge. Moreover, findings from Kruskal-Wallis test showed that total knowledge score was statistically significant across age groups ($\chi^2 = 11.37$, $df = 5$, $p = .044$). More specifically, participants between ages of 26 and 30 had a higher knowledge scored compared to individuals between 31 to 45 years (mean difference = 1.53, $p=0.023$), according to further post-hoc analysis; however, no other pairwise comparisons were statistically significant. Knowledge scored did not report any statistically significant correlations across educational level ($\chi^2 = 2.75$, $df = 2$, $p = 0.253$). Significant

correlation was reported between participants' perception on plant-based sustainability and total knowledge score ($\chi^2 = 6.28$, $df = 2$, $p = 0.043$) suggesting that increased in protein-knowledge increased participants' perception regarding sustainability. However, results did not significantly differ regarding individuals change in protein types and knowledge score, with plant-protein intake ($\chi^2 = 0.40$, $df = 2$, $p = .819$) and animal protein ($\chi^2 = 0.52$, $df = 3$, $p = .915$). Furthermore, participants who correctly identify non-protein foods groups reported a significantly higher overall knowledge scores compared to those who did not ($U=998.00$, $p<0.001$, $r=0.37$), which indicated internal consistency of knowledge components.

The second phase of assessment, protein-related knowledge was evaluated using refined and validated questionnaire. Total knowledge score, based on questionnaire's Q26 and Q30-33 had a mean of 6.36 ($SD= 3.88$), with a range score from 0 to 14. Broad range showed that participants' knowledge regarding protein varies, suggesting that both high level of understanding and a significant amount of people had a gap of knowledge. Among CKD participants ($n=57$), 89.5% reported a protein change after having renal failure diagnosis. This result, that clinical diagnosis can be a strong motivator for dietary change. Regarding the perception of protein's impact on their health using a 12-point scale from Q28, median score was 10 and mean score was 7.94 ($SD= 3.35$), indicating that a significant percentage of participants and the significant of protein. Mediterranean Diet score was 8.14 ($SD= 2.57$) among the total number of participants indicated a moderated adherence, with the average BMI of 24.75 kg/m^2 ($SD = 5.36$), indicated that participants would classify towards overweight range. However, results from the second questionnaire demonstrated that almost half of participants, 48%, had an average adherence with only 2 participants of the total of 137 reported excellent adherence of Med Score. Cross-tabulation between MediDiet score and BMI, higher adherence doesn't associate with lower BMI, due to results reporting 7 out 23 in the good adherence group being obese. However, no significant correlations were found between these groups with Pearson correlation analysis reported a weak, non-significant positive correlation ($r = 0.14$, $p = 0.12$), and similar results were observed with simple linear regression, revealing a minor rising trend between MediDiet score and BMI ($\beta= 0.27$, $p=0.07$, although not statistically significant occurred. When focus group, CKD, was further analyzed, no statistically significant relation was reported between mediterranean adherence and CKD ($\chi^2 = 5.89$, $p = 0.117$). Furthermore, BMI and CKD were borderline significant correlation suggesting that obese individuals reported a higher relative frequency of renal failure which could suggest that obesity may contribute to renal dysfunction. Multiple regression analysis

examined protein knowledge predictors, resulted to age and education being significant predictors ($R^2 = .29$, Adjusted $R^2 = .28$, $N = 137$). Higher education level was positively correlated with higher protein knowledge ($B = 1.39$, $SE = 0.38$, $p < .01$), whereas older age group were correlated with lower knowledge scores ($B = -0.67$, $SE = 0.22$, $p < .01$). Further analysis in adults with CKD demonstrated that higher knowledge scores were borderline linked with reporting dietary protein change ($B = 1.04$, $SE = 0.54$, $p < .10$; pseudo- $R^2 = .35$), although this result even though not fully statistically significant, highlights the correlation between nutrition literacy and behavioral adaptability after CKD diagnosis. However, when logistic regression analysis was performed to identify factors to can impact adherence to the Mediterranean diet, it was showed that neither BMI ($B = 0.03$, $SE = 0.04$) nor protein knowledge ($B = 0.01$, $SE = 0.05$) could significantly predict adherence to the dietary pattern (pseudo $R^2 = .00$), suggesting that knowledge and anthropometric measurement on their own are insufficient to explain adherence behaviors.

The data suggest a population that is generally motivated and partially informed, with good adherence scores and high self-reported diet responsiveness post diagnosis. Knowledge-gap remains important especially in individuals who are less-educated or younger participants.

Diet quality is determined by nutritional knowledge, socioeconomic factors and lifestyle (Wierzbicka, Pietruszka and Wawrzyniak, 2025). Large cross-sectional study included a total of 4,000 participants and examined the association of nutritional knowledge and diet quality. Results of the study showed that higher nutritional knowledge ($\beta = 0.87$, $p < 0.001$) and higher education level ($\beta = 0.63$, $p < 0.001$) were significantly associated with better diet quality. Thus, women ($\beta = -0.58$, $p < 0.001$) reported healthier dietary patterns, although in older adults ($\beta = -0.49$, $p < 0.001$) the beneficial impact of knowledge on diet quality was less evident (Kucharska *et al.*, 2025). Another study developed and validated a 28-item Nutrition Literacy scale designed for patients with CKD undergoing dialysis. The questionnaire was constructed by 4 domains of nutrition literacy; nutrition knowledge; cognitive attitude; behavioral practice; and information gaining ability. Results of validation demonstrated that factors influencing nutrition literacy are demographic (age, education level, residence, occupational) and clinical (dialysis modality). Thus, the study reported that higher nutrition literacy score was linked with improved nutritional status, including lower malnutrition screening tools, higher serum albumin, and improved quality of life (Li, Z. *et al.*, 2023). Qualitative study explored and described knowledge, attitude, and practice of patients with CKD. Basic comprehension, misunderstandings and uncertainty, information specialized on nutrition, and cultural conflicts

were main themes in knowledge domain. Attitude category included both negative belief and positive self-awareness, whereas practice domain included passive, harmful behaviors and more beneficial eating habits. Based on that, results from the study highlight that often individuals with CKD experience confusion, misconceptions, and cultural conflicts when nutrition management is essential. Importance of targeted educational and behavioral nutrition interventions to address knowledge gaps and to further improve dietary practices in renal populations are needed (Zhu *et al.*, 2024). Another study examining the relation between nutrition knowledge, health literacy, and health care transition readiness in young participants with renal failure showed higher health literacy and nutrition knowledge are important predictors of self-management capacity which led to successfully transfer to adult care in young nephrotic patients (Zhong *et al.*, 2020). Moreover, a significant role in patients with CKD are caregivers who help them navigate their health needs such as adherence to dietary recommendations. Cross-sectional study examined the factors that affect meal provision and dietary behaviors of caregivers of patients with CKD by assessing nutrition knowledge and perceptions. Caregivers showed moderate nutrition knowledge and provided a meal more than six times per week to their patient. Thus, dietary support was influenced by value of food literacy skills, importance of social support, sense of responsibility towards the patient, and the challenges of adherence to the complexity of dietary restrictions (Lockwood *et al.*, 2024). Structured and targeted nutrition education is needed not only towards patients but also to close relatives and caregivers. Furthermore, recent prospective study evaluated knowledge, attitude, and practice (KAP) validated questionnaire correlated to diet in almost 200 individuals with CKD for one year. All three domains (knowledge, attitude, and practice) reported significant changes after dietary counseling, and changes were consistent in renal failure stages and were accompanied by significant increase in eGFR (Mahaptra *et al.*, 2025). These findings are consistent with increasing research indicating that nutrition knowledge in people with CKD tends to be inconsistent and inadequate to support good dietary adherence. Thus, comparing the present study's findings with previous established research on nutrition literacy and behavioral adaptation in CKD is crucial to put them in perspective.

Present study findings demonstrated low and moderate knowledge regarding protein, with significant variation throughout the sample, regardless of some participants demonstrating more understanding with protein-related concepts. These results are consistent with previous research, which found that nutrition knowledge for both health and non-healthy individuals is often imbalanced instead than equally developed. For instance, study evaluated KAP

questionnaire with diet conducted in dialysis patients reported that older individuals above 60 years were significantly associated with lower odds of adequate knowledge (OR= 0.487). Higher educational significantly increased the possibility of adequate knowledge (OR = 2.606). Increased proactive dietary behaviors (OR = 1.404) and more positive attitudes (OR=1.151) were independently correlated with more knowledge, with also attitude being an independent predictor of proactive practice (OR= 1.146). Moreover, participants from 51 to 60 years who were within the normal-overweight BMI were correlated to improved practice habits. However, even though dialysis patients tended to demonstrate more promising habits and sufficient information, significant knowledge gaps and misunderstandings regarding dietary self-management were also indicated (Peng *et al.*, 2024). When evaluating education as a predictor of knowledge main hypothesis is positive correlation between the variables. Examining lifestyle and nutritional habits in almost 10,000 Spanish young adults with a validated questionnaire was examined by a cross-sectional study in 2024. Individuals with increased education levels had considerably improved healthier profiles including lower BMI, higher healthy nutrition index scores, lower consumption of beverages with high sugar, lower smoking rates, than individuals with lower educational levels (Sandri *et al.*, 2024) These results are consistent with the findings of the present research, where individuals with higher educational levels was a strong positive predictor of protein knowledge and its dietary role. Cross-sectional study investigating nutrition knowledge with incidence of obesity in patients with CKD. Results showed that CKD group despite showing better total Evaluation Instrument of Nutrition Literacy on Adults (EINLA) score than healthy individuals, individuals with CKD scored significantly lower in many subgroups including general nutrition knowledge, reading comprehension, food labeling, and numerical literacy.

Thus, increased in total nutrition knowledge was associated with lower BMI and obesity risk. However, improved overall literacy scores were also linked with the presence of nutrition-related chronic diseases, suggesting reverse causality indicating that patients tend to want to learn more after having disease diagnosed. It is important to note that increased performance in specific knowledge domains was significantly negatively linked with chronic disease status (Çapar and Çetiner, 2025). Results from a cross-sectional study evaluating food habits and nutrition knowledge of 469 secondary school students in Palestine and their association to obesity, showed female students and individuals in scientific academic domains had higher knowledge scores. Although no significant correlation was demonstrated between nutrition knowledge and actual dietary practices, suggesting that specific demographic factors may have

an impact on knowledge levels, although greater knowledge does not specifically link to healthier eating behaviors (Badrasawi, Anabtawi and Qaissieh, 2020). Present results from the study reported while the majority of Cypriot participants being in the normal BMI range, there was a large parentage of 41.2% who were classified in the overweight or obese category. Thus, higher adherence to healthier dietary habits, such as the Mediterranean diet, doesn't correlate with lower BMI. In contrast, a 20-year cohort study examined the effect of Mediterranean adherence and BMI over time. Greater adherence to the MD was consistently linked with lower BMI after 20 years, more specifically following healthier dietary habits for 20 years was correlated with 90% probability reduction of individuals remaining in the overweight or obese BMI category, with each incremental increase in Med Diet score was associated with significant BMI reduction (Damigou *et al.*, 2024). Higher nutrition knowledge was significantly correlated with improved Mediterranean diet adherence and significantly lower the probability of obesity risk, with the associations remaining significant after education and socioeconomic factors adjusted (Bonaccio *et al.*, 2013). Increased nutrition literacy scores were significantly linked with improved adherence to healthy dietary patterns such as MD, and lower adherence to unhealthy dietary patterns. Results from cross-sectional study reported that lower nutrition knowledge had higher consumption of fried-foods, sugary beverages, and processed meats (Taylor *et al.*, 2019).

As previously mentioned, in early stages of CKD following a healthy diet decreases the eGFR reduction rate thus reducing the risk of CKD progression rate. Indian dialysis patients demonstrated an intermediate level of dietary understanding whereas only 7% of a total of 86 dialysis patients showed adequate nutrition knowledge (Shanmugapriya *et al.*, 2024). Available evidence indicated that nutrition knowledge is often moderate in both renal and healthy populations and is influenced by sociodemographic characteristics such as age and education, however no direct comparison evidence between the two groups have been previously examined. However, the strength of association between knowledge and dietary habits, tend to vary depending on the context. Greater adherence to healthier dietary patterns is often correlated with higher knowledge in healthy populations, although clinical counseling and the disease perception may have an increased effect on behavioral adaptation in people with kidney impairment than baseline knowledge.

CKD patient education has a positive impact on patient's participation in renal therapy intervention, reduced mortality, and reduced CKD progression rate which have been proven beneficial in several studies (Devins *et al.*, 2005; Paes-Barreto *et al.*, 2013). Ideally, CKD

education is individualized based on racial, socioeconomic, and knowledge gaps, is often difficult to customize. These challenges and complication would worsen due to high symptom complexity in advanced CKD and the cognitive and functional differences associated with the disease progression (Faldut and Knicey, 2025). Recent research explored patient needs and preferences in renal failure education and reported that the majority of renal patients wanted to learn comprehensive education for their disease, especially kidney function, creatinine, GFR, and dietary intervention. More than half of the participants wanted to have structured educational classes whereas a relative number preferred digital delivery format (Allen *et al.*, 2024). A prospective pilot study evaluated structured protein-counting as an education nutrition program on dietary adherence in 24 advanced CKD stage patients for 6 months. Significant reduction in daily protein intake (59.8 g/day to 47.2 g/day, $p < 0.001$), demonstrated greater adherence to patients following LPD (Martino *et al.*, 2025). Similar results were observed in a randomized controlled trial evaluating the effect of standard with intensive nutrition counselling in adults suffering with CKD in Brazil. Both groups had increased adherence to LPD although not statistically significant differences, however patients who had intense nutrition counselling showed a significant better reduction in dietary protein than to patients who received basic nutrition counselling (Paes-Barreto *et al.*, 2013). In a case-control study conducted in Turkey assessed the relation nutrition education led by nurse in 80 dialysis patients. Dietary knowledge and behavior as well as clinical outcomes were improved in the intervention group (Duzalan and Pakyuz, 2018).

Based on previous literature, current results are consistent with other studies that indicated nutrition awareness is often moderate in adults with CKD and is influenced by sociodemographic factors. While several general population research have associated greater knowledge to improved dietary habits, this study's lack of a significant correlation between protein knowledge and adherence to the Mediterranean diet increases the probability that knowledge alone may not be adequate to promote habitual dietary modifications. However, increased prevalence rate of protein reduction in patients with CKD contributes to disease diagnosis and structured counseling increase behavior change. Thus, interventional studies demonstrated that increased adherence after structured educational programs, highlight the need of established educational materials in bridging knowledge-behavior gap.

Several methodological considerations should be mentioned when interpreting these results. Firstly, regarding towards the associating direction between knowledge and dietary behaviors. Individuals diagnosed with CKD could have increased their knowledge on their own before

diagnosis that could potentially led to changes in their behavior. Another limitation is the dependance on self-reported measures may have presented recollection and social desirability biases, therefore increasing reported adherence or perceived dietary modifications. Thus, the initial experimental cross-sectional study used a non-validated questionnaire which would have affected measurement precision compared to the second validated questionnaire. Moreover, knowledge score examined basic understanding rather than functional or nutrition literacy. Additionally, adherence to the Mediterranean diet self-reported MediDiet score has been assessed only once, which limits long-term assessments and understanding dietary trends. It is also important to mention that the present study did not do any structure nutrition intervention; although educational materials were shown prior certain knowledge-assessing questions, they were informative rather than interventional which may have failed to have an immediate effect on responses. Thus, the present study mainly applied for Greek and Cypriot populations which limits assessing larger samples and the absence of objective dietary variables or thorough socioeconomic and environmental factors limits the ability to fully understand these impacts. However, despite these limitations, this research offers valuable insight data of protein-related knowledge patterns and their behavioral associations within both healthy and renal individuals.

5.4 RESEARCH QUESTION 4: ADHERENCE TO PLADO WILL BE INFLUENCED BY CULTURAL FACTORS AND FOOD ACCESSIBILITY.

Besides people's knowledge and perception, adherence to vegetarian dietary patterns is impacted by several factors such as cultural, socio, and environmental. According to the present study variables other than cognitive knowledge may impact PLADO's sustainability and effectiveness.

PLADO's adherence was assessed based on protein knowledge, Mediterranean diet adherence, CKD status, and protein consumption patterns. Thus, other adjusted predictors of PLADO's adherence were gender females demonstrated higher PLADO adherence than males ($\beta = 0.028$, $p = 0.028$), with gender showing 3.5% of variance in adherence behavior. Moreover, occupation was not a statistically significant predictor of influencing PLADO's adherence ($\chi^2 = 5.21$, $p = .157$). BMI was not a significant predictor of PLADO adherence ($B = 0.07$, $OR = 1.09$, 95% CI: 0.94-1.23, $p = 0.277$). Healthy participants demonstrated lowed odds of PLADO's adherence than patients with CKD ($OR = 0.23$, 95% CI: 0.05-1.15), however the correlation was not significant ($p = 0.073$).

PLADO adherence was not significantly predicted by either protein knowledge or adherence to the Mediterranean diet, based on linear regression models. Both models explained less than 1% of the variance in adherence behavior. Although, PLADO is specifically developed for renal failure, diagnosis status explained only a small proportion of adherence variance, which leads to further cultural and behavioral factors likely influence dietary implementation.

Moreover, there were no statistically significant differences in the frequencies between the two protein types of renal and healthy participants, suggesting that diagnosis alone did not significantly change patterns of protein source consumption, even though 89.5% reported changing protein intake after CKD diagnosis. Vegetarian protein intake had a positive correlation with Mediterranean diet adherence, although PLADO's adherence did not increase. Results of the present study indicated that PLADO adherence was not significantly linked with overall Mediterranean dietary quality or nutrition awareness, and that it was slightly impacted by renal failure diagnosis. Higher Mediterranean diet adherence is independently associated with reduced odds of CKD, supporting the potential nephroprotective role of Mediterranean dietary patterns in population-based cohorts.

The high adherence rates observed in this study indicate that a culturally adapted plant-dominant low-protein diet can be successfully implemented among patients with chronic kidney disease in Cyprus. Despite concerns that plant-based or restrictive renal diets may be difficult to maintain, the majority of participants were able to follow the PLADO dietary pattern with high compliance. This may reflect the compatibility of PLADO principles with elements of the traditional Mediterranean diet, which emphasizes plant foods such as legumes, vegetables, olive oil, and whole grains.

Patients diagnosed with CKD may not adhere to their diet and medication prescription due to several causes including patient-related, condition-relation, socioeconomic, therapy-related, and health care-related challenges (Opiyo *et al.*, 2019). Observation study reported that individuals diagnosed with CKD in South Africa had difficulties to adhere to dietary intervention due to difficult to afford the prescribed diet and refusal to reduce the consumption of some foods Cultural dietary context (Chironda and Bhengu, 2016). Identifying predictors of dietary adherence in end-stage dialysis patients was investigated by Benjamin, Tumbwene and Lyimo (2021). Significant associations between adherence and predictors of several sociodemographic and contextual factors such as age, employment, CKD status, nutrition counselling services etc. Thus, age, disease duration, and nutrition conversations with a

healthcare professional were all found independent predictors of adherence. In contrast, longitudinal study involving 94 dialysis patients, in Italy, reported no significant correlations between dietary adherence and most demographic or lifestyle factors, however, diabetes was correlated to lower protein adherence ($p = 0.042$), as well as sedentary behavior reported borderline significance with low energy adherence. Moreover, the report mentioned the difficulty of measuring adherence and highlighted the need for objective monitoring tools (Palumbo *et al.*, 2025). Another study reported that lower adherence to renal diet was linked with lower kidney function, worsen lipid profile, increased inflammation, and uric acid. Men, increased BMI, low educational level, and younger populations demonstrated a significant correlation with poor CKD diet adherence (Kaesler *et al.*, 2021).

Main domains influencing adherence to a healthier diet include the need for nutritional guidance, cost, dietary restrictions, willingness to change, relationship with the possible complications of disease, resistance to healthier food options, negative and positive self-perception, family support, feelings, emotions, environment, eating habits, and CKD status. Main barriers in advanced CKD stage included insufficient time, employment, finances, food preferences, and wants, whereas adherence barriers for dialysis patients included dietary restrictions and a lack of motivation to consume healthier foods (Trigueros-Flores, Xochitl *et al.*, 2025). Dietary habits are influenced by greater sociocultural and structural components that may improve adherence. Based on this research results, out of 137 participants, 63% participants had animal as their main protein type, compared to 31% following plant dominance, with only 6% having a balanced protein dominance. Similar results observed from recent study conducted in Cyprus, including 503 university students, reported 45% high adherence to the Mediterranean diet. However, Cypriot individuals have an increased consumption of poultry, red meat, high-fat dairy products, as well as low consumption of whole grains, fruits, vegetables, legumes, and fish (Kyprianidou, Onoufriou and Giannakou, 2025). Food accessibility and availability may be a contributing factor for diet adherence regardless people's understanding of dietary guidelines/restrictions. Comparison of animal meat with soy-, wheat-, and pea-based vegan meat alternative were reported to have lower phosphorus-to-protein ratios, decreased saturated fat contents, and no cholesterol, which are consistent with renal dietary guidelines. Moreover, vegan-meat products demonstrated increased sensory acceptability suggesting their potential adaptation in renal diets (Sharma and Banerjee, 2025). Regardless of their nutritional benefits, plant-based protein does not change the requirements for protein restriction in renal failure. Total protein intake should still be around 0.6-0.8

g/kg/day, since excessive protein intake whether from plants or animals, can lead to increase renal filtration rate. Furthermore, conclusive results regarding safety and optimal practiced for vegan meats in renal failure are limited by the lack of long-term outcome studies, suggesting further investigation.

The observed inverse relationship between CKD stage and dietary adherence may reflect the increasing complexity of nutritional management in patients with more advanced kidney disease. Individuals with later-stage CKD often face stricter dietary restrictions, medication regimens, and symptom burdens that may make adherence to structured dietary interventions more challenging. Nevertheless, the relatively modest magnitude of the correlation suggests that PLADO remains feasible across different CKD stages when appropriate dietary counseling and clinical monitoring are provided.

Lack of association between knowledge and PLADO adherence suggests that knowledge is importance however not adequate for sustained dietary change. Thus, main variables affecting adherence patterns include phycological, cultural, and economic. Compering food costs of plant-based proteins and animal-based protein sources showed that meat and milk alternatives and their animal-based products were compared in six European countries. In Germany, meat substitutes were 24 to 115% more expensive than conventional meat products, whereas milk replacements ranged from 35 and 58% more than cow's milk. Based on these data, plant-based protein alternatives should be more affordable in order to be more accessible to the overall population (Siegrist *et al.*, 2024). Lower socio-economic status groups have increased mortality and morbidity risks, almost globally. More specifically, the possibility of being married, higher educational levels, and higher annual salary were increased in Cypriot individuals diagnosed with hypertension and hyperlipidemia (Kyprianidou *et al.*, 2023). Based on our results, the importance of education is highlighted demonstrating the association with nutritional understanding, however knowledge alone could not predict diet adherence.

Even though, CKD relatively predicted PLADO adherence, based on the present study results, the absence of association between knowledge and PLADO's adherence could indicate that structural and habitual factors may have a stronger correlation that individual nutrition knowledge. Educational strategies must be implemented to patients with CKD and to the overall general population to increase awareness regarding nutrition with especially focus on protein. Nutrition interventions specialized in chronic diseases should be emphasized in order to enhance effectiveness of these individualized interventions. PLADO is not adopted as a

lifestyle pattern therefore, campaigns on general healthy eating, cannot be imposed. Healthcare professionals should be familiar with this new dietary approach to effectively promote it to patients with CKD. Moreover, it requires renal-specific dietary composition, with protein restriction, and increase of the appropriate plant-based proteins. Patients at early-stage of CKD should be provided with structured dietary intervention guidelines after diagnosis by renal dietitians. Renal dietitians role has a significant impact in reducing CKD progression rate or preventing the disease, which led to increase access to renal dietitians in nephrology clinics (Kistler *et al.*, 2024). Results showed that females adhered more frequently to PLADO recommendations therefore, leading to more gender-sensitive educational strategies which may improve adherence. 27.2% of adherence variation to the Mediterranean diet was explained by culinary abilities which were shown in females compared to males (Gonçalves *et al.*, 2025). Food accessibility is also a barrier. Individuals with kidney impairment should have access to fresh legumes, plant-proteins, and low-protein products should be implemented in Cypriot supermarkets, as the incidence rate of CKD is increasing. For instance, in Italy they have formulated a low-protein pasta, ideal when following renal diet. Including low-phosphorus, low-potassium and unsalted products should also be considered to make food more accessible. Another possible implementation could be affordable plant-based ready-made meals which they can be delivered to patients. The meals would be individualized designed based on renal dietitians meal plans. Lastly, the overall adherence showed feasibility challenges, with only 7% following PLADO out of 56 adults with CKD, and Cypriot individuals prefer consuming animal-dominant protein patterns, structured support interventions should be implemented. Based on literature, protein counting education in general population and focus groups should be also integrated by all clinical dietitians to increase protein awareness, and adherence to healthier dietary habits.

5.5 STRENGTHS OF THE STUDY

By evaluating PLADO regimens across all CKD stages in the Cypriot renal population, the present study offers new geographic findings. To our knowledge, no previous research has been conducted to measure PLADO's effectiveness and adherence. One of the strengths of the study is that is multi-phase design research, which integrating evidence, exploratory analysis, instrument validation, and cross-sectional intervention study within a combined framework. This method enabled to identify information gaps, creating a validated measurement tool for healthy and CKD populations, and the structured evaluation of dietary implementation of PLADO over time. Thus, the study effectively implemented theoretical nutritional guidelines

into a structured practical setting. Firstly, the study improved the comprehension of behavioral and clinical changes over time, increased internal validity, and provided with meaningful data by developing a baseline reference point. The process of diagnostic to intervention process demonstrates an implementation-focused approach that is consistent with renal care management. Moreover, the dietary intervention was based on realistic approaches when comparing PLADO with conventional LPD instead of PLADO and other strict vegetarian diets such as veganism. This allowed cultural adaptation, as very-low protein-dominant diets should be administered with the supplementation of keto-analogues which are not available in Cyprus. Comparing PLADO and conventional LPD increased applicability and sustainability of the study. Furthermore, the pre-post method, allowed evaluating changes following structured PLADO intervention within a real-world clinical setting. Comparing baseline and post-intervention clinical outcomes aid to offer first insights into the feasibility and possible effects of PLADO for individuals with CKD in Cyprus. Thus, even though this was a small sample, results showed that education improves understanding regarding protein, patients can follow as strict diets as PLADO. This implementation method bridges a significant research need in renal nutrition, as clinical trials frequently demonstrates efficiency in controlled environment although they don't provide enough implementation strategies in real-world adaptation.

These additional analyses strengthen the overall interpretation of the intervention findings. First the responder analysis demonstrates that the beneficial PLADO signal was not confined to mean group change but was evident at the individual patient level. Second, calculated effect sizes support the clinical relevance of the observed changes, especially for renal biomarkers and phosphorus control. Third, the safety analysis addresses a key concern frequently raised regarding plant-dominant diets in CKD, such as hyperkalemia or nutritional compromise and suggests that these complications were not prominent in the available dataset. Fourth, subgroup analysis indicate that the potential benefits of PLADO may extend across multiple CKD stages, including more advanced disease, when implemented under appropriate clinical supervision. Finally, the comparative PLADO-KDOQI analysis reinforces the superiority trend observed across several parameters, particularly inflammatory markers, lipid profile, and acid-base balance.

Although regression analysis did not identify significant baseline predictors of response, this likely reflects the limited sample available for exploratory modeling and highlights the need for larger randomized controlled studies incorporating detailed adherence, comorbidity, and medication data.

5.6 LIMITATIONS OF THE STUDY

Despite its strengths, including a multi-phase design and validated assessment tools, the study is limited by modest sample size in the intervention phase and the observational nature of questionnaire-based findings. One of the main limitations is the small sample size, which reduces the statistical power thus findings cannot be generalized. As a feasibility-oriented study, the results should be interpreted with caution as exploratory than definite. Although the intervention sample size was sufficient to detect moderate effects based on post hoc power calculations, the study may have been underpowered for smaller biochemical changes and subgroup analyses.

Moreover, the absence of repeated measures of biomarkers throughout the intervention period which limits the ability to assess behavioral trajectories or temporal patterns of change. Another limitation of the present study is the absence of proteinuria assessment as an outcome measure. Proteinuria is a well-established marker of kidney disease progression and response to therapeutic interventions. However, the analysis of proteinuria was not included in the original study protocol or ethics approval, and therefore it could not be formally incorporated into the study outcomes. Consequently, the evaluation of renal outcomes in the study relied primarily on serum-based indicators, including eGFR, creatinine, and urea levels.

Although validated questionnaires are considered appropriate tools for assessing nutrition knowledge, dietary behavior, and adherence patterns, the present study relied partly on self-reported responses, which may be subject to recall bias, reporting inaccuracies, and social desirability bias. Future research should incorporate more objective assessment methods where feasible, including dietary biomarkers, repeated 24-hour dietary recalls, digital food tracking applications, direct observation methods, or biochemical monitoring, in order to improve measurement accuracy and strengthen the validity of dietary adherence assessment.

Furthermore, specific adherence measurements for the intervention group or control group were not conducted, therefore conclusions of long-term PLADO adherence should be taken under consideration. As previously proven, individuals diagnosed with CKD were more likely to adhere to healthier dietary habits due to disease status, which may lead to inconclusive data and findings for adherence may not be as relevant to larger renal groups. Thus, as this was not a randomized-controlled trial, it reduces the ability of contributing factors affecting intervention. Moreover, cultural patterns may impact the effectiveness of PLADO intervention to non-Mediterranean regions.

5.7 IMPLICATIONS FOR CLINICAL PRACTICE

Medical nutrition therapy in renal management is essential. Results from this study have several implications for clinical practice. Firstly, following PLADO as dietary treatment appears to be effective in patients with CKD especially when supported by individualized nutrition education. For the purpose to offer individualized nutritional guidelines, results highlight the significance of conducting baseline dietary assessments to identify knowledge gaps and protein-dominance dietary patterns before intervention. Additionally, to clarify misconceptions and increase patient need to be involved to their nutrition therapy, organized and repeated nutrition educations are essential.

The validated questionnaire facilitates monitoring dietary habits over time and conduct standard evaluations. This will help to detect possible unhealthy dietary habits as well as nutrition literacy to individuals who are at high risk of developing CKD. Therefore, early implementation of PLADO, in individuals with kidney dysfunction at earlier stages, may be beneficial before worse outcomes emerge. Lastly, effective implementation involves multidisciplinary coordination among renal care teams including nephologist, renal dietitian, health-provider, psychologist, and family member in order to provide optimal adoption. The findings of the present study also support the importance of adopting a holistic lifestyle approach in the prevention and management of CKD. Although nutritional intervention represented the primary focus of this research, CKD progression is strongly influenced by multiple modifiable lifestyle factors, including physical inactivity, obesity, poor sleep quality, smoking, metabolic dysfunction, and low adherence to medical and dietary recommendations. Therefore, effective renal care should extend beyond isolated dietary prescription toward comprehensive patient-centered lifestyle management.

In this context, the PLADO dietary approach may function most effectively when integrated with regular physical activity, weight management strategies, adequate sleep hygiene, cardiovascular risk reduction, smoking cessation, and continuous nutrition education. Such multidimensional interventions may contribute not only to improved renal biomarkers, but also to enhanced metabolic health, inflammatory regulation, quality of life, and long-term dietary adherence among patients with CKD.

5.8 RECOMMENDATIONS FOR FUTURE RESEARCH

Future research includes conducting large randomized controlled trial to assess long-term clinical outcomes of PLADO on CKD progression and renal replacement therapy. Larger intervals for follow-up would allow monitoring of long-term safety and sustained renal function patterns. Additionally, reporting the optimal ratio of plant-based protein needed for effective kidney protection is still a significant remaining concern, particularly when distinguishing PLADO from other strict vegetarian patterns. Moreover, future research will aim to expend the present findings through the development of prospective studies designed to further investigate factors linked with CKD progression. Finding opportunities, including postdoctoral research grants, will be explored to support the continuation and expansion of this research.

A key objective of future work will be the inclusion of additional biochemical markers such as proteinuria, in order to provide a more comprehensive evaluation of renal function and disease progression. Investigating the causal relationships and clinical mechanisms underlying CKD.

Furthermore, future studies will examine the effects of specific pharmacological treatments and targeted exercise interventions on renal outcomes and overall patient health. Assessing how these interventions influence biochemical markers and disease progression could provide valuable insights for optimizing management strategies.

Further research should be conducted regarding later CKD stages to evaluate feasibility and safety of PLADO regimens. Multicenter and cross-cultural research is needed in order to assess PLADO outside of Mediterranean regions. Lastly, PLADO-specific questionnaire expanded cognitive validation should aid standardized monitoring easier for future renal nutrition studies.

Although this study focused on the clinical effectiveness and implementation feasibility of a plant-dominant low-protein diet (PLADO) in Cypriot individuals with CKD, future research should incorporate microbiota profiling to further elucidate the mechanistic pathways underlying dietary effects in renal disease. Emerging evidence suggests that dietary protein source influences gut microbial composition, uremic toxin production, and systemic inflammation, all of which may contribute to CKD progression. Moreover, future studies evaluating plant-dominant dietary interventions in CKD should consider incorporating standardized proteinuria measurements as part of the study protocol to provide a more comprehensive evaluation of renal outcomes. Thus, integrating stool sample analysis, 16S

rRNA sequencing, and metabolomic profiling in longitudinal dietary intervention studies would provide deeper insight into the gut–kidney axis and clarify whether plant-dominant protein strategies exert renoprotective effects through microbiota-mediated mechanisms. Such multidimensional investigations could enhance precision nutrition approaches and strengthen causal inference regarding dietary modulation in CKD management. Future intervention studies investigating PLADO implementation should combine questionnaire-based assessments with objective dietary and clinical monitoring tools to provide a more comprehensive evaluation of adherence and behavioral change.

Finally, future research will involve multidisciplinary collaboration, incorporating expertise from additional medical specialties to enhance the scope, methodological rigour, and clinical applicability of the study.

5.9 EVALUATION OF THE STUDY AIM AND OBJECTIVES

The primary aim of this study was to evaluate the clinical effectiveness and implementation feasibility of a culturally adapted plant-dominant low-protein diet (PLADO) in slowing the progression of chronic kidney disease (CKD) among Cypriot patients, compared to a conventional low-protein dietary approach.

Overall, the findings of the intervention phase provide preliminary support for the clinical potential of PLADO in CKD management. Although not all biomarkers reached statistical significance, the magnitude and consistency of improvement across renal and inflammatory markers favor the plant-dominant dietary approach. These findings suggest that PLADO may represent a feasible and biologically plausible strategy for attenuating renal function decline within a Mediterranean population.

5.9.1. Objective 1: To determine the effect of PLADO on renal function decline.

This objective was addressed through longitudinal assessment of eGFR, serum creatinine, and serum urea levels over the nine-month intervention period. The PLADO group demonstrated greater improvements in renal function markers compared to the conventional low-protein diet group, including a larger reduction in serum creatinine and a more pronounced increase in eGFR. Although statistical significance was not uniformly achieved, the direction and magnitude of change support the hypothesis that a plant-dominant protein distribution may confer renal protective effects. These findings align with existing literature highlighting

reduced dietary acid load and improved metabolic efficiency associated with plant-based protein sources.

5.9.2. Objective 2: To evaluate the impact of PLADO on metabolic and biochemical parameters relevant to CKD progression.

Metabolic parameters, including lipid profile, inflammatory markers, and acid–base balance, were monitored throughout the intervention. The PLADO group exhibited notable reductions in inflammatory markers, particularly CRP, alongside favorable changes in lipid parameters and metabolic stability. Electrolyte levels remained within acceptable ranges, suggesting that concerns regarding hyperkalemia or protein insufficiency were not clinically evident in this cohort. These findings support the metabolic safety and potential anti-inflammatory benefit of the PLADO intervention.

5.9.3. Objective 3: To compare dietary adherence rates, dietary satisfaction, and intervention feasibility between groups.

Adherence was monitored through structured dietary follow-up and assessment tools validated during earlier study phases. The PLADO intervention was found to be feasible within the Cypriot cultural context, with comparable adherence rates to the conventional low-protein diet. The incorporation of familiar Mediterranean plant-based foods likely facilitated acceptability. These findings demonstrate that a culturally adapted plant-dominant dietary model can be realistically implemented in routine renal practice.

5.9.4. Objective 4: To assess the effect of PLADO on patient-reported outcomes, including quality of life and dietary acceptability.

Patient-reported measures indicated satisfactory acceptability of the PLADO dietary pattern. While formal quality-of-life instruments may not have demonstrated statistically significant differences, subjective feedback and adherence patterns suggest that plant-dominant approaches did not negatively impact dietary satisfaction. This is clinically relevant, as long-term sustainability of renal dietary interventions depends heavily on patient acceptance.

5.9.5. Objective 5: To identify cultural, social, and economic determinants influencing adherence to PLADO.

The cross-sectional questionnaire phase revealed significant variability in protein-related knowledge, dietary behaviors, and perceptions of sustainability within the Cypriot population.

Knowledge gaps were particularly evident among younger and less-educated participants. These findings underscore the importance of structured nutritional education and culturally tailored counseling when implementing plant-dominant renal diets. Thus, adherence is influenced not solely by clinical prescription but also by nutrition literacy and socio-cultural context.

Taken together, the study objectives were substantially addressed across the multi-phase research design. The integration of literature review, questionnaire validation, baseline epidemiological analysis, and intervention monitoring provides a comprehensive evaluation of both the theoretical and practical dimensions of PLADO implementation. While larger randomized controlled trials are required to confirm long-term efficacy and generalizability, the present findings offer meaningful preliminary evidence supporting the clinical and contextual viability of plant-dominant low-protein dietary strategies in CKD management.

5.10 ROAD TRIP OF PHD

This PhD trip from 2020 to 2026 aimed on the development, validation, and clinical implementation of the Plant-dominant Low-protein Diet (PLADO) in patients with CKD, with emphasis on the Cypriot population. The research grew through several research phases while also combining student teaching assistantship, clinical practice, scientific dissemination, and interdisciplinary collaboration. Figure 5.2 presents a visual Gantt-chart throughout the years.

Phase I: Foundation and Exploratory Research (2020 – 2022)

The PhD program began with the successful completion of doctoral modules, examinations, and proposal development. Then an exploratory cross-sectional study was developed to evaluate dietary protein perception, knowledge gaps, and CKD-related nutrition habits in Cypriot general population. During this phase, a structured questionnaire was developed, and initial statistical analysis was performed. PhD accreditation and pre-viva assessments were successfully performed. Results from the exploratory study were presented as poster at the 11th Cyprus Dietetic and Nutrition Association Conference. Simultaneously, I started my Student Teaching Assistantship, giving lectures at several nutrition levels (BSc and MSc), which initiated the beginning of academic growth.

Phase II: Methodological Refinement and Knowledge expansion (2022 – 2023)

This step of the research aimed to improve the methodology and broadening the theoretical framework. Systematic evaluation was developed and then modified into a narrative review of PLADO regimens in patients with CKD. Bioethics forms were updated, and methodological improvements were conducted.

Participating in national and international conferences, such as winter conference of nutrition society in the UK, and public health contributions (including World Kidney Day activities) helped to widen scientific engagement.

In September 2023, I was hired as a Clinical Dietitian at Nefrozoi Dialysis Center. This position gave direct clinical exposure to patients with CKD, significantly improving the practical aspect of the study.

Academic responsibilities expanded to include teaching and supervising BSc and MSc Clinical Dietetics students, as well as placement-based instruction for visiting students from the University of Missouri (USA).

Phase III: Validation and Clinical Intervention (2024 – 2025)

After receiving the Bioethics approval in 2024, the questionnaire underwent revision and validation by an expert panel. Validation analysis improved the research tool's diagnostic and evaluative effectiveness.

A 6-month clinical intervention comparing PLADO with conventional LPD was conducted in Cypriot adults with CKD. Baseline and post intervention analysis was monitored on data collection, adherence tracking, renal biomarkers, and patient-reported outcomes. This phase led to:

- Publication of a narrative review in *Nutrients* (2025)
- Publication of the validated questionnaire study in *Frontiers* (2025)
- Oral presentation of intervention results at the 13th Cyprus Dietetic and Nutrition Association Conference.
- Involvement in scientific and organizing committee of the CyDNA conference.

Phase IV: Synthesis and Thesis completion (2025 – 2026)

Validation and intervention results went through final statistical analysis. Thesis chapters were completed and merged.

In parallel, participation in the Nutri-Age study on intermittent fasting in menopause women have widen research engagement beyond renal groups, which indicated multidisciplinary collaboration and methodological transferability.

Doctoral thesis was completed in early 2026.

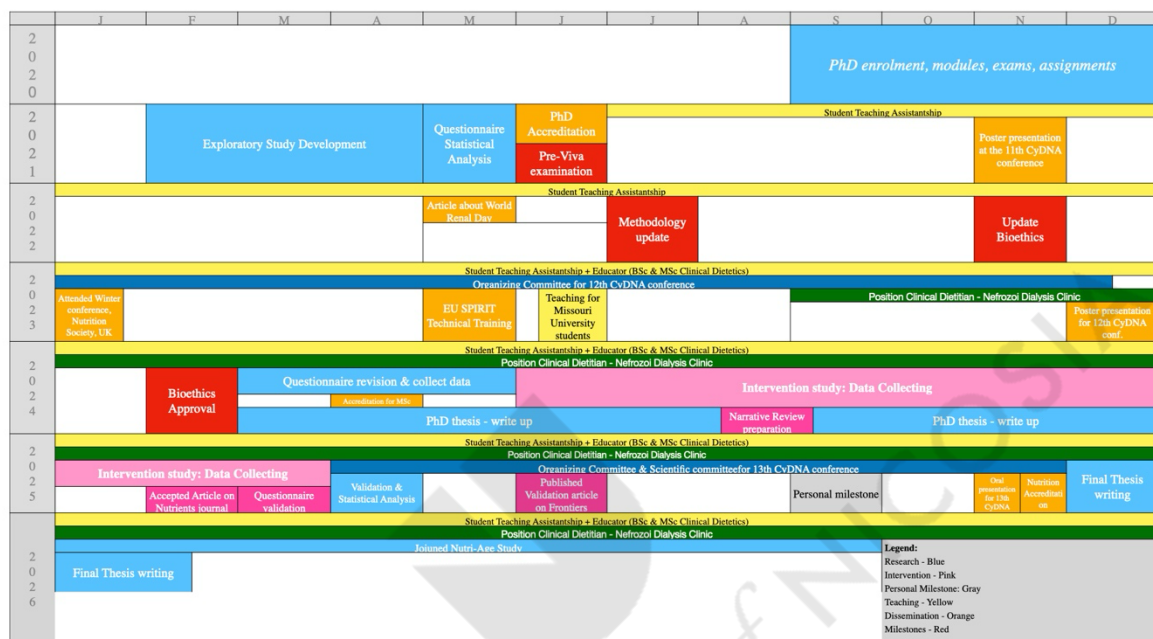


Figure 5.2: Gantt-Chart for PhD (2020 - 2026)

Key Achievements:

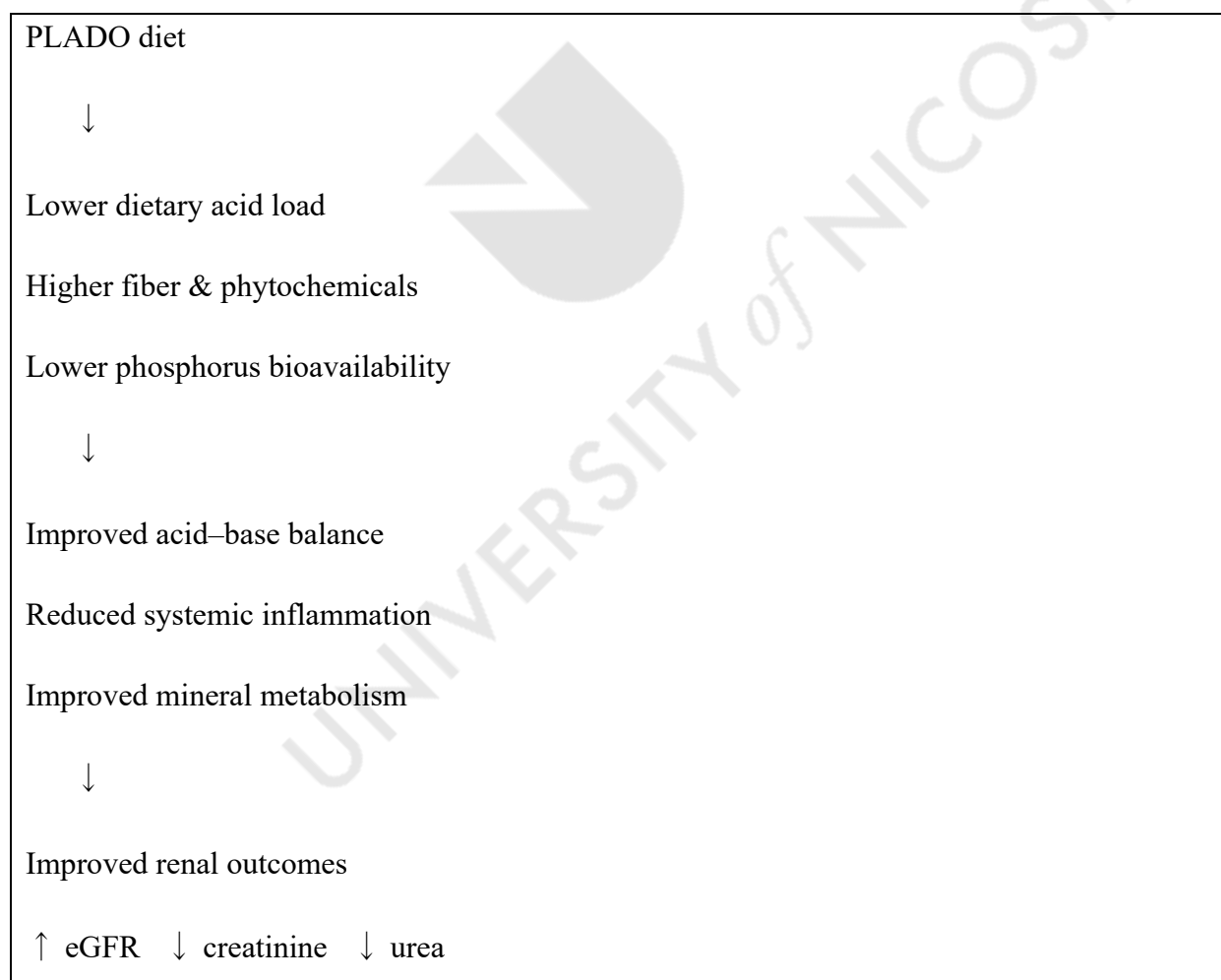
- Developed and validated a CKD-focused dietary knowledge assessment questionnaire.
- Implemented a 6-month PLADO intervention.
- Peer-reviewed publications in international journals (Nutrients, Frontiers).
- Integration of research within a real-world dialysis setting.
- Academic teaching across all levels of university students.
- Participation in scientific and organizing committee of Cyprus Nutrition and Dietetic Association conferences.
- Public health engagement and dissemination actions.
- Interdisciplinary research collaboration.

5.11 CONCLUSIONS

CKD incidence rate in Cyprus is estimated at 204 per million population. According to recent data from Cyprus General Healthcare System (GeSY), CKD diagnosed patients who have been referred to a clinical dietitian, estimated renal failure prevalence rate of 4.7%. Advanced CKD was at 0.8% of the population, while 0.29% were undergoing renal transplant therapy. Although, from the years 2014 to 2021 the number of dialysis initiation in Cypriots increased by 70%. These numbers highlight the importance of the disease, and the need of early diagnosis and intervention to decrease the progression rate of renal failure. Nutrition intervention is essential to the disease to ensure adequate energy intake, preventing complications, reduce morbidity, hospitalization, and disease progression (Oliveira *et al.*, 2019). Low-protein diets, total protein intake between 0.6 to 0.8 g/kg/day, have been proven to lower eGFR when compared to higher protein intake in patients with CKD. Previous guidelines from KDIGO in 2012 reported that protein intake in adults with kidney dysfunction should be more than 75% from high-biological values sources, which are animal-proteins. Although new guidelines from the same organization in 2024 reported the shift towards more plant-based products as animal-products may increase phosphorus and acid load. This led to the development of plant-dominant low-protein diet (PLADO), which is consisted of a total protein intake of 0.6 to 0.8 g/kg/day with more than half of the protein to be plant-based sources (Kalantar-Zadeh *et al.*, 2020). However, even though has gained a lot of attention in regard of CKD management, there is a lack of evidence in several critical domains. Randomized controlled trials have evaluated the benefits of higher vegetarian-protein consumption in adults with CKD however structured implementation of PLADO is limited. Moreover, most available evidence have been conducted outside Mediterranean region, and no published data have investigated the effectiveness of PLADO as well as clinical outcomes in Cypriot renal populations. No validated tools have been developed to measure population's awareness, knowledge, and perceptions of protein sources, with no clear evidence on the impact of structured nutrition education on clinical and behavioral outcomes among patients with CKD. Based on these, this study aims to address these gaps by developing and validating a questionnaire assessing people's knowledge regarding protein-types and to investigate the effectiveness and adherence of PLADO intervention on Cypriot renal population. This chapter brings together the overall findings of the present study and is structured into four domains. Summary of the findings is firstly presented, followed by a critical evaluation of strengths and limitations of the study, and clinical implications and future suggestions concluding the section.

Algorithm 5.3 and figure 5.3 illustrate the proposed biological mechanisms through which the plant-dominant low-protein diet (PLADO) may influence renal outcomes in patients with CKD. The increased consumption of plant-based proteins and fiber combined with reduced intake of animal-derived sulfur-containing amino acids contributes to a lower dietary acid load and improved metabolic acid–base balance. Additionally, plant-based diets provide higher levels of antioxidants and phytochemicals, which may reduce systemic inflammation. Reduced phosphorus bioavailability from plant sources may further improve mineral metabolism. These mechanisms collectively support the observed improvements in renal biomarkers, including increased eGFR and reductions in serum creatinine and urea.

Algorithm 5.3 : Proposed Mechanistic Pathway Linking the Plant-Dominant Low-Protein Diet (PLADO) to Improved Renal Outcomes in Chronic Kidney Disease.



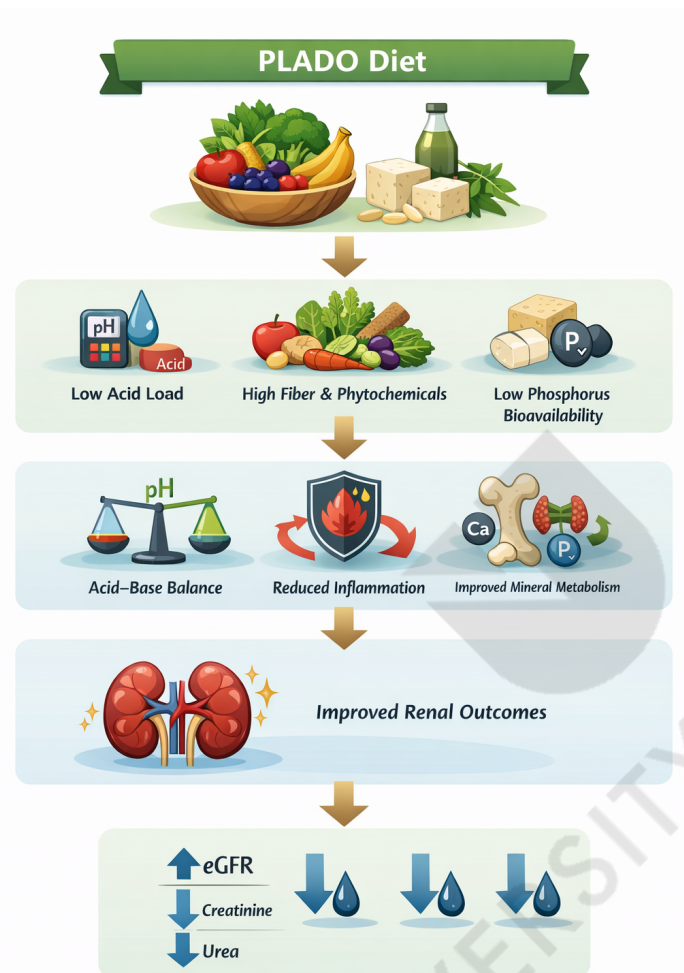


Figure 5.3: Proposed Mechanistic Pathway Linking the Plant-Dominant Low-Protein Diet (PLADO) to Improved Renal Outcomes in Chronic Kidney Disease.

CHAPTER 6 CONCLUSION

6.0 CONCLUSIONS

The present study is multi-phase research which in addition to assessing patient knowledge, adherence, and effects of structured nutrition education within a Mediterranean region, the present study aimed to investigate the scientific support, variability, and clinical significance of applying PLADO in patients with CKD.

Literature review created the scientific rationale for PLADO in management of CKD by integrate results from observational and randomized controlled trials. This highlighted possible complications with protein sufficiency, the risk of hyperkalemia, and long-term adherence while also highlighting the benefits of vegetarian-protein intake in reducing renal disease progression rate, improving metabolic markers, and lowering dietary acid load. Importantly, the review found limited data regarding region-focus, especially in Mediterranean, highlighting the significance for broader research. PLADO has been developed especially for renal populations, emphasizing in plant-dominant low-protein intake, and promotes environmental sustainability. Differences of PLADO and other vegetarian diets is that PLADO is a plant-dominant low-protein diet indicating that protein distribution is more than 50% of the total protein intake with minimal consumption of animal-based products. Vegetarian diets, however, are plant-exclusive protein intake, with no or limit consumption of animal-based protein. Results from several research including randomized controlled trials, observational cohort studies, and meta-analyses supported the beneficial properties of PLADO in renal management. Evidence showed that plant-based protein improved nutrient density therefore promoting overall healthy and potentially decreasing possible complications of protein restriction due to their increases levels of essential vitamins, minerals, fiber, and antioxidants compared to animal-based foods which are in saturated fat, cholesterol, and phosphorus. Moreover, higher acid load produces sulfuric acid and hydrogen ions within the body leading to low-grade metabolic acidosis rate which is linked with metabolic modifications including insulin resistance, diabetes, and hypertension, all contributing factors to CKD progression rate. Animal-protein is higher in dietary acid load compared to plant-protein, therefore plant-based diets is beneficial in reducing acid load therefore improving kidney function. Furthermore, anti-inflammatory components, including beneficial bacteria found in plant-based products leads to improved inflammatory profile, reducing oxidative stress, and increase gut microbe in patients with kidney impairment. Food industry accounts for 25% of global greenhouse gas emissions,

thus peoples' dietary decisions can influence the development of climate crisis, especially regarding to global warming challenge. One of the main dietary modifications is the reduction of animal-based consumption and to increase plant-based products. Therefore, plant-based is a promising alternative option in order to reduce greenhouse gas emissions in the environment.

Based on the literature review, several questions were developed. The absence of validated tools to evaluate peoples' perception, awareness, and sustainability for general dietary protein with focus on plant-based diet was the initial step. An exploratory cross-sectional analysis conducted using an online questionnaire was conducted which revealed significant knowledge gaps and behavioral variations regarding dietary protein intake within Cypriot population. The total sample of the questionnaire was 120 participants, 63 males and 57 females, mainly without renal failure. Majority of the sample were from 31 to 45 years ($n=45$), followed by younger individuals from 18 to 25 years ($n=38$), with a total of 57 individuals being at undergraduate level, 54 at postgraduate level, and only 9 participants had secondary education level. When examining the relation of education and age as predictors for total knowledge score regarding protein, results showed that females had a significant higher knowledge score compared to men ($U = 1154.00$, $z = -3.47$, $p = .001$), and there was a significant difference in total knowledge score across age groups ($\chi^2 = 11.37$, $df = 5$, $p = .044$), indicating that participants within 26 to 30 years showed significantly higher knowledge scores compared to 31 to 45 years (mean difference = 1.53, $p = .023$). However, no significant differences were observed in education level, changes in plant-protein, and changes in animal-protein with knowledge score. Moreover, individuals who considered plant-based diets to be sustainable showed a significant tendency to higher knowledge scores compared to those who were unsure. Most participants, 70%, were classified in the low-protein knowledge, whereas only 30% demonstrated moderate-protein knowledge, with no participants achieving high-protein knowledge. 72 participants answered positively when asked whether they knew which foods groups contain protein and found a significant correlation with total protein-knowledge than individuals who did not know which food groups contain protein. Overall, the findings demonstrated the importance of nutrition literacy and dietary behaviors and highlights the gap of nutrition awareness and implementation of plant-dominant dietary diets. After some adjustments to the online tool, the questionnaire went through the validation process in order to create a standardized measurement to tool and can be adopted by healthcare professionals and to contribute to renal nutrition research.

Through expert panel assessment, the validation phase confirmed the questionnaire's methodology, clinical application, relevance, and clarity. The tool was appropriate for evaluating dietary knowledge, people's perception, and behaviors toward protein sources, and adherence with PLADO guidelines for both healthy and renal Cypriot populations.

After establishing the questionnaire's validity, it was then used to conduct baseline data regarding knowledge, protein-source distribution, dietary patterns and behaviors, plant-based sustainability, and provide a reference point for further longitudinal evaluation. A total of 137 participants has responded to the questionnaire, of which 82 were females, and 55 were males with the majority being above 61 years old. Total knowledge score had a mean of 6.35 with a wide range of 0 to 14, suggesting wide variability in nutrition literacy. Average BMI was at 24.75 which was at the upper limit of "normal" range, borderline overweight, followed by 41.2% who were either overweight or obese. 48% demonstrated average adherence to the Mediterranean Diet score, whereas only 2 participants reported excellent adherence. Thus, 23 participants reported a good Mediterranean diet score, however 7 participants were in the obese range, indicated that higher MediDiet score doesn't correlated with healthier body weight, however non-significant association was reported. Moreover, individuals in the obese range showed a higher borderline significance in CKD, suggesting a possible link. Suggesting larger sample sizes or longitudinal data may clarify this potential association. A total of 57 participants were diagnosed with renal failure, with 32% being at stage 5, followed by 14% at stage 3a. Furthermore, BMI reported that gender was a significant predictor, with males reaching 2.98-points higher BMI compared to females ($p < 0.001$). Age group was also significantly correlated with BMI ($p = 0.003$), while CKD status did not demonstrate a significant association ($p = 0.594$). Thus, neither knowledge nor BMI significantly predicted Mediterranean diet adherence suggesting that dietary behaviors may depend on social, cultural, or environmental factors, which were not captured in this model. However, higher education and older age group showed strong positive predictor of total protein-knowledge and its dietary role. Thus, increased knowledge scores were marginally predictive of participants reporting changes in protein intake after CKD diagnosis, which supports that nutrition literacy may increase behavior dietary modification in chronic diseases. According to the findings of the study, a population tends to be educated and determined, with high adherence rated and dietary sensitivity after diagnosis. Although, according to regression models, there are still knowledge gaps, especially in younger and less education groups, therefore, improving dietary patterns that are consistent with CKD nutritional guidelines, future intervention should emphasize in

individualized nutrition education and increase on participants' current motivation. Therefore, after acknowledging these gaps, a 6-month intervention study has been developed.

The intervention study was consisted of 60 adults with CKD which were divided into two groups (n=30 each). Both groups had an equal gender distribution (female = 15; males = 15). Their biomarkers and clinical indicators were monitored at baseline and the end of the intervention. The intervention group followed a 7-day cyclic PLADO for 9 months, customized to patient's needs and wants, following PLADO guidelines. Control group, who also followed a 7-day cyclic LPD based on KDOQI guidelines, with flexibility in food sources. Control group showed minor but consistent improvements regarding renal function indicators, serum creatinine decreasing by 0.1 mg/dL, eGFR increased by 1.0 mL/min/1.73 m². Both serum albumin and hemoglobins levels showed improvement with +2.9% and +0.9%, respectively. Electrolyte levels remained stable, indicated adequate metabolic control. Moreover, lipid profiles also showed positive improvements with lower levels of LDL cholesterol and increased of HDL cholesterol, post-intervention. Notably, inflammation markers declined by 2.4%, suggesting that conventional LPD has anti-inflammatory dietary effects. PLADO group showed more promising results than the conventional LPD, including increased on kidney function, nutritional markers, and significant reductions in inflammation markers. Serum creatinine decreased by 0.3 mg/dL, eGFR increased by 5 mL/min/1.73 m² and serum urea declined by 7 mg/dL. Significant anti-inflammatory effect was observed in the intervention group, where CRP dropped by 20.9%. Thus, improvements were also observed in the lipid profile as well as acid-base status. However, the lack of statistical significance, the direction and magnitude of change in individual markers strongly favor the PLADO group. Improvements in kidney function and inflammation markers were notably larger in the intervention group than the control. These results are consistent with existing literature that supports the effect of plant-dominant diets regarding greater kidney and cardiovascular outcomes. However, larger-scale randomized controlled trials are needed to confirm these promising trends.

Overall, the findings of the intervention phase support the primary hypothesis that a plant-dominant low-protein dietary pattern may provide clinically meaningful advantages in patients with CKD compared to conventional low-protein diets. Although not all biomarkers reached statistical significance, the consistent direction of change across renal, inflammatory, and metabolic markers strengthens the biological plausibility and clinical relevance of PLADO in CKD management.

When integrating findings across all phases of the study, a coherent narrative emerges. The literature review established the scientific rationale for plant-dominant protein strategies in CKD. The questionnaire phase identified significant knowledge gaps and behavioral variability within the Cypriot population, highlighting the need for structured education. The validation process ensured methodological rigor and applicability of the assessment tool. The baseline analysis demonstrated variability in dietary adherence and CKD distribution, while the intervention phase provided preliminary clinical evidence supporting the feasibility and potential effectiveness of PLADO. Together, these findings contribute a comprehensive framework linking nutrition literacy, dietary behavior, and clinical outcomes in renal populations.

From a clinical perspective, these findings suggest that PLADO may represent a safe and potentially advantageous alternative to conventional low-protein diets in CKD management. The observed improvements in renal function markers and inflammatory parameters indicate that structured plant-dominant approaches can be implemented without compromising nutritional adequacy. Moreover, the questionnaire findings emphasize the importance of individualized nutrition education, particularly among younger and less-educated groups.

Beyond clinical outcomes, the environmental dimension of PLADO strengthens its relevance within modern healthcare systems. Given the substantial contribution of animal-based food production to greenhouse gas emissions, the integration of plant-dominant dietary strategies aligns renal nutrition with global sustainability goals. Thus, PLADO offers both a clinically and environmentally responsible approach to CKD dietary management.

In conclusion, this multi-phase research provides scientific, educational, and preliminary clinical evidence supporting the feasibility and potential benefits of PLADO in a Mediterranean renal population. While larger randomized controlled trials are required to confirm long-term efficacy, the present study establishes an important foundation for culturally adapted plant-dominant dietary strategies in CKD. By integrating nutritional literacy, clinical monitoring, and sustainability considerations, this work contributes to the advancement of precision renal nutrition and offers a forward-looking model for chronic disease management.

The present thesis provides preliminary evidence supporting the feasibility and potential clinical benefits of a culturally adapted Plant-Dominant Low-Protein Diet (PLADO) in the nutritional management of CKD within the Cypriot population. Although Mediterranean dietary adherence emerged as an important contextual dietary factor associated with healthier

nutritional behaviors and lower CKD risk, the primary contribution of this research lies in the implementation and evaluation of the PLADO dietary intervention. The findings suggest that a plant-dominant low-protein approach may support improvements in renal biomarkers, inflammatory status, and dietary adherence while remaining culturally adaptable within a Mediterranean setting.

Overall, this study contributes to the growing field of precision renal nutrition by demonstrating that PLADO may represent a practical and sustainable dietary strategy for CKD management when adapted to local dietary traditions and patient-centered clinical care.

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CHAPTER 8 APPENDICES



Review

A Plant-Dominant Low-Protein Diet in Chronic Kidney Disease Management: A Narrative Review with Considerations for Cyprus

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Abstract: Chronic kidney disease (CKD) is a major global health challenge, significantly contributing to morbidity and mortality due to its strong association with cardiovascular complications, metabolic imbalances, and reduced quality of life. Among the various interventions for CKD management, nutrition therapy plays a critical role in slowing disease progression and improving patient outcomes. The Plant-Dominant Low-Protein Diet (PLADO) has emerged as a promising dietary strategy that prioritizes plant-based protein sources while restricting overall protein intake, offering potential renal, cardiovascular, and metabolic benefits. This review evaluates current evidence on the efficacy of PLADO in CKD management, analyzing its impact on renal function, cardiovascular health, and systemic inflammation. Key findings suggest that PLADO can delay CKD progression, reduce dialysis dependence, and mitigate cardiovascular risks through lower dietary acid load, increased fiber intake, and anti-inflammatory properties. Additionally, PLADO has been shown to support gut microbiota diversity and reduce uremic toxin production, offering metabolic advantages beyond kidney health. While PLADO appears nutritionally adequate, concerns remain regarding protein sufficiency, potassium management, and long-term adherence. Its successful implementation requires tailored meal planning, patient education, and regular clinical monitoring to optimize outcomes and mitigate potential risks. This review highlights the importance of integrating PLADO into CKD management as a holistic, patient-centered dietary approach, particularly in regions like Cyprus, where no studies have evaluated its applicability. By synthesizing existing research, this review provides insights for clinicians, dietitians, and researchers to further explore long-term outcomes, adherence strategies, and feasibility across diverse healthcare settings. Future studies should focus on large-scale randomized controlled trials (RCTs) to establish PLADO's role in CKD dietary guidelines and clinical practice.

Keywords: chronic kidney disease (CKD); plant-dominant low-protein diet (PLADO); renal nutrition; plant-based protein; metabolic acidosis; dietary adherence; nephrology care; CKD dietary practices in Cyprus

1. Introduction

Chronic kidney disease (CKD) affects millions of individuals around the world and has a significant public health impact due to its relationship with cardiovascular complications, decreased quality of life, and premature mortality [1]. As CKD progresses, the accumulation of metabolic waste products and the deterioration of renal function necessitate effective management strategies to mitigate its adverse outcomes. Among these, nutrition therapy has emerged as a cornerstone of renal disease management, offering opportunities to

Appendix 2: Certificate of Editor's Choice for Narrative Review.

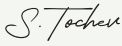
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Appendix 3: Published Article of Questionnaire's Validation.



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Development and validation of a questionnaire for the knowledge assessment and management of PLADO diet in kidney and healthy population in Cyprus

Anna Michail , Constandinos Zesimos, Iris Sergiou,
Katerina Tzini and Eleni Andreou  *

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Chronic kidney disease (CKD) requires dietary strategies that balance protein restriction, nutritional adequacy, and sustainability. As plant-dominant dietary models gain prominence in renal nutrition, understanding public perceptions of protein sources and their health impacts is increasingly critical. However, no validated assessment tool exists to evaluate such perceptions within the Cypriot population. This study presents the development and validation of a novel questionnaire designed to assess perceptions of sustainability, nutritional value, and health impacts of plant- and animal-based proteins, with a focus on kidney health. The instrument was developed through literature review, expert input ($n = 10$), cognitive pretesting, and pilot testing ($n = 120$). Validation included content validity indexing (I-CVI), Modified Kappa statistics, internal consistency via Cronbach's alpha, and exploratory factor analysis (EFA). Expert agreement was high, with an S-CVI/Ave of 0.89 and 93% of items achieving I-CVI ≥ 0.83 . Internal consistency across subscales ranged from $\alpha = 0.71$ to 0.82. EFA supported construct validity, explaining 36% of the variance. The final 42-item questionnaire covers eight domains, including sustainability beliefs, dietary behavior, and protein knowledge. A unique feature is its embedded educational content—glossary terms, visuals, and explanatory prompts—designed to evaluate baseline knowledge and learning outcomes. Pilot results revealed knowledge gaps and uncertainty about the sustainability of plant-based proteins among CKD respondents. This validated tool fills a significant gap in renal nutrition education and research and offers a reliable, culturally relevant means to assess dietary perceptions. It supports patient education, public health interventions, and clinical practice in promoting sustainable, kidney-friendly diets. Broader application and cross-cultural adaptation are recommended to enhance global utility.

KEYWORDS

chronic kidney disease, protein perception, questionnaire validation, plant-based diet, sustainability, renal nutrition, dietary education, Cyprus

1 Introduction

Understanding consumer perceptions of sustainability, nutrition, and the health impact of dietary protein sources is increasingly relevant in the context of evolving dietary guidelines and public health strategies. In particular, individuals with chronic kidney disease (CKD) require careful dietary management, especially regarding protein intake,

Appendix 4: Final Version of the Questionnaire.

Questionnaire on consumer perception of the sustainability, nutritional value and copy of animal protein and vegetable protein alternatives in the health of Cypriots with renal and non-renal diseases - A follow-up survey. (The effect of the Plant-dominated low protein diet (PLADO) on eGFR and the effect on chronic kidney disease in Cypriot kidney patients. EEBK OP 2024.01.53).

Dear Participant,

You are invited to voluntarily participate in a research study conducted as part of the study titled: "The effect of the Plant-Dominated Low Protein Diet (PLADO) on eGFR and its impact on chronic kidney disease in Cypriot Kidney Patients. EEBK OP 2024.01.53" (Phase 2).

Additionally, this study explores consumer perceptions regarding the sustainability, nutritional value, and health impact of animal protein and plant-based protein alternatives - A follow-up survey. Particular emphasis will be placed on individuals with kidney disease.

This research is conducted by the Department of Life Sciences at the University of Nicosia under the auspices of the Cyprus Dietetic & Nutrition Association and the Pancyprrian Kidney Patients Organization (P.O.N.).

Study Objectives: This study aims to assess the perception of Cypriot consumers regarding the sustainability, nutritional value, and health effects of animal protein and its plant-based alternatives.

The study methodology includes focus groups and an online survey. Maximum differentiation scaling was used to rank the importance of specific characteristics of animal and plant proteins in terms of sustainability and nutritional value, alongside questions to assess participants' knowledge of the topic. The follow-up survey includes questions where respondents will determine whether animal and plant-based protein products are sustainable, natural, healthy, reliable, or ethical.

The specific objectives of the study are:

- To investigate the dietary behaviors of individuals with kidney disease regarding the consumption of animal and plant protein sources.
- To provide nutritional education through the questionnaire to inform participants about protein sources and their essential role.
- To evaluate the effect of a low-plant-protein diet (PLADO) on estimated glomerular filtration rate (eGFR) in Cypriot kidney patients.

Appendix 5: Ethical Approval.



ΚΥΠΡΙΑΚΗ ΔΗΜΟΚΡΑΤΙΑ



ΕΘΝΙΚΗ ΕΠΙΤΡΟΠΗ ΒΙΟΗΘΙΚΗΣ ΚΥΠΡΟΥ

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Αίτηση γνωμοδότησης για την πρόταση με τίτλο:
«The effect of Plant Dominant low protein diet (PLADO) on eGFR and
the effect in chronic kidney disease in Cypriot renal patients»

Αναφορικά με την αίτηση σας ημερομηνίας 18 Φεβρουαρίου 2024 για το πιο πάνω θέμα, επιθυμώ να σας πληροφορήσω ότι από τη μελέτη του περιεχομένου των εγγράφων που έχετε καταθέσει η Εθνική Επιτροπή Βιοηθικής Κύπρου (ΕΕΒΚ) **γνωμοδοτεί θετικά υπέρ της διεξαγωγής της εν λόγω έρευνας.**

2. Η Επιτροπή επιθυμεί να τονίσει ότι παραμένει ευθύνη δική σας η διεξαγωγή της έρευνας με τρόπο που να τηρούνται οι πρόνοιες του νέου Ευρωπαϊκού Γενικού Κανονισμού Προστασίας Προσωπικών Δεδομένων (2016/679) και του περί της Προστασίας των Φυσικών Προσώπων Έναντι της Επεξεργασίας των Δεδομένων Προσωπικού Χαρακτήρα και της Ελεύθερης Κυκλοφορίας των Δεδομένων αυτών Νόμος του 2018 (Ν. 125(Ι)/2018), ως αυτός εκάστοτε τροποποιείται.

3. Σας ενημερώνουμε ότι για σκοπούς καλύτερου συντονισμού και αποφυγής επανάληψης ερευνών με το ίδιο θέμα ή/και υπό εξέταση πληθυσμό μέσα σε σύντομο σχετικά χρονικό διάστημα, η ΕΕΒΚ δημοσιεύει στην ιστοσελίδα της το θέμα της έρευνας, τον φορέα και τον υπό εξέταση πληθυσμό.

4. Κατά τη διάρκεια εκπόνησης της έρευνας, ο συντονιστής / επιστημονικός υπεύθυνος θα ενημερώνει την ΕΕΒΚ για κάθε τροποποίηση των αρχικά κατατεθειμένων εγγράφων (πρωτόκολλο ή άλλα ερευνητικά έγγραφα) και θα υποβάλλει τις απαιτούμενες έντυπες τροποποιήσεις στην Επιτροπή.

.../2

Λαέρτου 22, 2365 Άγιος Δομέτιος, Λευκωσία

Ηλεκτρονικό Ταχυδρομείο: cnbc@bioethics.gov.cy, Ιστοσελίδα: www.bioethics.gov.cy

Appendix 6: Participants Information Sheet and Consent Form.

PARTICIPANT INFORMATION SHEET AND CONSENT FORM

STUDY INFORMATION

Protocol Title:

The Effect of Plant Dominant Low Protein Diet (PLADO) in eGFR and Its Impact on Chronic Kidney Disease in Cypriot Renal Patients – focus group study.

Principal Investigator:

Prof. Eleni Andreou for Anna Michail PhD candidate, Life Sciences Department, School of Life and Health Sciences, University of Nicosia,

PURPOSE OF THE RESEARCH STUDY

You are being invited to participate in a research study. Before you take part in this research study, the research must be explained to you, and you must be given the chance to ask questions. Please read carefully the information provided here. If you agree to participate, please sign the consent form. You will be given a copy of this document to take home with you.

The proposed study, titled "**The Effect of Plant Dominant Low Protein Diet (PLADO) in eGFR and Its Impact on Chronic Kidney Disease in Cypriot Renal Patients,**" aims to investigate the potential benefits of a low-protein diet, specifically PLADO, on renal function among Cypriot renal patients. Chronic Kidney Disease (CKD) is a significant health concern globally, including in Cyprus, and its management often requires complex interventions. PLADO is emerging as a promising dietary approach that may help slow down the progression of CKD.

This study is justified as it addresses an immediate need for alternative CKD management strategies in Cyprus and contributes to the global understanding of nutrition-based interventions. If PLADO proves effective, it could reduce the burden of CKD, enhance patients' quality of life, and potentially lower healthcare costs.

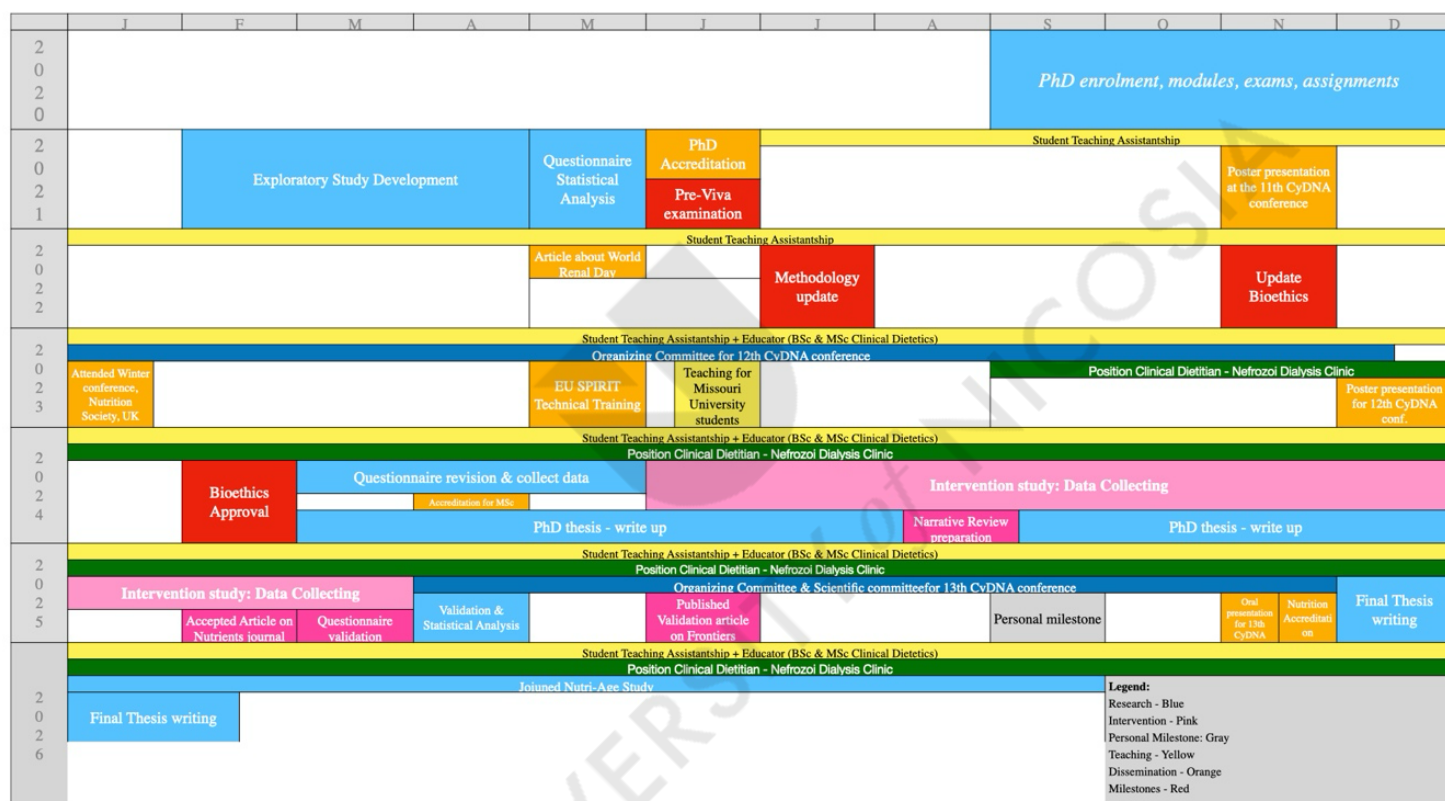
You were selected as a possible participant in this study because you have met the inclusion criteria of the study.

This study will recruit 20 participants from the clientele of Prof. Eleni Andreou and Anna Michail.

STUDY PROCEDURES AND VISIT SCHEDULE

If you agree to take part in this study, you will be randomized to the conventional face-to-face dietary education and individualized meal plan following Mediterranean meal plan in kidney patients (control group) or following the PLADO diet (intervention group) by a dietitian (either Prof. Eleni Andreou or Anna Michail) at their private offices. Randomization means assigning you to one of the 2 groups by chance. The

Appendix 7: PhD roadmap



Appendix 8: Full Meal Plan analysis.

Dietplan 7 90 day trial Menu Analysis PLADO-1600-SUMMARY

Menu code : PL-1600-SUM

Description : PLADO-1600-SUMMARY

Number of foods : 148

Total food weight : 11.61kg

Day 1 to 7, 41 meals, 65 courses

Analysis of selected nutrients :

Nutrient	Unit	Total	per day	per meal	per course
Water	g	7678.7 m	1097.0	187.3	118.1
Total Nitrogen	g	53.87 e	7.70	1.31	0.83
Protein	g	325.4	46.5	7.9	5.0
Fat	g	444.2	63.5	10.8	6.8
Available Carbohydrate (mse)	g	1368.4 m	195.5	33.4	21.1
Energy (kcal)	kcal	10508	1501	256	162
Energy (kJ)	kJ	44057	6294	1075	678
Starch (mse)	g	861.9 m	123.1	21.0	13.3
Total Sugars (mse)	g	436.2 m	62.3	10.6	6.7
Glucose	g	89.9 m	12.8	2.2	1.4
Fructose	g	147.5 m	21.1	3.6	2.3
Sucrose (mse)	g	132.8 m	19.0	3.2	2.0
Maltose (mse)	g	13.4 m	1.9	0.3	0.2
Lactose (mse)	g	13.1 m	1.9	0.3	0.2
Non-starch polysaccharides	g	155.3 +	22.2	3.8	2.4
Total dietary fibre (AOAC method)	g	213.7 +	30.5	5.2	3.3
Saturated fatty acids	g	117.7 m	16.8	2.9	1.8
Mono-unsaturated fatty acids	g	187.6 m	26.8	4.6	2.9
Poly-unsaturated fatty acids	g	74.7 m	10.7	1.8	1.1
Total trans fatty acids	g	2.91 m	0.42	0.07	0.04
Cholesterol	mg	1998.9 m	285.6	48.8	30.8
Sodium (Na)	mg	6542	935	160	101
Potassium (K)	mg	14062 m	2009	343	216
Calcium (Ca)	mg	5221	746	127	80
Magnesium (Mg)	mg	1737 m	248	42	27
Phosphorus (P)	mg	6527 m	932	159	100
Iron (Fe)	mg	84.63 m	12.09	2.06	1.30
Copper (Cu)	mg	7.32 m	1.05	0.18	0.11
Zinc (Zn)	mg	47.47 m	6.78	1.16	0.73
Chloride (Cl)	mg	10500 m	1500	256	162
Manganese (Mn)	mg	29.53 m	4.22	0.72	0.45
Selenium (Se)	ug	230.6 m	32.9	5.6	3.5
Iodine (I)	ug	419.8 m	60.0	10.2	6.5
Retinol	ug	1319 m	188	32	20
Carotene	ug	22149 m	3164	540	341
Vitamin D	ug	21.58 m	3.08	0.53	0.33
Vitamin E	mg	77.06 m	11.01	1.88	1.19
Thiamin	mg	9.42 m	1.35	0.23	0.14

Appendix 9: Foods included in the Cypriot meal plans.

Food Item	Food Category	Serving Size	Protein Source
Greek Yogurt Fage 0%	Dairy	150 g	Animal
Greek Yogurt 2%	Dairy	150 g	Animal
KOKO plain yogurt	Dairy alternative	150 g	Plant
Halloumi (light)	Cheese	30 g	Animal
Anari fresh	Cheese	30 g	Animal
Feta cheese	Cheese	30 g	Animal
Edam cheese (light)	Cheese	30 g	Animal
Almond milk (unsweetened)	Plant beverage	200 ml	Plant
Oats	Whole grain	40 g	Plant
Special K cereal	Breakfast cereal	30 g	Plant
Rice Krispies cereal	Breakfast cereal	30 g	Plant
White tortilla	Bread product	1 tortilla	Plant
Wholegrain tortilla	Bread product	1 tortilla	Plant
White bread	Bread	1 slice	Plant
Rusks	Bread product	2 rusks	Plant
Wholegrain rusks	Bread product	2 rusks	Plant
Wholegrain bread	Bread	1 slice	Plant
Rustic bread	Bread	1 slice	Plant
Artisan gluten-free bread	Bread	1 slice	Plant

Cypriot pitta (white)	Bread	1 pitta	Plant
Cypriot pitta (wholegrain)	Bread	1 pitta	Plant
Spaghetti pasta (white, cooked)	Pasta	1 cup	Plant
Spaghetti pasta (wholegrain, cooked)	Pasta	1 cup	Plant
White rice (cooked)	Grain	1 cup	Plant
Wholegrain rice (cooked)	Grain	1 cup	Plant
Chicken breast (cooked)	Poultry	100 g	Animal
Egg (boiled)	Egg	1 egg	Animal
Salmon (cooked)	Fish	100 g	Animal
Sea bass (cooked)	Fish	100 g	Animal
Pork souvlaki in pitta	Traditional dish	1 portion	Both
Turkey slice	Processed meat	1 slice	Animal
Lountza	Processed meat	30 g	Animal
Lentils with rice (Moutzientra)	Legume dish	1 cup	Plant
Chickpeas with tomato and spinach	Legume dish	1 cup	Plant
Chickpeas boiled	Legumes	1 cup	Plant
Black-eyed peas cooked	Legumes	1 cup	Plant

Hummus	Legume spread	2 tbsp	Plant
Tahini salad	Seed spread	2 tbsp	Plant
Peanut butter	Nut spread	1 tbsp	Plant
Olive oil	Fat	1 tsp	—
Carob syrup	Sweetener	1 tbsp	—
Jam (0% sugar)	Sweetener	1 tbsp	—
Butter (unsalted)	Fat	1 tbsp	Animal
Red apple	Fruit	1 small	Plant
Pear	Fruit	1 medium	Plant
Banana	Fruit	1 medium	Plant
Strawberries	Fruit	1 cup	Plant
Frozen berries	Fruit	1 cup	Plant
Iceberg lettuce	Vegetable	1 cup	Plant
Bell pepper	Vegetable	1 medium	Plant
Carrots fresh	Vegetable	1 cup	Plant
Carrots boiled	Vegetable	1 cup	Plant
Zucchini	Vegetable	1 cup	Plant
Cucumber	Vegetable	1 medium	Plant
Almonds	Nuts	12 almonds	Plant

Walnuts	Nuts	7 halves	Plant
Sunflower seeds	Seeds	1 cup	Plant
Trahanas	Traditional grain dish	1 cup	Animal
Bulgur with vermicelli and tomato sauce	Grain dish	1 cup	Plant
Burekia with anari cheese	Traditional dish	1 portion	Both
Pastitsio	Traditional dish	1 portion	Both
Courgettes with eggs	Traditional dish	1 portion	Both
Kolokasi with meat	Traditional dish	1 portion	Both
Kolokasi without meat	Vegetable dish	1 portion	Plant
Koupes (bulgur & minced meat croquettes)	Traditional dish	1 portion	Both
Corn boiled	Vegetable	1 cup	Plant
Boiled potato	Vegetable	1 medium	Plant
Cooked peas	Legume	1 cup	Plant

Appendix 10: Seven-day PLADO Meal Plan and Nutritional Composition.

Day	Meal	Foods and Portions	Energy (kcal)	Total Protein (g)	Animal Protein (g)	Plant Protein (g)	Fiber (g)	Sodium (mg)	Potassium (mg)	Calcium (mg)	Phosphorus (mg)
1	Breakfast	Almond milk (262 g), oats (40 g), almonds (6)	230.3	8.47	0	8.47	4.60	188	370	556	452
	Snack	Carrots (150 g), hummus (15 g), rusks (25 g)	189.0	5.78	0	5.78	6.40	170	575	63	139
	Lunch	White tortilla (50 g), chickpeas (83 g), hummus (15 g), lettuce (200 g), cucumber (201 g), olive oil	620.1	17.19	0	17.19	12.17	357	1023	127	328
	Snack	Apple (150 g), peanut butter (16 g)	172.0	4.40	0	4.40	4.55	4	263	71	78
	Dinner	Salmon (30 g), carrots (60 g), olive oil, white rice (140 g)	378.1	11.38	7.20	4.18	2.50	53	301	39	198
	Daily Total		1589.5	47.22	7.20	40.02	30.23	772	2533	857	1195
2	Breakfast	Wholegrain bread (60 g), boiled egg (50 g), butter (14 g)	327.9	13.81	6.10	7.71	4.07	304	215	93	224
	Snack	Strawberries (120 g)	38.0	1.00	0	1.00	2.00	1	184	19	29
	Lunch	Rice (220 g), lettuce (200 g), cucumber	606.8	10.99	0	10.99	4.84	38	740	83	182

		(201 g), bell pepper (100 g), olive oil									
	Snack	Apple (150 g), sunflower seeds (23 g)	212.5	5.40	0	5.40	5.60	4	308	82	389
	Dinner	Spaghetti (124 g), chicken breast (30 g), olive oil, anari cheese (15 g)	409.9	19.32	12.75	7.20	0.70	56	166	46	181
	Daily Total		1595.1	50.52	18.85	32.30	17.21	401	1613	324	1005
3	Breakfast	Almond milk (262 g), Special K cereal (50 g), carob syrup (20 g)	279.7	10.37	0	10.37	0.67	533	245	598	146
	Snack	Burekia with anari (15 g)	45.9	1.23	0	1.23	0.36	6	86	4	0
	Lunch	Lentils with rice (270 g), lettuce (200 g), cucumber (201 g), olive oil	818.0	20.44	0	20.44	5.21	1201	1112	101	286
	Snack	Frozen berries (142 g)	65.0	1.40	0	1.40	5.60	1	191	26	0
	Dinner	Courgettes with eggs (180 g), olive oil, white bread (25 g)	467.0	15.88	0	15.88	3.94	735	656	133	288
	Daily Total		1675.6	49.32	14.61	34.70	15.77	2477	2291	861	720
4	Breakfast	Wholegrain bread (30 g), Edam cheese	172.9	15.86	12.00	3.86	2.04	562	203	286	130

		(28 g), turkey slice (26 g)									
	Snack	Apple (150 g), sunflower seeds (23 g)	212.5	5.40	0	5.40	5.60	4	308	82	389
	Lunch	Sea bass (30 g), wholegrain rice (145 g), lettuce (200 g), cucumber (201 g), olive oil	510.2	15.02	7.20	7.82	6.20	94	911	86	251
	Snack	Carrots (150 g), hummus (15 g), rusks (25 g)	189.0	5.78	0	5.78	6.40	170	575	63	139
	Dinner	Spaghetti (70 g), walnuts (28 g), peas (80 g), olive oil	600.6	12.66	0	12.66	6.70	193	371	42	175
	Daily Total		1685.3	54.71	19.20	42.71	26.93	1023	2369	560	1083
5	Breakfast	Almond milk (262 g), oats (40 g), almonds (6)	230.3	8.47	0	8.47	4.60	188	370	556	452
	Snack	Frozen berries (142 g)	65.0	1.40	0	1.40	5.60	1	191	26	0
	Lunch	Black-eyed peas (171 g), white bread (25 g), olive oil	505.0	15.20	0	15.20	11.70	130	507	77	299
	Snack	Apple (150 g), sunflower seeds (23 g)	212.5	5.40	0	5.40	5.60	4	308	82	389
	Dinner	Pork souvlaki in pitta (100 g)	193.0	12.10	0	12.10	1.00	322	312	34	148

	Daily Total		1205.8	42.57	0.00	30.47	28.50	646	1688	775	1287
6	Breakfast	Wholegrain bread (60 g), boiled egg (50 g), butter (14 g)	327.9	13.81	6.10	7.71	4.07	304	215	93	224
	Snack	Apple (150 g), sunflower seeds (23 g)	212.5	5.40	0	5.40	5.60	4	308	82	389
	Lunch	White rice (158 g), lettuce (200 g), cucumber (201 g), bell pepper (100 g), olive oil	326.0	9.30	0	9.30	4.60	37	718	77	155
	Snack	Frozen berries (142 g)	65.0	1.40	0	1.40	5.60	1	191	26	0
	Dinner	Pastitsio (170 g)	578.0	23.80	0	23.80	1.70	748	218	386	270
	Daily Total		1509.4	53.71	6.10	23.81	21.57	1093	1650	664	1038
7	Breakfast	Almond milk (262 g), oats (40 g), almonds (6)	230.3	8.47	0	8.47	4.60	188	370	556	452
	Snack	Apple (150 g), peanut butter (16 g)	172.0	4.40	0	4.40	4.55	4	263	71	78
	Lunch	White tortilla (50 g), chickpeas (83 g), hummus (15 g), lettuce (200 g), cucumber (201 g), olive oil	620.1	17.19	0	17.19	12.17	357	1023	127	328
	Snack	Frozen berries (142 g)	65.0	1.40	0	1.40	5.60	1	191	26	0

	Dinner	Spaghetti (124 g), chicken (30 g), olive oil, anari cheese (15 g)	409.9	19.32	12.75	7.20	0.70	56	166	46	181
	Daily Total		1497.3	50.78	12.75	38.66	27.62	607	2014	827	1039

Appendix 11: World Kidney Day Awareness Article Distributed to Dietitians in Cyprus.



ΣΥΝΔΕΣΜΟΣ ΔΙΑΙΤΟΛΟΓΩΝ & ΔΙΑΤΡΟΦΟΛΟΓΩΝ ΚΥΠΡΟΥ

Ανακοίνωση Συνδέσμου Διαιτολόγων και Διατροφολόγων Κύπρου
για την Παγκόσμια Ημέρα Νεφρού 2026 (12/03/2026)

12 Μαρτίου 2026: Θέμα: Υγεία Νεφρών για Όλους. Φροντίδα για τους ανθρώπους, προστασία για τον πλανήτη.

Με αφορμή την Παγκόσμια Ημέρα Νεφρών (2^η Πέμπτη του Μάρτη), ο Σύνδεσμος Διαιτολόγων και Διατροφολόγων Κύπρου συμμετέχει ενεργά στην εκστρατεία ενημέρωσης και ευαισθητοποίησης που συντονίζεται από το **World Kidney Day**, με στόχο την ανάδειξη της σημασίας της πρόληψης, της έγκαιρης διάγνωσης και της σωστής διαχείρισης της Χρόνιας Νεφρικής Νόσου.

Η **χρόνια νεφρική νόσος (XNN)** αποτελεί μια σημαντική και συνεχώς αυξανόμενη παγκόσμια πρόκληση για τη δημόσια υγεία, επηρεάζοντας **1 στους 10 ανθρώπους παγκοσμίως**. Συχνά εξελίσσεται σιωπηλά στα αρχικά στάδια, χωρίς εμφανή συμπτώματα, μέχρι να προκαλέσει σοβαρές επιπλοκές στην υγεία.

Η νόσος αυξάνει σημαντικά τον κίνδυνο καρδιαγγειακών επιπλοκών, μειώνει την ποιότητα ζωής και μπορεί να εξελιχθεί σε νεφρική ανεπάρκεια, όπου αντιμετωπίζεται σε έναρξη της αιμοκάθαρσης ή σε μεταμόσχευση.

Η **έγκαιρη διάγνωση μπορεί να σώσει ζωές**. Απλές, μη επεμβατικές και οικονομικά αποδοτικές εξετάσεις αίματος και ούρων μπορούν να εντοπίσουν δυσλειτουργία των νεφρών, επιτρέποντας έγκαιρες παρεμβάσεις που επιβραδύνουν την εξέλιξη της νόσου. Η στόχευση πληθυσμών υψηλού κινδύνου – όπως άτομα με διαβήτη, υπέρταση, καρδιαγγειακή νόσο, παχυσαρκία ή οικογενειακό ιστορικό νεφρικής νόσου – είναι ιδιαίτερα αποτελεσματική.

Προγράμματα που βασίζονται στην κοινότητα μπορούν να διευρύνουν την πρόσβαση σε υποεξυπηρετούμενους πληθυσμούς. Η έγκαιρη ανίχνευση της XNN όχι μόνο διατηρεί τη νεφρική λειτουργία αλλά και μειώνει την ανάγκη για θεραπείες υψηλής κατανάλωσης πόρων, βελτιώνοντας τα μακροπρόθεσμα αποτελέσματα.

Οι **περιβαλλοντικές αλλαγές** προσθέτουν πλέον επιπλέον βάρος σε αυτή την κατάσταση. Οι κίνδυνοι που σχετίζονται με το κλίμα – όπως η ατμοσφαιρική ρύπανση, το θερμικό στρες, η αφυδάτωση και τα ακραία καιρικά φαινόμενα – αυξάνουν τον κίνδυνο εμφάνισης XNN και επιταχύνουν την εξέλιξή της. Η άνοδος της παγκόσμιας θερμοκρασίας ενισχύει επίσης την εξάπλωση τροπικών νοσημάτων που μπορούν να προκαλέσουν βλάβες στους νεφρούς.

Ταυτόχρονα, οι θεραπείες για το τελικό στάδιο νεφρικής ανεπάρκειας, ιδιαίτερα η αιμοκάθαρση, απαιτούν σημαντικούς πόρους: μεγάλες ποσότητες νερού, ενέργειας και πλαστικών μιας χρήσης, ενώ παράγουν και εκπομπές αερίων του θερμοκηπίου. Μια μόνο συνεδρία αιμοκάθαρσης μπορεί να έχει **ανθρακικό αποτύπωμα αντίστοιχο με την οδήγηση αυτοκινήτου για σχεδόν 240 χιλιόμετρα**. Έτσι δημιουργείται ένας φαύλος κύκλος: η νεφρική νόσος και η κλιματική αλλαγή επιδεινώνουν η μία την άλλη.

Ένα **παγκόσμιο σημείο καμπής** έχει πλέον φτάσει. Στην **78η Παγκόσμια Συνέλευση Υγείας**, ο Παγκόσμιος Οργανισμός Υγείας (WHO) υιοθέτησε το **πρώτο ψήφισμα που είναι αφιερωμένο αποκλειστικά στη νεφρική νόσο**. Αυτή η ιστορική απόφαση αναδεικνύει την υγεία των νεφρών ως παγκόσμια προτεραιότητα

Πρόεδρος: Ελένη Π. Ανδρέου, **Αντιπρόεδρος:** Χριστιάνα Φιλίππου, **Γραμματέας:** Άννα Παχίτα, **Ταμίας:** Δημήτρης Παπαμιχαήλ
Βοηθός Γραμματέα: Νικολέττα Ντορζή, **Μέλη:** Νικόλαος Ντάφλος, Ανδρέας Σάββα

Ταχ. Διεύθυνση: Τ.Θ. 28823, Τ.Τ. 2083 Λευκωσία, Κύπρος / Τηλ: 22452258- Fax: 22-452292; info@cydnadiet.org

Appendix 12: Mediterranean (Medi) Diet Scoring Tool

Mediterranean (Medi) Diet Scoring Tool

Complete the Medi diet Score Tool to see your baseline score out of 14 points. Studies show higher Medi diet scores are associated with better heart and mental health and a 32% reduced risk of depression. To learn more about the Medi diet, meet with the Registered Dietitian in your doctor's office.

	Question	Yes	No	Key Nutrition Concepts
1.	Is olive oil the main source of fat used in cooking?			Choose Healthier Fats Olive oil is high in healthy monounsaturated fat.
2.	Do you have <u>4 tablespoons (60 ml) or more</u> of olive oil each day? Include oil used for frying, salads, meals away from home.			Healthy fats are better than very low fat diets Drizzle olive oil onto meals or snacks.
3.	Do you sauté with olive oil, garlic, onion, tomato to make homemade sauce <u>2 or more times per week</u> ?			Prepare homemade sauces for pasta, rice or vegetables.
4.	Do you eat <u>4 servings or more</u> of vegetables each day? (1 serving is 125 ml or 250 ml raw leafy greens)			Eat plenty of fruits and vegetables Fruits and vegetables add fiber to the diet along with antioxidants and many vitamins and minerals for optimal health.
5.	Do you have <u>3 or more fruits or 1.5 cups or more</u> of fruit each day? (1 serving= 1 fruit or 125 ml)			
6.	Do you eat nuts <u>3 or more times</u> per week? (1 serving is 30 grams or 60 ml)			Snack on nuts and seeds Nuts are rich in unsaturated fat, phytosterols, fibre, vitamin E and iron, e.g. walnuts, almonds, hazelnuts. Enjoy daily. Chew well.
7.	Do you have <u>3 or more servings of fish or seafood</u> each week? (1 fish serving is 3.5-5 oz or 100-150 g, or 200g seafood or 4-5 pieces)			Eat fish rich in omega-3 fats Salmon, trout, mackerel, sardines, herring, anchovies contain omega-3 fats (EPA and DHA) for heart and brain health.
8.	Do you have <u>3 or more servings</u> of legumes (peas, beans, or lentils) each week? (1 serving is 175 ml or 150 g)			Increase foods rich in soluble fibres Legumes are high in fiber, protein, potassium and other essential nutrients. Add legumes such as beans, peas and lentils several times a week.
9.	Do you eat chicken or turkey more often than beef, pork, hamburger or sausage?			Choose lean proteins with little visible fat.
10.	Do you eat <u>less than 2</u> servings of red meat or processed meats each day including hamburger, ham or sausage? (1 serving is 75 g)			Choose lean meats and consider cooking methods Include fish, poultry, legumes (beans, peas, lentils), nuts and seeds often in the week. Reduce processed meats and deep-fried foods.
11.	Do you eat 1 tablespoon (15 ml) <u>or less</u> of butter, margarine or cream each day?			Add fats rich in mono and poly unsaturated fats Instead of cream and butter, choose plant-based fats like oils, nuts and seeds.
12.	Do you eat commercial baked goods such as cookies, doughnuts or cake <u>less than 2</u> times per week?			Eat less processed food Sweets can be high in saturated fat, salt or sugar. Enjoy once in a while.
13.	Do you have <u>less than 1</u> can (355 ml or 12 oz) of sugar sweetened beverages each day?			Limit sweet drinks like pop, sports drinks, juice, flavoured or iced coffees to avoid excess added sugars.
14.	Do you drink 7 or more glasses of wine each week? (1 serving is 3-6 oz)			If you drink alcohol, drink in moderation. If you don't currently drink alcohol, don't start. If you have questions about alcohol, discuss with your health care provider. Adolescents under 19 years of age and pregnant women should avoid alcohol.
TOTAL SCORE (total no. of 'yes' answers) Pick 1-2 areas to work on.				

Nutrition Program, Hamilton Family Health Team. Modified from the Dietitians of Canada Ontario Primary Health Care Action Group Mediterranean Diet Toolkit. Adapted from tools produced by Alison Hornby and Katherine Paterson BACPR 2012 and the PREDIMED study www.Predimed.es, Estruch et al. Primary Prevention of Cardiovascular Disease with a Mediterranean Diet Supplemented with Extra Virgin Olive Oil and Nuts. N Engl J Med 2018; 379:1387-1389. DOI: 10. 1056/NEJMc1809971.

