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"CAROL DAVILA" BUCHAREST
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LOW-PROTEIN-DIET SUPPLEMENTED WITH KETOANALOGUES OF ESSENTIAL AMINO ACIDS FOR PATIENTS WITH ADVANCED DIABETIC NEPHROPATHY (DIABETIC KIDNEY DISEASE). THE ROLE OF AN INTERACTIVE DIGITAL PLATFORM FOR MONITORING AND DIETETIC COUNSELING

PHD THESIS SUMMARY

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RESEARCH HYPOTHESIS AND OBJECTIVES

Diabetes mellitus (DM) is the most common etiology of chronic kidney disease (CKD) [1]. Among patients with clinically manifest diabetic nephropathy, the reduction in glomerular filtration rate (GFR) is 2-20 mL/min/year [2]. Therefore, half of the patients reach end-stage kidney disease (ESKD) within 10 years [2].

Additionally, 22% of the patients undergoing kidney replacement therapy (KRT) are diabetic [1]. Consequently, there is a growing interest in reducing the deterioration of kidney function and delaying the initiation of KRT in this category of patients. This can be achieved through glucose metabolism control, as well as managing risk factors in the progression of CKD that are independent of glycemic control, such as blood pressure, weight management, and control of secondary complications of CKD. Thus, a multifactorial approach is recommended.

The current interest is also directed towards lifestyle changes, including the role of nutrition in CKD.

The Western population that consumes processed red meat has a protein intake above the optimal level considered necessary to achieve nutritional balance (1.35 g protein/kg/day versus 0.8 g/kg/day). Furthermore, it has been reported that a Western-style diet, which is high in processed red meat, is associated with accelerated CKD progression, three times greater than what is considered within physiological limits (−3 mL/min/1.73 m²) and with increased proteinuria [3,4].

In the ARIC study (Atherosclerosis Risk in Communities), which included 14,882 patients with an initial GFR above 60 mL/min/1.73 m², predominant consumption of processed red meat was associated with a reduction of up to 25% in kidney function [5]. In contrast, patients who adopted the DASH diet (Dietary Approaches to Stop Hypertension), which includes reduced meat consumption and increased intake of vegetables, fruits, and low-fat foods, had a 14% lower risk of developing CKD [6]. A high protein intake leads to vasodilation of the afferent arteriole, increasing intraglomerular pressure and thus promoting glomerulosclerosis progression, while low-protein diets favor vasoconstriction of the afferent arteriole, decreasing intraglomerular pressure and the rate of CKD progression [4,7].

According to the literature, there is a real benefit in adopting low-protein diets (LPD) for non-diabetic patients with chronic kidney disease, as nutritional intervention reduces the decline

in kidney function, improves blood pressure (BP) control, and regulates acid-base, electrolyte, mineral, and bone disorders. The quality of amino acids appears to influence BP control. Elevated levels of methionine and alanine were found in serum patients who preferentially consumed animal proteins and have been associated with higher BP values. In contrast, increased levels of threonine and histidine in serum, present in vegan and vegetarian patients, have been linked to a better-controlled BP [8]. Plant proteins are generally neutral in terms of pH. Therefore, increasing vegetable intake contributes to a better control of acid-base balance [9]. Additionally, although vegan and vegetarian diets are high in potassium, hyperkalemia is relatively rare due to the high fiber content, which allows only a small amount of potassium to be reabsorbed [9,10]. Furthermore, plant proteins contain higher levels of phosphorus compared to animal proteins; however, only one-third of the phosphate from plant foods is bioavailable, unlike animal-derived phosphorus, which has a higher bioavailability [11–13].

In this regard, LPD may delay the initiation of KRT [11,14–19].

However, for diabetic patients with CKD, there are few studies with a small number of patients followed over a short period, and the results are controversial [20–25]. On the other hand, there are findings suggesting that LPD may reduce proteinuria and BP values—risk factors that impact CKD progression. It appears that mean arterial blood pressure (MAP) could be reduced by 13 mmHg through an optimal multifactorial approach, including a dietary intervention primarily based on a predominant vegetarian LPD [26].

Another challenge in adopting LPD is maintaining long-term compliance with the nutritional intervention. Given that diabetic patients already have a recommendation for a low-carbohydrate diet, adherence to an additional nutritional restriction may be even lower compared to the non-diabetic population, which means the benefits of LPD might be masked by non-compliance with the proposed nutritional plan.

Another aspect that should not be overlooked is the management of elderly patients with diabetes and CKD. The elderly represent a category of fragile patients who often have significant comorbidities, such as cardiovascular conditions. An additional concern regarding the use LPD in this group is the potential risk of protein-calorie malnutrition.

The literature presents conflicting data, suggesting a direct relationship between reduced proteinuria and adherence to LPD, while also indicating a potential increased risk of cardiovascular mortality [27].

One strong factor influencing the outcomes of LPD in the CKD population is the low compliance with nutritional interventions. Studies indicate that only about 20% of eligible patients who could benefit from LPD are adherent [28]. Therefore, increasing adherence to LPD could significantly impact the reduction of kidney function decline.

Digital platforms can provide benefits by educating patients about their condition, offering personalized recommendations, facilitating self-monitoring, and allowing real-time tracking of progress, both by the patient and the healthcare team [29]. However, these benefits may only be realized by patients who are familiar with digital platforms, which depends on their educational level. Moreover, the accuracy of the data relies on the information entered by the patient into the platform. Applicability is also limited for patients who do not use technology [29].

Nevertheless, according to the literature, studies examining the effects of digital platforms have shown positive results concerning the improvement of patients' quality of life and the alleviation of fatigue through physical activity monitoring programs [30]. Additionally, the use of digital applications has been associated with increased autonomy, enhanced social support, and reduced hospitalization duration, thereby improving the quality of life for patients with chronic diseases, including CKD and diabetes [31].

Currently, the role of digital intervention is established for patients on dialysis. By using an interactive platform, patients can monitor phosphate levels, salt intake, or interdialytic weight. Studies have reported similar effectiveness between digital applications and nutritional counseling in reducing serum phosphate levels, optimizing blood pressure, and increasing treatment adherence [32–34]. Furthermore, there has been an increase in knowledge and awareness of associated pathologies [35].

Therefore, we propose the following objectives:

1. Assessing the effects of low-protein diets supplemented with ketoanalogues of essential amino acids on the variation of proteinuria and kidney function in patients with type 2 diabetes and chronic kidney disease.
2. Evaluating the efficacy and safety of using low-protein diets supplemented with ketoanalogues of essential amino acids in elderly patients (>65 years) with type 2 diabetes and chronic kidney disease.
3. Creating a digital platform that can contribute to increasing adherence to various types of nutritional interventions for patients with chronic kidney disease.

RESEARCH METHODOLOGY

An interventional, prospective, unicentric, uncontrolled study was conducted over a period of 15 months.

The study consisted of three phases (**Figure 1**).

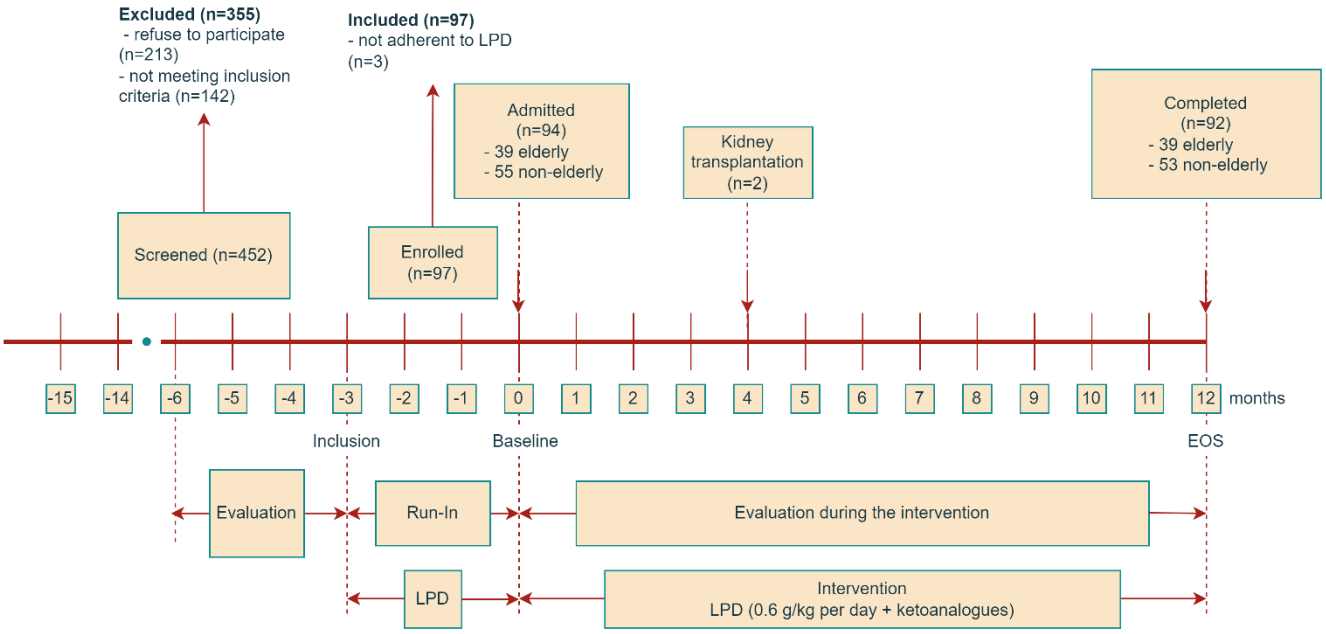

Figure 1 – Study plan

All patients with type 2 diabetes admitted in a year for CKD (n=452) at "Dr. Carol Davila" Teaching Hospital of Nephrology were evaluated for inclusion. Patients who met the selection criteria, accepted the nutritional intervention, and signed the informed consent entered a 3-month evaluation phase for enrollment, during which kidney function and proteinuria were assessed monthly. Patients with variations in kidney function and proteinuria of less than 10% were considered. In total, 97 patients were enrolled in the study.

During the evaluation phase for inclusion, the enrolled patients received nutritional counseling and initiated LPD (0.6 g/kg/day), predominantly vegetarian. Compliance to LPD was initially monitored bi-weekly, then monthly. Among the enrolled patients, 3 were not compliant to LPD. Only patients compliant to LPD were included in the study (n=94).

In the intervention phase (12 months), the LPD was supplemented with ketoanalogues of essential amino acids (KA) – 1 tablet per 10 kg (dry weight). Patients were monitored monthly (**Figure 1**). During the intervention period, 2 patients underwent kidney transplantation (the considerations were related to graft availability, not to the need to initiate KRT. Therefore, 92 patients completed the study [26,36,37].

Adult patients (>18 years) with type 2 diabetes and nephrotic-range proteinuria were considered for inclusion in the study.

Inclusion criteria were:

- Adult patients (>18 years)
- Diagnosis of type 2 DM
- CKD stage 4-5 (eGFR <30 mL/min/1.73 m², MDRD4 equation) [38] – stable (variations ± 10%)
- Proteinuria >3g/g urinary creatinine – stable (variations ± 10%)
- Good nutritional status assessed by the Subjective Global Assessment Score - SGA A [39]
    - Serum albumin >3.5 g/dL with a variation of less than 5% during the evaluation phase.
- Acceptance and signing of informed consent

Exclusion criteria were:

- Presence of elements suggesting overlap with other nephropathies requiring specific treatment (rapid increase in proteinuria and abrupt decrease in eGFR, presence of dysmorphic erythrocytes)
- Absence of microangiopathic complications
- Presence of significant comorbidities (acute heart failure, severe peripheral artery disease, liver cirrhosis, malabsorption, infections at the time of evaluation for enrollment and inclusion, active malignancies, and systemic diseases that required immunosuppressive treatment at the time of evaluation for enrollment or inclusion)
- Need for KRT at the time of evaluation for enrollment and inclusion.

The selection of vegetables, fruits, legumes, and cereals was made with the patients' consent. To improve compliance to the nutritional intervention, 5 meals per week including animal protein were allowed.

A carbohydrate intake of 200g/day was recommended, and the antidiabetic treatment was adjusted by the diabetologist. No patient received sodium-glucose cotransporter 2 inhibitors (iSGLT2).

Additionally, a low-sodium intake (<2g sodium or <5g salt) was recommended.

The daily calorie intake was set at 25-30 kcal/kg (dry body weight), individualized based on the patient's age, sex, current body mass index (BMI), and physical activity level.

Conventional treatment for chronic kidney disease was prescribed according to Guidelines [40–43]. Iron supplements and erythropoietin-stimulating agents were administered according to guideline recommendations [43]. For the control of mineral and bone disorders, calcium supplements, phosphate binders, and vitamin D supplements or vitamin D receptor activators were used as recommended [42].

The indication for initiating KRT was evaluated at each visit. The decision to start KRT was made by the Ethics Committee of the Hospital, considering the clinical status of each patient, independent of the investigators.

For the control of blood pressure and hypercholesterolemia, antihypertensive treatment (including renin-angiotensin-aldosterone system inhibitors - RAASi ± diuretics, calcium channel blockers, or beta-blockers as indicated) and lipid-lowering treatment (statins ± fibrates) were administered. The presence of RAASi or loop diuretics in the treatment regimen was evaluated at each monitoring visit.

STUDY 1 - LOW-PROTEIN-DIETS IN DIABETIC KIDNEY DISEASE

The main objective of this study was to evaluate the role of LPD diets supplemented with ketoanalogues on the variation of kidney function and proteinuria in patients with type 2 diabetes and advanced chronic kidney disease.

The primary efficacy parameters were proteinuria and the change in eGFR from inclusion to the end of the study (EOS).

Proteinuria was measured through 24-hour urine collection and expressed as g/g urinary creatinine.

The eGFR was estimated based on serum creatinine, age, sex, and ethnicity using the MDRD4 equation [38]. Serum creatinine was measured using the enzymatic method.

The secondary efficacy parameter was the variation in BP. Systolic and diastolic blood pressures were measured according to ESH-EHC guidelines [21], and MAP was calculated as MAP = SBP + 1/3(DBP - SBP) [193]. Hypertension was defined as either a blood pressure exceeding 140/90 mmHg or the administration of antihypertensive medications. Uncontrolled hypertension was defined as a MAP exceeding 97 mmHg (equivalent to the recommended target of 130/80 mmHg).

Safety parameters referred to nutritional status—energy intake, SGA, BMI, serum albumin, and C-reactive protein (CRP)—as well as glycemic control (HbA1c) were evaluated. Patient adherence to diet was assessed using urinary urea excretion and a food diary (3 days/week) for energy intake.

Compliance to LPD was defined as differences of less than ±10% between recommended and estimated protein and energy intake levels.

Data obtained at Inclusion, Baseline, 3, 6, and 9 months and EOS were used for statistical analysis.

Statistical analysis of the data was performed using Analyze-it version 6 (Analyze-it Software, Ltd., Leeds, UK) and IBM SPSS version 25 (IBM, New York, NY, USA).

Continuous variables are presented as mean or median with confidence intervals (95% CI), depending on the distribution (parametric or non-parametric).

The distribution was evaluated using Shapiro-Wilk test.

Categorical variables are presented as percentages.

Comparisons were evaluated as follows:

• Student's t-test (for comparing paired data regarding parametric continuous variables)

• Wilcoxon test (for comparing paired data regarding non-parametric continuous variables)

• ANOVA test (for comparing paired data involving more than 3 parametric continuous variables)

• Friedman test (for comparing paired data involving more than 3 non-parametric continuous variables)

• Chi-square test for qualitative variables

The slopes of relevant parameters were calculated using linear regression, with data from different study time points (Inclusion, Baseline, at 3, 6, 9, and 12 months).

Correlations between parameters were performed using Kendall's tau test.

Variables correlated with proteinuria were transformed to optimize data accuracy (using Z-score) and were subsequently entered into a linear regression model.

Differences were considered statistically significant at a p-value of 0.05.

This study is one of the few that investigates the effects of a LPD+KA combined with nephroprotective conservative treatment in patients with type 2 diabetes, advanced CKD, and nephrotic-range proteinuria [36]. Patients with type 2 diabetes and advanced CKD (median eGFR 11.7 mL/min), with nephrotic-range proteinuria (median proteinuria 4.8 g/g) were included (**Figure 1, Table I**). Notably, none of the reported studies included patients with nephrotic-range proteinuria, and very few included patients with such a low level of renal function. Ensuring intensive nutritional counselling and monitoring adherence were fundamental.

During the study, an impressive decrease in proteinuria from 5.2 to 1.6 g/g, a reduction of 3.5 g/g, was observed (**Figure 2**).

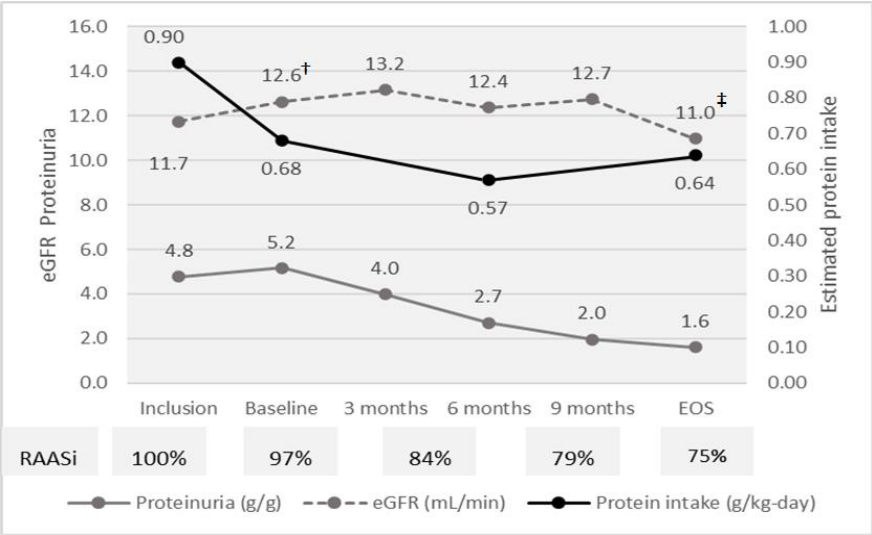

Figure 2. Efficacy parameters and compliance to diet at study moments. eGFR † Inclusion vs. Baseline p < 0.0001; ‡ Baseline vs. EOS p < 0.0001

The reduction in proteinuria was directly correlated with the initial level of proteinuria. In other studies that evaluated the effect of LPD+KA in chronic kidney disease associated with diabetes (DKD), the reduction in proteinuria varied from 2.4 to 4.2 g/g and was also directly correlated with the initial level of proteinuria: the higher the proteinuria at the start of the study, the greater the reduction during the study [20,44]. In our experience, the level of reduction in proteinuria was greater, likely because the initial proteinuria was also higher than in the reported studies. Therefore, patients with CKD and higher proteinuria would benefit the most from LPD.

Our data show a continuous reduction in proteinuria. Thus, we could not identify a threshold level at any of the study time points, as found by Chauveau et al. [45]. A threshold level would have been useful as a predictor of the response to nutritional intervention.

Table I- The variations of investigated parameters in study phases

	Baseline (n = 92)	End of Study (n = 92)	End of Study—Baseline Difference	Sig.
Efficacy Parameters				
Proteinuria (g/g creatinine)	5.2 (5.0 to 5.2)	1.6 (1.5 to 1.7)	−3.5 (−3.7 to −3.7)	<0.0001
Slope of proteinuria (g/g per mo.)	−0.3 (−0.32 to −0.28)			
eGFR (ml/min)	12.6 (11.7 to 13.1)	11 (10.3 to 11.5)	−1.5 (−1.7 to −1.2)	<0.0001
Slope of eGFR (mL/min per month)	−0.11 (−0.14 to −0.1)			
Mean arterial pressure (mmHg)	99 (90–109)	88 (85–88)	−11 (−17 to −7)	0.0002
Mean arterial pressure < 97 mmHg	47%	84%	6.0 (3.1 to 5.3) *	<0.0001
Safety parameters				
Body mass index (kg/m2)	27.1 (26.3 to 28.0)	26.0 (25.1 to 26.8)	−1.2 (−1.6 to −0.7)	0.004
Subjective global assessment A (%)	100%	100%	1(1 to 1) *	1
Serum albumin (g/dL)	3.9 (3.9 to 4.0)	4.1 (4.1 to 4.2)	0.2 (0.1 to 0.3)	<0.0001
C-reactive protein (mg/L)	14 (13 to 14)	9 (8 to 9)	−4.0 (−6.0 to −4.0)	<0.0001
Glycated hemoglobin (%)	8.1 (8.0 to 8.3)	8.1 (7.9 to 8.3)	−0.2(−0.56 to −0.01)	0.04
Nitrogen balance				
Urea (mg/dL)	127 (116 to 134)	145 (133 to 149)	12 (12 to 15)	<0.0001
Uric acid (mg/dL)	4.4 (4.2 to 4.4)	4.4 (4.0 to 5.1)	−0.2 (−0.5 to 0.3)	0.47
Mineral-bone disease parameters				
Phosphate (mg/dL)	7.6 (7.3 to 8.1)	4.1 (3.6 to 4.6)_	−4.1 (−4.6 to −3.6)	<0.0001
iPTH (pg/mL)	548 (537 to 553)	182 (174 to 195)	-370 (-370 to -370)	<0.0001
Adherence the diet				
Estimated protein intake (g/kg/day)	0.68 (0.67 to 0.69)	0.64 (0.63 to 0.63)	−0.03 (−0.05 to—0.01)	<0.0001
* Odd ratio. Data are presented as median and 95% confidence interval (95% CI). eGFR—estimated glomerular filtration rate; iPTH – intact-parathormone; RAASi—Renin–angiotensin–aldosterone inhibitors.				

Regarding the determinants of proteinuria, lower MAP was associated with lower proteinuria, as expected, even though MAP variations were small in our patients, highlighting the importance of blood pressure control in preventing the progression of CKD and supporting current guidelines and recommendations (**Figure 3**) [46]. The beneficial effects of this study regarding nutritional intervention on blood pressure control were discussed in a previously published article [26].

Proteinuria was also directly dependent on the level of the eGFR and protein intake, suggesting that the reduction in proteinuria was determined by a decrease in both eGFR and protein intake (**Figure 3).** However, the rate of decline in eGFR was only 1.5 mL/min/year—close to the physiological level of kidney function degradation. These aspects may be explained by a reduction in hyperfiltration.

Thus, LPD could reduce hyperfiltration through a hemodynamic pathway similar to that of RAASi. Since our patients were treated with RAASi, the diet appears to act synergistically with the pharmacological therapy in slowing the progression of CKD. However, the effects of RAASi have been difficult to differentiate from the effects of dietary intervention.

The decline rate of eGFR was 5 times smaller during the intervention phase compared to the pre-enrollment assessment phase. In one year, eGFR decreased by only 1.5 mL/min during the intervention (**Figure 2**), which is close to the accepted decline in the general population (1 mL/min/year) and about 3 times smaller than what is expected in this category of patients (4 mL/min per year) [47,48]. The rate of eGFR decline was -0.11 mL/min per month, a lower rate than that reported by Barsotti et al. (-0.22 mL/min/month) in patients with chronic kidney disease and similar to that reported by Chauveau et al. (-0.15 mL/min/month) [20,45,49]. Additionally, none of the patients included in our study required dialysis within a 12-month period. Thus, LPD+KA could reduce kidney function deterioration and delay the initiation of dialysis even in patients with advanced chronic kidney disease and nephrotic-range proteinuria.

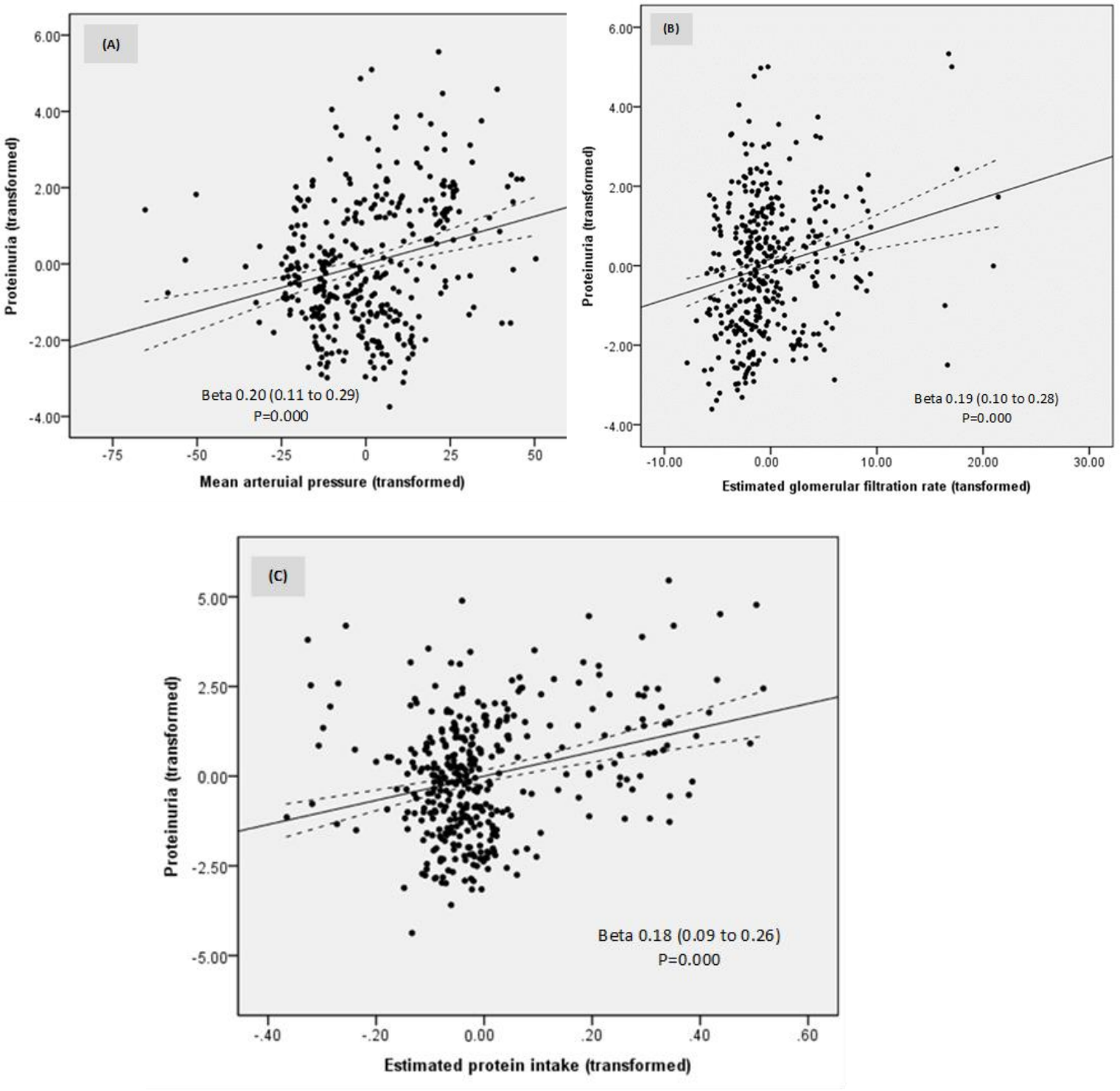

Figure 3. -Relationships between proteinuria, MAP (A), eGFR (B) and estimated protein intake (C)

It is noteworthy that the decline rate of eGFR was correlated with the initial level of eGFR. Patients with an initial eGFR > 14.2 mL/min experienced the slowest decline in eGFR over the study period (**Figure 4**). On the other hand, although patients with eGFR < 14 mL/min benefited less in terms of slowing the progression of chronic kidney disease, none required dialysis, suggesting that LPD+KA delayed the initiation of dialysis in these patients by improving the metabolic disturbances associated with advanced chronic kidney disease. Therefore, greater benefits in reducing the progression of chronic kidney disease would be achieved by starting nutritional intervention at eGFR > 14 mL/min, as observed by other authors.

Quartiles of eGFR at Baseline (mL/min)	Mean difference	SE		Sig.
29.1 - 10.65	0.349	0.0380		0.000
14.24 - 10.65	0.292	0.0337		0.000
11.73 - 10.65	0.239	0.0346		0.000
29.1 - 11.73	0.110	0.0380		0.025
29.1 - 14.24	0.057	0.0372		0.423
14.24 - 11.73	0.053	0.0337		0.399

Figure 4. - Slopes of eGFR by quartiles of eGFR at baseline

In this study, nutritional parameters improved. BMI decreased without any change in the SGA score, serum albumin increased, and blood glucose control was optimized. CRP decreased in relation to the increase in serum albumin due to reduced proteinuria, even though patients did not exhibit nephrotic syndrome. The decrease in BMI was consistent with other studies and was also highlighted in a meta-analysis [50]. In the context of chronic kidney disease, the reduction in BMI appears beneficial and not a sign of malnutrition, as it was associated with better glucose metabolism control, as noted by Bellizzi et al. [25].

At Inclusion, the median estimated protein intake was 0.89 g/kg/day, lower than the median protein intake estimated in the general population of Romania, but close to the upper limit recommended by KDIGO (Kidney Disease: Improving Global Outcomes), likely due to the spontaneous reduction in protein intake observed in patients with advanced chronic kidney disease [51–53]. Therefore, the beneficial effects observed in this study support a greater reduction in

protein intake in advanced chronic kidney disease, as recommended by KDOQI (The National Kidney Foundation Kidney Disease Outcomes Quality Initiative) [54].

Low adherence to the dietary protein restriction, especially in the long term, has often been reported and has led to questionable beneficial effects of nutritional intervention, predominantly for patients with chronic kidney disease [23,52]. In our patients, diet compliance was good. During the intervention, the median estimated protein intake was 0.63 g/kg/day (with a median difference from the prescribed value of only 0.03 g/kg/day), and adherence was observed in 62% of the assessments throughout the study.

Although only 21% of patients were fully adherent to the dietary protein restriction throughout the intervention, the median difference between adherent and non-adherent patients was only 0.02 g/kg/day, too small to influence the diet's effect on reductions in proteinuria and the decline rate of eGFR. Therefore, adopting a dietary protein restriction seems more important than a minor deviation from the prescribed protein intake.

Another challenge is the low acceptance of such nutritional interventions. Among the 452 patients assessed in this study, only 24% were eligible, accepted, and adhered to the diet.

The nutritional intervention provided energy intake according to recommendations, ensuring that all patients maintained good nutritional status throughout the intervention. The estimated energy intake was approximately 30 kcal/kg/day for 64% of participants at all study time points.

STUDY 2 – LOW-PROTOIN DIETS IN ELDERLY PATIENTS WITH DIABETIC KIDNEY DISEASE

The main objective of this study is to evaluate the efficacy and safety of implementing LPD+KA in elderly patients (>65 years) with advanced CKD.

Efficacy parameters were considered the reduction of proteinuria and the variation in kidney function in elderly patients (>65 years old) during the intervention.

Proteinuria was measured from 24-hour urine collection and expressed as g/g of urinary creatinine.

Kidney function was expressed as eGFR using the MDRD4 formula [55].

Secondary efficacy parameters included variation in BP and the occurrence of vascular events.

SBP, DBP were measured at each visit according to guidelines [56]. MAP was calculated using the formula MAP=DBP+1/3(SBP-DBP). Hypertension was defined as BP values above 140/90 mmHg or controlled BP under antihypertensive treatment.

The attending physician adjusted antihypertensive treatment using RAAS inhibitors, calcium channel blockers, and beta-blockers, as well as loop diuretics (furosemide), aiming for a blood pressure of 130/80 mmHg [56,57].

Vascular events included major cardiovascular events (acute coronary syndrome, coronary revascularization, congestive heart failure, or peripheral vascular events) or cerebrovascular events (ischemic or hemorrhagic stroke or transient cerebral ischemia).

Safety parameters were represented by SGA assessment, BMI, serum albumin, and monitoring glucose metabolism through periodic HbA1c checks.

Patients' adherence to diet was evaluated by estimating protein intake using urinary urea [58].

Energy intake was assessed by monitoring a food diary for 3 days/week.

Adherence was defined as variations of less than ±10% in estimated protein intake and estimated caloric intake compared to prescribed amounts.

Data obtained at Inclusion, Baseline, at 3, 6, 9 months, and at EOS were included in the statistical analysis.

Statistical analysis was performed using Analyse-it version 6 (Analyse-it Software, Ltd., Leeds, UK) and IBM SPSS version 25 (IBM, New York, USA).

Data obtained from elderly patients were compared with data from non-elderly patients.

Slopes of proteinuria and eGFR during the study phases were calculated using linear regression.

Continuous variables are presented as medians and 95% confidence intervals (95% CI) of the median.

Categorical parameters were expressed as percentages.

The type of distribution (parametric or non-parametric) was assessed using the Shapiro-Wilk test.

Comparisons were made as follows:

• Wilcoxon-Mann-Whitney test (for comparisons between groups with non-parametric variables)

• T-test for groups (for comparisons between groups with normally distributed variables)

• Chi-square test for categorical data

• Student's t-test (for paired data with normally distributed variables)

• Friedman test (for paired data with non-parametric variables)

• McNemar test (for paired categorical data)

Univariate correlations were performed using Kendall's tau test.

The interaction between eGFR and proteinuria based on study time points and age group was described using a two-way ANOVA model after log transformation of the dependent variables.

Factors associated with proteinuria and eGFR were analyzed in multiple linear regression models (elderly vs. non-elderly) after log transformation of all included variables.

Binary regression was used to assess the determinants of vascular events at Inclusion, Baseline, at 3, 6, 9, and 12 months after optimizing accuracy by transforming all included variables with the Z-score.

A p-value <0.05 was considered statistically significant.

We evaluated the efficacy, feasibility, and safety of LPD+KA in elderly patients with advanced CKD. This study is among the few published that not only investigate the effects of DHP in advanced diabetic nephropathy but also the safety concerning elderly patients.

We report a significant reduction in proteinuria of 3.6 g/g creatinine and a remarkable five-fold decrease in the decline of kidney function, with a difference of 1.5 mL/min over 15 months of intervention, similar to the physiological decline in eGFR. In this study, these findings were also observed in non-elderly patients (**Table II**).

Considering that the reduction in proteinuria was observed in patients treated with RAAS inhibitors for most of the intervention, LPD appears to have an additive effect on proteinuria reduction, as previously mentioned.

Proteinuria was directly correlated with eGFR, BMI, and glycemic control (HbA1c).

However, the effects of LPD seem to differ by age category. In elderly patients, HbA1c was associated with variation in proteinuria, suggesting that glycemic metabolism was better controlled in non-diabetics, whereas in younger patients, proteinuria was associated to BMI, indicating that weight was better controlled in the elderly.

eGFR decreased similarly in both patient categories, with only a 1.5 mL/min decline over one year (**Figure 5**). This is approximately half of the estimate seen in cases of CKD with nephrotic-range proteinuria (3.9 mL/min per year) and is close to the estimate in the general population.

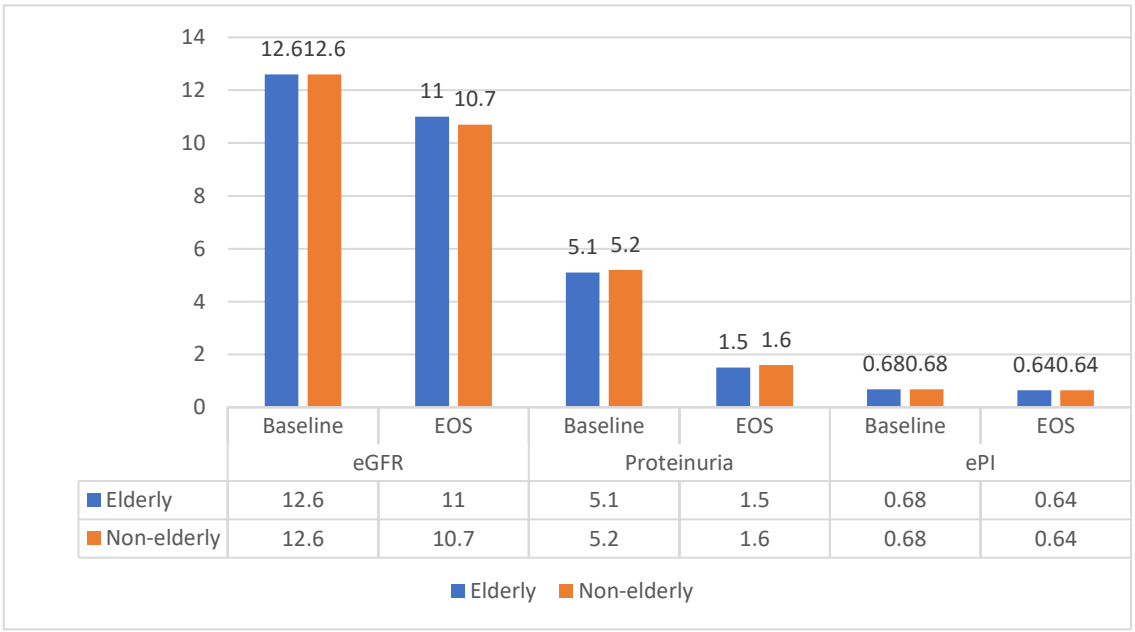

Figure 5 – The parameters monitored by age category during the intervention show that all differences are statistically significant for all displayed parameters, but there are no differences based on age category.

Table II – Variations in study parameters by age group

	End of study – Baseline difference (Elderly patients)	Sig.	End of study – Baseline difference (Non-elderly patients)	Sig.	Sig.[Δ]
Efficacy parameters					
Proteinuria (g/g creatinine)	-3.6 (-3.8 to -3.1)	<0.0001	-3.4 (-3.8 to -3.2)	<0.0001	0.91
eGFR (ml/min)	-1.5 (-1.9 to -1.1)	<0.0001	-1.5 (-1.9 to -1.1)	<0.0001	0.94
Secondary parameters					
Systolic blood pressure (mmHg)	-10 (-40 to 8)	0.10	-10 (-25 to 10)	0.26	0.66
Diastolic blood pressure (mmHg)	-10 (-15 to -5)	<0.0001	-15 (-15 to -10)	<0.0001	0.17
Mean arterial pressure (mmHg)	-11 (-19 to -7)	<0.0001	-11 (-24 to -6)	0.002	0.83
Vascular events (%)*	15.4	0.01	23	0.0005	0.39
• Cardiovascular events (%)*	2.6	0.32	13	0.008	0.07
• Cerebrovascular events (%)*	12.8	0.03	13	0.008	0.96
Safety parameters					
Body mass index (kg/m^2)	-1.0 (-1.9 to -0.6)	0.0003	-1.2 (-1.6 to -0.4)	<0.0001	0.96
Subjective global assessment A (%)	0	-	0	-	-
Serum albumin (g/dL)	0.22 (0.0 to 0.35)	0.02	0.2 (0.1 to 0.4)	0.002	0.66
C-reactive protein (mg/L)	-5 (-7 to -3)	<0.0001	-4 (-6 to -3)	<0.0001	0.26
Glycated hemoglobin (%)	-0.03 (-0.6 to 0.2)	0.87	-0.3 (-0.9 to 0.2)	0.09	0.21
Estimated energy intake (kcal/kg-day)	-0.3 (-2.7 to 2.7)	1	-0.3 (-3.0 to 0.8)	1	0.61
Adherence to energy intake (%)*	2	0.76	2	0.78	0.92
Adherence to the diet					
Estimated protein intake (g/kg-day)	-0.03 (-0.05 to 0.00)	0.02	-0.05 (-0.06 to 0.01)	0.09	0.73
Adherence to protein restriction (%)*	38.5	0.001	28.3	0.01	0.36
Therapy					
RAASi (% patients)*	-31	0.0005	-21	0.0009	0.27
Furosemide (% patients)*	31	0.003	21	0.02	0.84

[Δ] Differences between the variations in study parameters by age group; *Proportion difference
Data are presented as median and 95% confidence interval (95% CI)
eGFR - estimated glomerular filtration rate; RAASi – Renin angiotensin aldosterone inhibitors

According to the study, there was a significant increase in eGFR during the inclusion phase (1.1 mL/min) related to the initiation of LPD. Subsequently, an increase in eGFR was observed between months 6 and 9, likely due to adjustments in antihypertensive therapy, replacing RAASi with furosemide.

The reduction in proteinuria and the rate of decline in eGFR were inversely associated with the estimated protein intake, suggesting that LPD may delay the progression to end-stage kidney failure.

Blood pressure control was optimized during the intervention for both seniors and younger patients. In this sub-analysis, we noted a significant reduction in mean arterial pressure (MAP) (-11 mmHg) with generally better blood pressure control (median BP 130/60 mmHg) achieved through careful monitoring of patients. Adherence to a low-sodium diet also contributed to blood pressure control.

This study noted a strong association between uncontrolled MAP and the incidence of vascular events, similar to previously published data [59].

Vascular events occurred in 15% of elderly patients, with no significant differences compared to non-elderly patients.

In a binary regression model, the presence of vascular events was associated with more advanced kidney disease and uncontrolled MAP (**Table III**). Nutritional intervention did not influence the incidence of vascular events, supporting the safety of LPD among elderly patients with chronic kidney disease. However, contradictory results have been reported in the literature in some studies that found an increased risk of cardiovascular mortality in elderly patients with protein restriction [60].

Table III – Determinants of vascular events

	B ± S.E.	**Exp(B) (95% CI)**	**Sig.**
eGFR	−5.28 ± 1.48	0.01 (0.00 to 0.09)	0.00
Mean arterial pressure	1.06 ± 0.51	2.88 (1.07 to 7.74)	0.04
Body mass index	0.33 ± 0.38	1.38 (0.66 to 2.90)	0.39
Glycated hemoglobin	0.67 ± 0.43	1.96 (0.85 to 4.51)	0.11
Estimated protein intake	−0.27 ± 1.06	0.77 (0.10 to 5.96)	0.80
Estimated energy intake	−0.54 ± 0.36	0.59 (0.29 to 1.18)	0.13
Elderly *	0.81 ± 0.65	2.24 (0.63 to 7.94)	0.21
Constant	−9.35 ± 2.22	0.00	0.00

The safety of nutritional intervention is always under debate, especially among the elderly. Our results show that the nutritional status improved during the study, with a significant reduction in BMI, without changes in the SGA score, an increase in serum albumin, and a decrease in inflammation (**Figure 6**), results supported by other published studies [11]. The decrease in BMI was a consequence of lifestyle improvements.

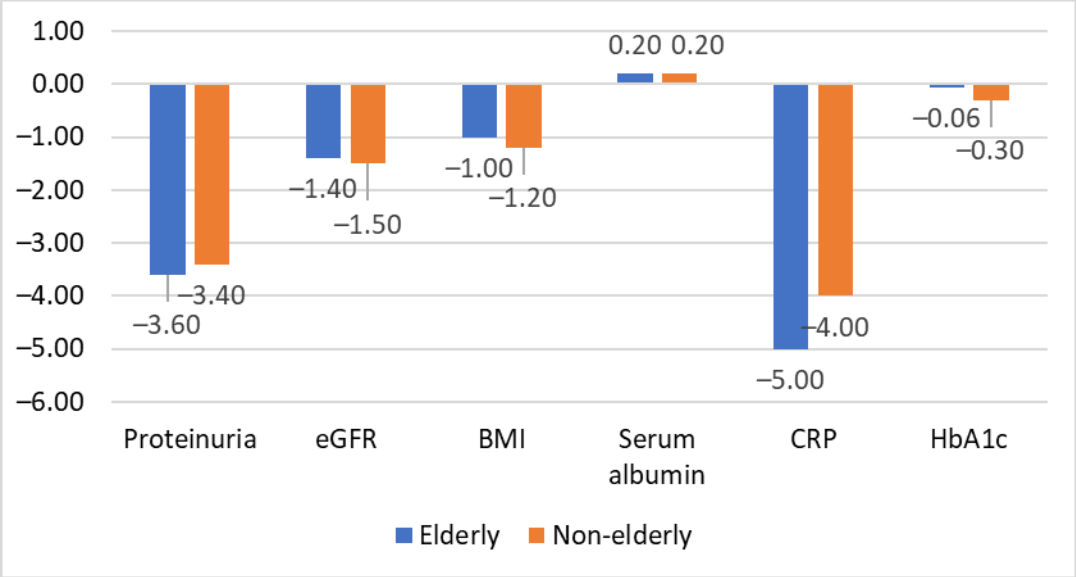

Figure 6 - Difference (EOS–Baseline) in the Intervention phase. All differences EOS–Baseline are significant for all parameters, but there are no significant differences between age groups for any parameter.

The estimated calorie intake was similar to the prescribed intake throughout the study period for both categories of patients.

HbA1c remained stable during the study in both elderly and non-elderly individuals.

Currently, the estimated protein intake requirement is 0.66 g/kg per day, with a recommendation of 0.8 g/kg per day for all adults over 18 years, including elderly adults [61]. Moreover, the elderly experience a progressive reduction in basal metabolic rate, associated with spontaneous weight loss (including muscle mass) [62]. Another important aspect is that elderly individuals, compared to non-elderly ones, exhibit anabolic resistance, requiring higher concentrations of amino acids.

The main challenge in using LPD is in patients with diabetes, who already have carbohydrate restrictions, especially among the elderly, who are less likely to change their dietary habits and sometimes have less support from family members. However, a strict evaluation of diet and nutritional status can improve motivation and adherence to dietary intervention [63].

Although the number of participants was small (only 24% of the evaluated patients met the selection criteria and agreed to the intervention), the patients who entered the study remained compliant to the LPD, with even a 39% improvement in adherence during the study. These results were linked to nutritional and clinical counseling.

No patient in the elderly group required KRT, and no patient died.

Therefore, LPDs appear to be safe even among elderly patients with advanced chronic kidney disease.

However, some studies suggest that despite the nutritional safety of LPDs, there is an association between the onset of malnutrition, patient age, and the presence of multiple comorbidities [64,65]. Another study reported that in patients with CKD stages G4-G5, deterioration in nutritional status is a more important predictor of renal events than increased protein intake, highlighting the importance of monitoring nutritional status in CKD patients [66] These data, along with the results of the current study, underscore the importance of careful patient selection and close monitoring for the safe implementation of LPDs.

STUDY 3 – FUTURE PERSPECTIVES ABOUT USING DIGITAL PLATFORMS IN PATIENTS WITH CHRONIC KIDNEY DISEASE – STUDY PROTOCOL PROPOSAL

Digital platforms can bring benefits by educating patients about their conditions, providing personalized recommendations, enabling self-monitoring, and allowing real-time tracking of progress by both the patient and the medical team [29]. On the other hand, these benefits are typically seen only in patients who are familiar with digital platforms, which also depends on the patients' educational level. Additionally, the accuracy of the data relies on the information entered into the platform by the patient. Furthermore, the applicability is limited for patients who do not use technology [29].

According to the literature, studies investigating the effect of digital platforms have shown positive results regarding the improvement of patients' quality of life, reduction of fatigue through physical activity monitoring programs, and a decrease in episodes of depression through the use of mental health programs [30]. Moreover, the use of digital applications has been associated with increased autonomy, the provision of social support, and a reduction in hospitalization duration, thus improving the quality of life for patients with chronic diseases, including CKD and diabetes [31].

This study aims to evaluate the effectiveness of using an interactive digital platform for monitoring and dietary counseling on the compliance of patients with a low-protein diet supplemented with ketoanalogues of essential amino acids, as well as on the clinical and biological progression of the patients.

The study will be a single-center, prospective, interventional, randomized controlled trial. A digital platform specifically created for this study will be used, featuring a patient-friendly interface that can monitor the patient's food journal.

The first phase, which is the enrollment phase, will last for 3 months. Eligible patients will be instructed to adopt a low-protein diet (0.6 g/kg/day), primarily vegetarian, supplemented with ketoanalogues. Additionally, in this phase, patients will be randomized 1:1 into two groups: one with standard monitoring plus application use, and a control group with standard monitoring—

nutritional counseling, a 3-day food journal, and protein intake estimation using urinary urea [58] (**Figure 7**).

Patients who adhere to the low-protein diet will be eligible to continue the study. In total, the study will last 15 months.

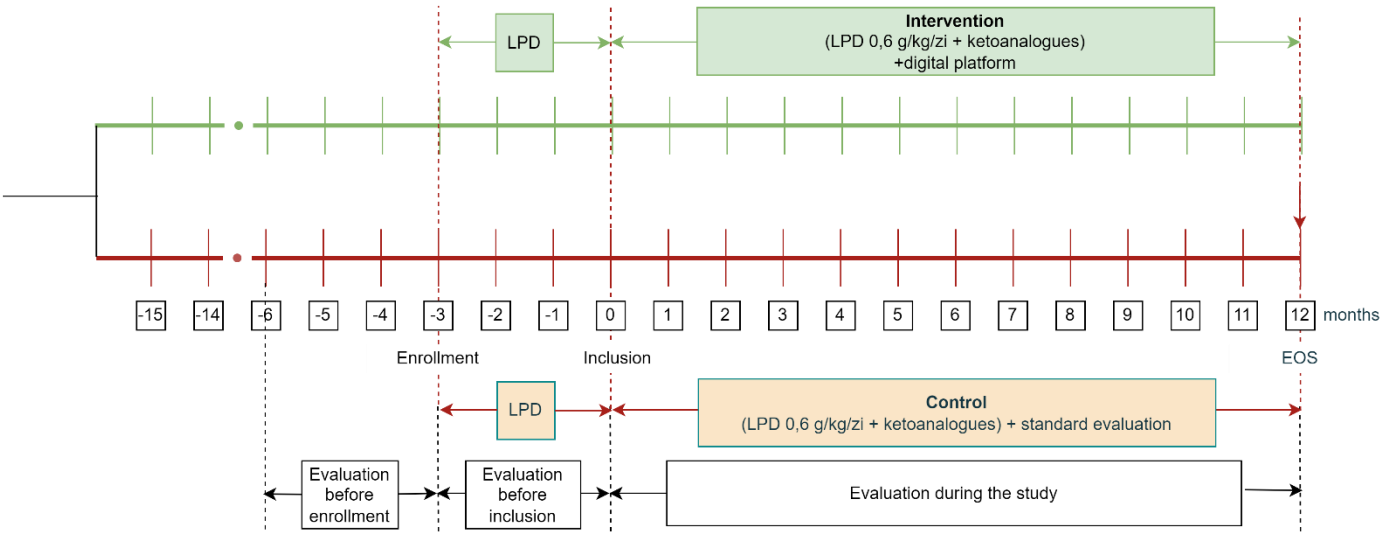

Figure 7 -Study diagram

The nutritional intervention consists of using a low-protein diet (0.6 g/kg/day) supplemented with ketoanalogues (1 capsule of Ketosteril per 10 kg of ideal dry body weight), predominantly vegetarian, with a caloric intake of 25-30 kcal/kg/day, corresponding to the patient's age, sex, physical activity level, and nutritional status at the time of examination, along with a general treatment considered nephroprotective [40].

Patients will be divided into two groups: one with nutritional intervention and traditional monitoring, and another with nutritional intervention and digital monitoring.

The primary efficiency parameters are:

- Increase in compliance with the low-protein diet (LPD) by at least 20%
- Reduction in the decline of kidney function

  Kidney function will be expressed as eGFR using the CKD-EPI formula [67].

Compliance with the LPD is defined as an estimated protein intake of +/- 20% compared to the prescribed intake. Protein intake will be estimated using urinary urea [58] and by monitoring a 3-day food journal, and for patients receiving the intervention, through the digital platform.

Digitalization in the nutritional care of patients with renal diseases can play an important role in increasing adherence.

However, the use of digital platforms is only feasible for patients who regularly use digital applications and depends on their level of medical education and understanding. Moreover, socioeconomic status impacts the ability to use the digital platform. Therefore, this solution is "niche" and favored for a specific category of patients. As a result, current monitoring (nutritional counseling by a healthcare professional) should not be neglected, and a "hybrid" approach may benefit a broader range of patients.

The few studies that have examined the role of digital platforms have observed an increase in autonomy, improved overall condition through reduced fatigue and depressive episodes, but regarding direct effects on slowing CKD progression and delaying renal replacement therapy, current data are insufficient for a definitive conclusion. Additionally, digital applications may reduce cardiovascular risk through better blood pressure control via self-monitoring of salt intake [68] and help optimize weight by monitoring caloric intake [69].

Digital platforms also allow the personalization of treatment for CKD patients. By analyzing data collected from patients, the medical team can tailor treatment by adjusting medications, providing personalized dietary recommendations, and implementing symptom management strategies.

We believe that nutritional care supported by mobile and digital technology should be accessible and provided to all individuals with renal conditions. Therefore, it is necessary to develop applications that are validated for this patient category.

Moreover, digital platforms for monitoring nutritional interventions should be adapted according to cultural characteristics.

Another useful feature of such an application is that monitoring diet or treatment should be facilitated by creating a program that is easy to access, regardless of the patient's social characteristics. In this regard, mobile applications may yield better results compared to other forms of digital monitoring.

Furthermore, accessibility should, at least partially, be independent of internet services. Thus, optimizing digital platforms could provide real-time information about patients' clinical status and their dietary plans.

Additionally, ensuring communication within groups with similar characteristics could increase adherence to nutritional plans and the use of applications. This type of social support can reduce the feeling of isolation and provide a safe space for discussing personal experiences [70].

The use of these monitoring tools appears to have a favorable economic impact, suggesting that implementing a validated digital platform could enhance the medical education level of the population, thereby improving prevention or, as needed, the diagnosis of certain conditions [71].

Digital platforms could have a significant impact on the early detection of CKD, particularly through the use of artificial intelligence and machine learning algorithms [72].

The proposed study would have the largest number of participants focusing exclusively on the compliance of pre-dialysis CKD patients with LPD. Additionally, the platform used includes a culturally coherent food database. We believe that data obtained from such a randomized study could provide a new perspective on adherence to prescribed nutritional interventions, considering that current compliance with LPD among patients is approximately 20%, despite nutritional counseling.

GENERAL CONCLUSIONS AND PERSONAL CONTRIBUTION

The doctoral thesis makes a significant contribution by including patients with diabetes mellitus and chronic kidney disease with nephrotic-range proteinuria, a group generally excluded from prospective clinical studies that analyze the effects of low-protein diets.

This approach offers a new and valuable perspective on managing these patients with specific and complex needs.

The nutritional intervention implemented in the study demonstrated a significant reduction in proteinuria, with an average decrease of 3.5 g/g in one year. This remarkable reduction was closely linked to the adherence to the low-protein diet supplemented with keto-analogues of essential amino acids and it was also observed an improving in the blood pressure control, likely due to an additive hemodynamic effect with conservative nephroprotective treatment.

Furthermore, the rate of kidney function decline was halved during the intervention, with a decrease in estimated glomerular filtration rate of only 1.5 mL/min in one year, comparable to the physiological decline and significantly lower than the average for patients with diabetic nephropathy.

An innovative aspect of the thesis is the identification of the threshold at which patients could benefit from reducing the progression rate of CKD, established at an eGFR of 14 ml/min. In this context, no patient in the pre-dialysis stage required initiation of renal replacement therapy within one year, emphasizing the importance of controlling CKD complications, optimized through nutritional intervention.

Another important aspect analyzed is the inclusion of elderly patients in the study. Contrary to some existing literature, elderly patients with advanced diabetic nephropathy benefited similarly to non-elderly patients from the nutritional intervention. There were no significant differences between the age groups in terms of reducing proteinuria, slowing kidney function decline, and controlling intermediate metabolisms. Additionally, adherence to the low-protein diet in the elderly was independently associated with a reduction in kidney function decline.

The thesis also demonstrates that there was no association between vascular events and adherence to the recommended diet. Vascular events were more closely related to a lower eGFR

and uncontrolled blood pressure values. Moreover, there were no cases of protein-calorie malnutrition, with patients maintaining an adequate nutritional status throughout the study.

The thesis highlights the challenges related to patient addressability to restrictive nutritional plans. Although only 50% of eligible patients agreed to participate in the intervention, they showed an adherence rate of 64%. Even non-adherent patients benefited from a reduction in proteinuria and kidney function decline, underscoring the need for nutritional counseling programs, potentially implemented through a digital platform.

The thesis proposes the development of a protocol for implementing a digital platform for nutritional counseling, based on literature data suggesting increased patient engagement with digital information. Such a platform could improve patient autonomy, blood pressure control, weight management, and, ultimately, quality of life and long-term adherence to lifestyle changes.

The doctoral thesis significantly contributes to the understanding of the role of low-protein diets in managing patients with diabetes mellitus and advanced CKD. The results obtained highlight the substantial impact on reducing proteinuria, stabilizing kidney function, controlling intermediate metabolisms, and delaying the need for renal replacement therapy. Additionally, the thesis opens the door for increasing patient adherence through the use of a dedicated digital platform for nutritional counseling.

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