



## ORIGINAL ARTICLE

# The low-protein diet for chronic kidney disease: 8 years of clinical experience in a nephrology ward

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## ABSTRACT

**Background.** Guidelines indicate that a low-protein diet (LPD) delays dialysis in severe chronic kidney disease (CKD). We assessed the value of these guidelines by performing a retrospective analysis in our renal clinical practice.

**Methods.** The analysis was performed from 1 January 2010 to 31 March 2018 in 299 CKD Stage 4 patients followed for 70 months in collaboration with a skilled nutritionist. The patients included 43 patients on a controlled protein diet (CPD) of 0.8 g/kg/day [estimated glomerular filtration rate (eGFR) 20–30 mL/min/1.73 m<sup>2</sup> body surface (b.s.)], 171 patients on an LPD of 0.6 g/kg/day and 85 patients on an unrestricted protein diet (UPD) who were not followed by our nutritionist (LPD and UPD, eGFR <20 mL/min/1.73 m<sup>2</sup> b.s.).

**Results.** eGFR was higher in CPD patients than in UPD and LPD patients ( $21.9 \pm 7.4$  mL/min/1.73 m<sup>2</sup> versus  $17.6 \pm 8.00$  mL/min/1.73 m<sup>2</sup> and  $17.1 \pm 7.5$  mL/min/1.73 m<sup>2</sup>;  $P = 0.008$ ). The real daily protein intake was higher in UPD patients than in LPD and CDP patients ( $0.80 \pm 0.1$  g/kg/day versus  $0.6 \pm 0.2$  and  $0.63 \pm 0.2$  g/kg/day;  $P = 0.01$ ). Body mass index (BMI) was stable in the LPD and CPD groups but decreased from  $28.5 \pm 4.52$  to  $25.4 \pm 3.94$  kg/m<sup>2</sup> in the UPD group ( $P < 0.001$ ). The renal survival of UPD, LPD and CPD patients was 47.1, 84.3 and 90.7%, respectively, at 30 months ( $P < 0.001$ ), 42.4, 72.0 and 79.1%, respectively, at 50 months ( $P < 0.001$ ) and 42.4, 64.1 and 74.4%, respectively, at 70 months ( $P < 0.001$ ). The LPD patients started dialysis nearly 24 months later than the UPD patients. Diet was an independent predictor of dialysis [–67% of RR reduction (hazard ratio = 0.33; confidence interval 0.22–0.48)] together with a reduction in BMI.

**Conclusions.** An LPD recommended by nephrologists in conjunction with skilled dietitians delays dialysis and preserves nutritional status in severe CKD.

**Keywords:** dialysis, low-protein diet, severe CKD

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## INTRODUCTION

Chronic kidney disease (CKD) has a prevalence of 7.5% in men and 6.5% in women in Italy [1]. Because of the social and financial burden of dialysis, prevention of the development and progression of CKD has become a milestone for nephrology. Beyond the roles of Renin Angiotensin Aldosterone System (RAAS) blockers [2–4], statins [5, 6] and optimal management of diabetes and metabolic syndrome [7, 8] in delaying end-stage kidney disease (ESKD), also considering that CKD is also a cardiovascular disease [9, 10], the management of CKD based on a nutritional strategy with a low-protein diet (LPD) emerged in 1921 [11] and was followed by Giovannetti's Diet in the 1960s [12]. The review by Kalantar-Zadek and Fouque [13] illustrates the pathophysiological rationale of reduced protein intake in improving CKD progression. The LPD induces constriction of the afferent arterioles and reduces intraglomerular hyperfiltration in conjunction with the vasodilatory effect of RAAS blockers on the efferent arterioles. Despite these premises, the utility of the LPD in CKD is still debated because clinical studies have shown disappointing results. Indeed, the usefulness of the LPD has been obscured by several biases affecting many trials, such as patient adherence [14, 15], insufficient consistent cohorts of patients [16] or primary surrogate endpoints, such as estimated glomerular filtration rate (eGFR) [16, 17]. This issue was addressed in the Modification of Diet in Renal Disease (MDRD) trial [18], but it has been re-evaluated by further *post hoc* analyses that were focused on patient adherence and meta-analyses [19, 20]; these analyses considered ESKD and death as the primary endpoints and showed that the patient mean number needed to treat with the LPD to reduce the risk of dialysis or death is similar to that of RAAS blockers. Despite the controversial findings in the literature, a reduced protein diet has been indicated by guidelines to be a fundamental tool for managing CKD [21], but there are few published studies that link the results of controlled, randomized studies and meta-analyses to real clinical practice.

## Aims

This study provides a report of real-world nutritional management of CKD patients to confirm the value of the guidelines through a retrospective analysis of our clinical experience with renal nutrition.

## MATERIALS AND METHODS

### Patients

We performed a retrospective analysis of 299 patients affected by CKD Stages 4 and 5 from 1 January 2010 to 31 March 2018. Subjects with follow-up of <6 months were excluded.

Our organization provided a clinic for patients with an eGFR of 15–30 mL/min/1.73 m<sup>2</sup> b.s. followed by either a dietitian or a nephrologist, and one clinic for those with an eGFR of <15 mL/min/1.73 m<sup>2</sup> b.s. where a nurse and a psychologist were also involved.

The patients were divided into three groups:

- 43 patients on a controlled protein diet (CPD) of 0.8 g/kg/day with an eGFR of 20–30 mL/min/1.73 m<sup>2</sup> b.s.;
- 171 patients on an LPD of 0.6 g/kg/day (LPD) with an eGFR of <20 mL/min/1.73 m<sup>2</sup> b.s.

- 85 patients on an unrestricted protein diet (UPD) following a liberalized diet for poor compliance or socio-economic or family reasons, with an eGFR of <20 mL/min/1.73 m<sup>2</sup> b.s.

The diets included:

- An energy intake of 30/35 kcal/kg of ideal body weight/day (personalized).
- A protein intake of 0.6 g/kg (ideal body weight)/day (in use in patients with an eGFR <20 mL/min/1.73 m<sup>2</sup> b.s.) or 0.8 g/kg (ideal body weight)/day (in use in patients with an eGFR from 20 to 30 mL/min/1.73 m<sup>2</sup> b.s.).
- A phosphorus intake of 600–800 mg/day.
- A potassium intake of 2000–2500 mg/day.
- A salt intake of 5–6 g/day.

Before the first visit, the dietitian provided the basics of nutritional therapy and gave a 3-day food diary to assess eating habits and usual energy intake.

The visits were made after 1 month and every 3–6 months in parallel with nephrological follow-up. At the first visit, the patient recall, comorbidities, food diary record, age, real and ideal body weight, height, body mass index (BMI), 24-h diuresis, food intolerances, physical activity and professional habits were recorded. The dietitian also provided protein-free products to assess patient preferences and tastes.

### Laboratory assessments

Blood assessments included creatinine, urea, sodium, potassium, calcium, phosphorus, parathyroid hormone (PTH), venous bicarbonate, uric acid, haemoglobin, iron status, albumin, glycated haemoglobin, total cholesterol, high-density lipoprotein cholesterol, triglycerides and albuminaemia.

Urine test included urinary sodium/24 h, urinary urea/24 h, urinary phosphorus/24 h and urinary proteins/24 h.

### Methods

The eGFR level was estimated using the CKD Epidemiology Collaboration (CPK-EPI) formula [22].

The BMI was calculated as follows:

$$\text{weight (kg)/height}^2$$

The ideal body weight was calculated using the patient's height [23]:

$$22.1 \times \text{Height}^2 \text{ in men and } 20.6 \times \text{Height}^2 \text{ in women}$$

Protein intake was estimated using the Maroni-Mitch formula [24]:

$$\text{Protein intake (g/day)} = 6.25 \times (\text{urea urinary nitrogen g/day} + 0.031 \times \text{weight in kg}) + \text{proteinuria g/day.}$$

### Statistics

Statistical analysis was performed with STATA 14 for Windows.

The descriptive analysis was performed with the mean  $\pm$  SD for continuous variables and proportions for ordinal parameters. The comparison of the continuous variables between the three groups of patients was performed using one-way analysis of variance with Bonferroni *post hoc* analysis and chi-square test for ordinal parameters. Dialysis was the primary end-point, and renal survival was examined using Kaplan–Meier analysis and the Log-Rank test.

Starting and ending BMI, creatinine and eGFR were compared with paired t-tests.

Multivariate analysis was carried out using Cox regression, including the diet therapy, the trend in BMI, albumin, eGFR, pharmacological therapies, age, type of nephropathy, sex, albumin, calcium, phosphorus, PTH, haemoglobin and urinary sodium as covariates. Statistical significance was considered at  $P < 0.05$ .

RESULTS

Baseline data

Out of 299 patients, 85 UPD patients had a mean age of  $74.5 \pm 13.8$  years (females/males ratio = 33/52), 171 LPD patients had a mean age of  $70.7 \pm 13.3$  years (females/males ratio = 59/112) and the 43 CPD patients had a mean age of  $71.6 \pm 12.7$  years [females/males ratio = 14/29;  $P$  = not significant (NS)] (Table 1). There were 295 Caucasian, 2 Asian, 1 African and 1 South American patients. The main causes of CKD were nephrocardiovascular disease ( $n = 207$ ; 69.23%; 98 diabetic), glomerular disease ( $n = 38$ ; 12.71%), genetic disease ( $n = 25$ ; 8.36%), drug toxicity ( $n = 3$ ; 1.0%), contrast nephropathy ( $n = 1$ ; 0.33%), CKD due to urologic causes ( $n = 14$ ; 4.69%), hepatorenal syndrome ( $n = 1$ ; 0.33%) and unknown nephropathy ( $n = 1$ ; 0.33%), and nine patients (3.01%) were histologically diagnosed with diabetic nephropathy. The prevalence of diabetic patients between the UPD, LPD and CPD cohorts was not significantly different.

There was a slightly higher prevalence of patients using uric acid-lowering therapies (allopurinol or febuxostat) in the CPD group. The distribution of patients consuming

RAAS blockers, calcium antagonists,  $\beta$ -blockers and statins was similar.

Serum creatinine was higher in the UPD and LPD patients (respectively,  $3.4 \pm 1.7$  mg/dL and  $3.3 \pm 1.6$  mg/dL) than CPD ( $2.6 \pm 0.9$  mg/dL) patients (UPD and LPD versus CPD;  $P = 0.02$  and  $P = 0.03$ , respectively).

No differences were observed in BMI or other biohumoral parameters.

The average daily protein intake in the UPD, LPD and CPD subjects was  $0.80 \pm 0.1$ ,  $0.6 \pm 0.2$  and  $0.63 \pm 0.2$  g/kg/day, respectively (UPD versus LPD patients;  $P = 0.015$ ).

Daily salt intake in the UPD patients was higher than that in the LPD and CPD patients ( $P$  for trend = 0.02).

Renal survival after 30, 50 and 70 months of follow-up

The median follow-up was 30 months for the entire patient cohort (range 11.2–113.8 months) (Figure 1). The mean follow-up in the UPD, LPD and CPD groups was  $23.5 \pm 17.3$ ,  $42.9 \pm 22.9$  and  $38.9 \pm 22.7$  months (UPD versus LPD and CPD patients;  $P < 0.001$ ), respectively.

At 30 months, the numbers of patients needing dialysis in the UPD, LPD and CPD groups were 45/85 (52.9%, renal survival 47.1%), 27/171 (15.7%, renal survival 84.3%) and 4/43 (9.3%, renal survival 90.7%;  $P < 0.001$ ), respectively.

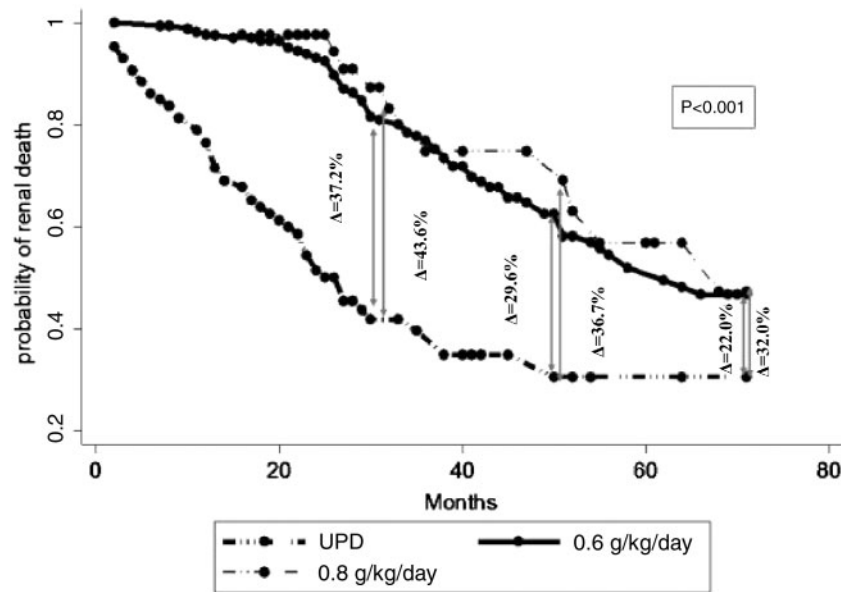
At 50 months, the numbers of patients needing dialysis in the UPD, LPD and CPD groups were 49/85 (57.6%, renal survival 42.4%), 48/171 (28.0%, renal survival 72.0%) and 9/43 (20.9%, renal survival 79.1%;  $P < 0.001$ ), respectively.

At 70 months, the numbers of patients needing dialysis in the UPD, LPD and CPD groups were 49/85 (57.6%, renal survival

Table 1. Patient baseline characteristics

Total = 299 patients	LPD 171 patients	CPD 43 patients	UPD 85 patients	P-value for trend
Age (years)	$70.7 \pm 13.3$	$71.6 \pm 12.7$	$74.5 \pm 13.8$	1.08
Diabetes, n/N	60/111	18/25	29/55	0.80
Males/females, n/N	59/112	14/29	33/52	0.71
Serum creatinine (mg/dL)	$3.3 \pm 1.6$	$2.6 \pm 0.9$	$3.4 \pm 1.7$	0.02
eGFR (mL/min/1.73 m <sup>2</sup> )	$17.1 \pm 7.5$	$21.9 \pm 7.4$	$17.6 \pm 8.0$	0.008
Azotaemia (mg/dL)	$134.0 \pm 53.3$	$116.9 \pm 36.2$	$152.1 \pm 81.1$	0.16
Sodium (mEq/L)	$142.4 \pm 3.4$	$143.3 \pm 3.1$	$138.0 \pm 4.5$	0.51
Potassium (mEq/L)	$4.8 \pm 0.6$	$4.5 \pm 0.5$	$4.8 \pm 0.6$	0.37
Calcium (mg/dL)	$9.3 \pm 0.4$	$9.3 \pm 0.4$	$9.5 \pm 0.7$	0.60
Phosphorus (mg/dL)	$4.0 \pm 0.8$	$3.5 \pm 0.8$	$4.0 \pm 1.3$	0.14
PTH (pg/mL)	$232.6 \pm 152.6$	$171.3 \pm 100.0$	$150.3 \pm 101.2$	0.21
Haemoglobin (g/dL)	$12.1 \pm 1.7$	$11.7 \pm 0.8$	$11.8 \pm 1.3$	0.63
Protein intake (g/kg ideal body weight/day)	$0.6 \pm 0.2$	$0.63 \pm 0.2$	$0.80 \pm 0.1$	0.01
BMI (kg/m <sup>2</sup> )	$28.5 \pm 5.5$	$28.1 \pm 4.5$	$28.5 \pm 5.7$	0.94
Urinary sodium 24 h (mmol)	$130 \pm 41.3$	$127.1 \pm 47.2$	$191.8 \pm 84.4$	0.02
HbA1c (%)	$8.7 \pm 4.4$	$6.68 \pm 1.0$	$9.58 \pm 2.9$	0.20
Allopurinol/febuxostat, n/N (%)	64/171 (37)	24 (66)	26 (30)	0.04
Statins, n (%)	75 (43)	19 (44)	30 (35)	0.58
$\beta$ -blockers, n (%)	51 (29)	20 (46)	23 (27)	0.07
Calcium antagonists, n (%)	69 (40)	16 (30)	26 (30)	0.13
RAAS blockers, n (%)	76 (43)	20 (45)	27 (32)	0.09
Diuretics, n (%)	90 (52)	25 (58)	38 (50)	0.50

Data expressed as the mean  $\pm$  SD unless and otherwise mentioned. Better renal function was observed in the subjects in the CPD group (0.8 g/kg/day) than either those in the LPD group (0.6 g/kg/day) or in the UPD group [ $P$  for trend = 0.02 for creatinine and 0.008 for eGFR (CPD versus LPD and UPD:  $P = 0.02$  and  $P = 0.03$  for creatinine;  $P = 0.012$  and  $P = 0.013$  for eGFR)]. The real daily protein intake was higher in the UPD patients than either in the LPD patients or the CPD patients [ $P$  for trend = 0.01 (LPD versus UPD:  $P = 0.015$ )]. The daily intake of salt was higher in the UPD patients than either the LPD patients or the CPD patients [ $P$  for trend = 0.02 (post hoc analysis  $P = 0.04$ )], and greater use of uric acid-lowering therapies was observed in the CPD group than the other two groups [ $P$  for trend = 0.04 (UPD versus LPD and CPD:  $P = 0.02$ )].



**FIGURE 1:** Kaplan-Meier analysis. Kaplan-Meier survival analysis in the UPD, LPD and CPD subjects. At 30 months, the percentages of renal death in the UPD, LPD and CPD groups were 45/85 patients (52.9%, renal survival 47.1%), 27/171 patients (15.7%, renal survival 84.3%) and 4/43 patients (9.3%, renal survival 90.7%;  $P < 0.001$ ), respectively. At 50 months, these values were 49/85 patients (57.6%, renal survival 42.4%), 48/171 patients (28.0%, renal survival 72.0%) and 9/43 patients (20.9%, renal survival 79.1%;  $P < 0.001$ ), respectively. At 70 months, these values were 49/85 patients (57.6%, renal survival 42.4%), 61/171 patients (35.6%, renal survival 64.4%) and 11/43 patients (25.6%, renal survival 74.4%;  $P < 0.001$ ), respectively.

**Table 2.** Trends of plasma creatinine levels and eGFR during the follow-up

		Basal creatinine (mg/dL)	Final creatinine (mg/dL)	P-value, final versus basal	Increase of creatinine (mg/dL)	P-value	Percentage of increase of creatinine	P-value
Patients not requiring dialysis	UPD	2.7±0.9	3.8±1.7	0.004	1.1±1.6	–	47.5±78.2	–
	LPD	2.9±0.9	3.4±1.2	<0.001	0.5±1.1	0.1 <sup>a</sup>	22.0±39.9	0.06 <sup>a</sup>
	CPD	2.7±1.0	2.7±1.3	NS	0.05±1.1	0.009 <sup>b</sup>	4.7±35.9	0.004 <sup>b</sup>
Patients requiring dialysis	UPD	3.8±1.8	7.0±1.7	<0.001	3.2±2.3	–	125.2±121.1	–
	LPD	3.5±1.3	7.3±1.9	<0.001	3.7±2.1	NS <sup>a</sup>	128.2±90.9	NS <sup>a</sup>
	CPD	3.0±0.7	6.9±1.8	<0.001	3.8±2.1	NS <sup>b</sup>	143.5±84.3	NS <sup>b</sup>

Trend of eGFR during the follow-up

		Basal eGFR (mL/min/1.73 m <sup>2</sup> )	Final eGFR (mL/min/1.73 m <sup>2</sup> )	P-value, final versus basal	Reduction of eGFR (mL/min/1.73 m <sup>2</sup> )	P-value	Percentage of reduction of eGFR	P-value
Patients not requiring dialysis	UPD	21.3±7.7	14.7±7.3	<0.001	6.0±6.2	–	25.3±22.6	–
	LPD	19.2±6.6	16.3±6.4	<0.001	2.9±6.0	0.038 <sup>a</sup>	11.7±13.2	0.018 <sup>a</sup>
	CPD	21.5±7.5	21.8±8.4	NS	0.36±6.8	0.001 <sup>b</sup>	7.1±42.0	0.001 <sup>b</sup>
Patients requiring dialysis	UPD	15.6±7.6	6.7±2.0	<0.001	8.7±7.8	–	46.2±27.9	–
	LPD	15.7±6.4	6.3±1.8	<0.001	9.2±7.1	NS <sup>a</sup>	53.2±21.5	NS <sup>a</sup>
	CPD	17.2±5.2	7.0±3.2	<0.001	10.2±7.0	NS <sup>b</sup>	53.5±34.7	NS <sup>b</sup>

A significant increase in creatinine and a reduction in eGFR were observed in the UPD and LPD groups in patients not requiring dialysis and those who needed it. These data were not observed in the CPD patients not requiring dialysis. Of note, the increase in creatinine and worsening of eGFR were higher in the UPD group than in the LPD (not significantly) and CPD groups not requiring dialysis.

<sup>a</sup>LPD versus UPD.

<sup>b</sup>CPD versus UPD.

42.4%), 61/171 (35.6%, renal survival 64.4%) and 11/43 (25.6%, renal survival 74.4%;  $P < 0.001$ ), respectively.

The LPD and CPD patients began dialysis with a delay of 24 and 21 months compared with the UPD patients (mean time free of dialysis =  $41.0 \pm 21.2$  and  $37.8 \pm 16.0$  versus  $17.0 \pm 13.8$ ;  $P < 0.001$  and  $P = 0.003$ ).

## Renal function and nutritional parameters

### Stratifying patients according to dialysis admission

**Renal function.** Table 2 shows the trends in creatinine and eGFR in patients requiring dialysis and those not requiring dialysis at the beginning and the end of follow-up. Notably, a larger increase in creatinine and a larger decrease in eGFR were observed in the

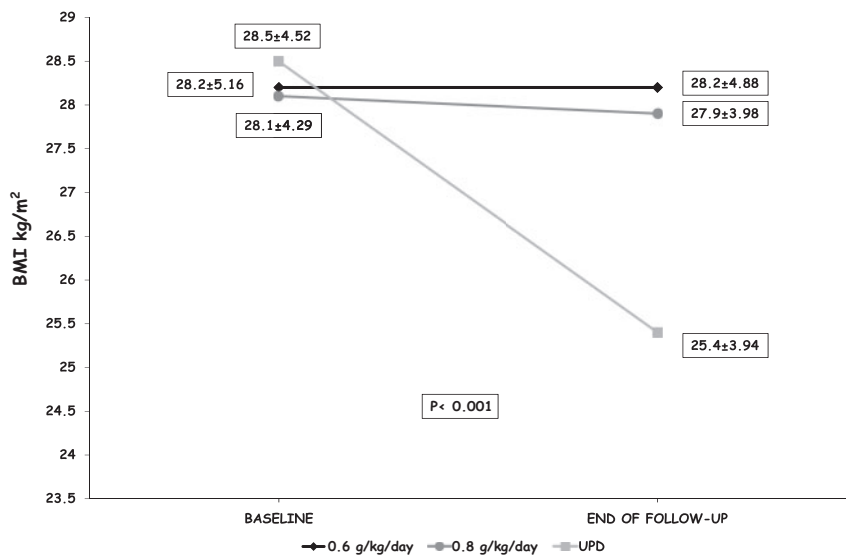


FIGURE 2: The trend in BMI from baseline to the end of follow-up. There was not a significant difference in basal BMI with values of  $28.5 \pm 4.52$  kg/m<sup>2</sup> in UPD patients,  $28.2 \pm 5.16$  kg/m<sup>2</sup> for the group on the LPD and  $28.1 \pm 4.29$  kg/m<sup>2</sup> for those in the CPD group. BMI held relatively stable through the end of follow-up with values of  $28.2 \pm 4.88$  kg/m<sup>2</sup> for the patients on the LPD and  $27.9 \pm 3.98$  kg/m<sup>2</sup> for those on the CDP. BMI significantly decreased to  $25.4 \pm 3.94$  kg/m<sup>2</sup> for patients not followed by the dietician (UPD versus LPD and CPD patients;  $P < 0.001$ ).

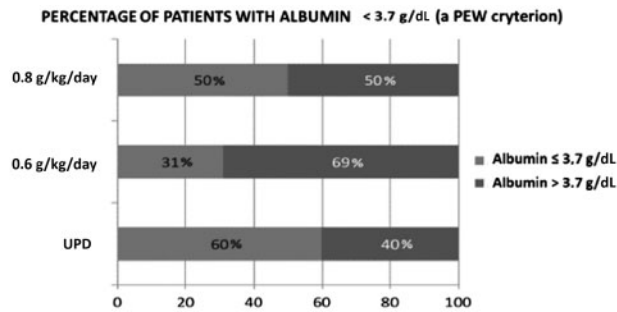


FIGURE 3: Percentage of patients with albumin levels  $< 3.7$  g/dL at the end of follow-up. The percentage of patients with albuminaemia  $< 3.7$  g/dL was 60% in the group of patients not followed by a dietician, 31% in the LPD group and 50% in the CPD group.

UPD group [increase in creatinine:  $1.1 \pm 1.6$  mg/dL ( $47.5 \pm 78.2\%$ ), decrease in eGFR =  $6.0 \pm 6.2$  mL/min/1.73 m<sup>2</sup> ( $25.3 \pm 22.6\%$ )] than the LPD group [ $0.5 \pm 1.1$  mg/dL ( $22.0 \pm 39.9\%$ ), decrease in eGFR =  $2.9 \pm 6.0$  mL/min/1.73 m<sup>2</sup> ( $11.7 \pm 13.2\%$ )] ( $P = 0.06$  for the percentage increase in creatinine and  $P = 0.018$  for the percentage decrease in eGFR) and the CPD group [ $0.05 \pm 1.1$  mg/dL ( $4.7 \pm 35.9\%$ ), increase in eGFR =  $0.36 \pm 6.8$  mL/min/1.73 m<sup>2</sup> ( $7.1 \pm 42.0\%$ )] ( $P = 0.004$  for the percentage gain in creatinine and  $P = 0.001$  for the percentage decrease in eGFR) in subjects not requiring dialysis.

**Nutritional parameters**

BMI. The baseline BMIs in the UPD, LPD and CPD individuals were  $28.5 \pm 4.52$ ,  $28.2 \pm 5.16$  and  $28.1 \pm 4.29$  kg/m<sup>2</sup>, respectively ( $P = \text{NS}$ ).

The final BMIs in the UPD, LPD and CPD subjects were  $25.4 \pm 3.94$ ,  $28.2 \pm 4.88$  and  $27.9 \pm 3.98$  kg/m<sup>2</sup>, respectively (UPD versus LPD and CPD group;  $P < 0.001$ ) (Figure 2).

Comparing the differences between initial BMI and final BMI values in patients beginning dialysis and those not beginning dialysis, we observed that dialysis patients had BMI decrease of  $3.7 \pm 3.4$ ,  $0.02 \pm 2.8$  and  $0.51 \pm 1.1$  kg/m<sup>2</sup> in the UPD, LPD and CPD

groups, respectively (UPD versus LPD and CPD;  $P < 0.001$ ). Patients not on dialysis had BMI decrease of  $2.2 \pm 2.4$ ,  $0.02 \pm 2.0$  and  $0.04 \pm 2.7$  kg/m<sup>2</sup> in the UPD, LPD and CPD individuals, respectively (UPD versus LPD and CPD groups;  $P < 0.001$ ).

Albuminaemia. At the end of follow-up, albuminaemia was  $3.46 \pm 0.5$  g/dL in the UPD patients,  $3.9 \pm 0.4$  g/dL in the LPD subjects and  $3.8 \pm 0.4$  g/dL in the CPD patients (UPD versus LPD:  $P = 0.003$ ). An albuminaemia of  $< 3.7$  g/dL was present in 60%, 31% and 50% of the UPD, LPD and CPD individuals, respectively (Figure 3).

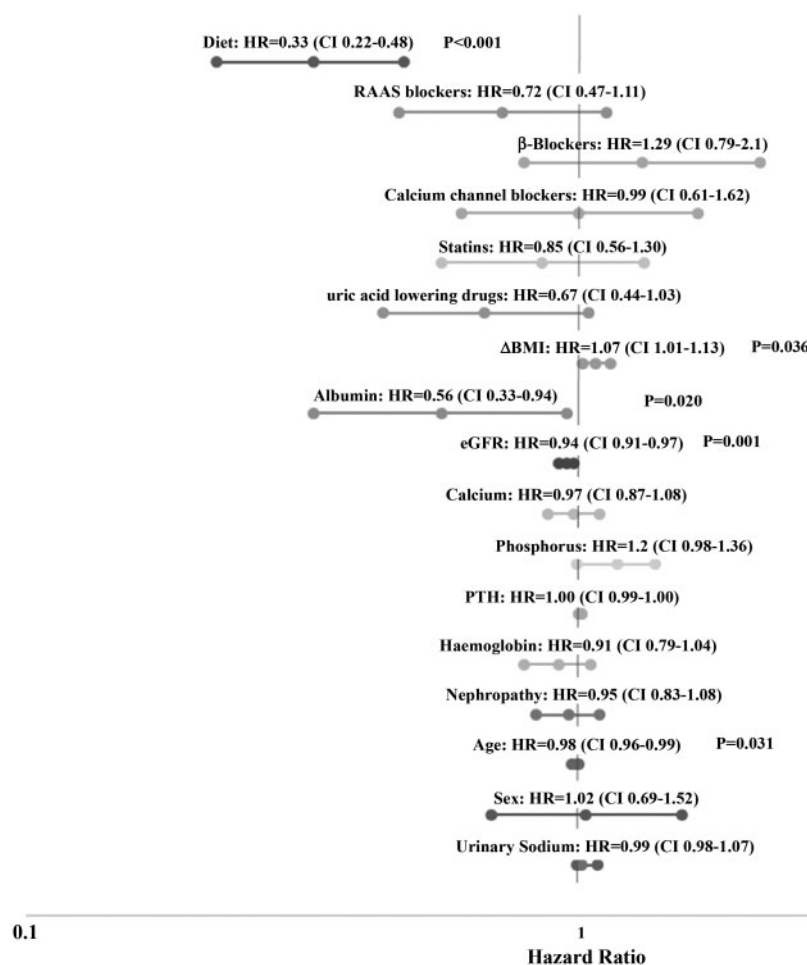
**Multivariate analysis**

A Cox multivariate analysis of independent predictors of renal death found that nutrition therapy ( $-67\%$  of relative risk (RR) reduction [hazard ratio (HR) = 0.33; confidence interval (CI) 0.22–0.48];  $P < 0.001$ ), eGFR (HR = 0.94; CI 0.91–0.97;  $P = 0.001$ ), age (HR = 0.98, CI 0.96–0.99;  $P = 0.031$ ), albumin (HR = 0.56; CI 0.33–0.94;  $P = 0.02$ ) and reduction in BMI (HR = 1.07; CI 1.00–1.13;  $P = 0.036$ ) were significant predictors (Figure 4).

**DISCUSSION**

This study showed that individuals affected by severe CKD in the LPD and CPD groups had 37.2 and 43.6%, 29.6 and 36.7%, and 22.0 and 32% higher renal survival than the UPD patients at 30, 50 and 70 months, respectively. Of note, 10 patients belonging to the UPD group had stabilization of renal survival (42.4%) beyond the 50th month of observation, but they started with a modestly higher mean eGFR ( $19.0 \pm 4.7$  mL/min/1.73 m<sup>2</sup> b.s.) than the other patients. Additionally, a slightly lower renal survival was observed in the LPD than in the CPD patients, but the latter had a higher eGFR and greater consumption of uric acid-lowering compounds, possibly preserving renal function [25, 26]. At the end of follow-up, a lower decrease in eGFR and a lower increase in creatinine (not significant in LPD subjects) were observed in LPD and CPD individuals than in UPD individuals not requiring dialysis. This finding is an interesting result, but





**FIGURE 4:** Cox multivariate analysis. The independent predictors of renal death were nutrition therapy [−67% RR reduction (HR = 0.33; CI 0.22–0.48);  $P < 0.001$ ], eGFR (HR = 0.94; CI 0.91–0.97;  $P = 0.001$ ), age (HR = 0.98; CI 0.96–0.99;  $P = 0.031$ ), reduction in BMI (HR = 1.07; CI 1.00–1.13;  $P = 0.036$ ) and albumin (HR = 0.56; CI 0.33–0.94;  $P = 0.020$ ).

we cannot draw any conclusion about this finding because of the retrospective and uncontrolled nature of the analysis. Therefore, we currently agree with the conclusions in the recent literature [27].

The independent predictors of ESKD from multivariate analysis were nutritional therapy (RR = −67%), decreased BMI (near 7% of the risk of ESRD for each point of loss of BMI), albumin (44% of risk reduction of ESRD for each g/dL of increase), eGFR (−6% for each mL/min of decrease) and age (−2% for each year).

Our clinical feedback about the LPD was in line with the guidelines [28–30]. The past literature showed that each increase in protein intake of 0.1 g/kg/day evaluated by 24 h urinary excretion and a food diary increased the relative risk of ESKD by 5% (95% CI 1.01–1.10) and 9% (95% CI 1.04–1.14), respectively [31]. Previous meta-analyses [19, 20] and *post hoc* analysis of the MDRD study [32, 33] showed that each reduction of dietary protein by 0.2 g/kg/day was associated with a −29% of risk of progression of CKD and −50% of risk of ESKD. Despite the findings of the most recent meta-analysis [27], which indicated a moderate level of evidence of the beneficial effects of delaying ESKD using a very LPD (0.3–0.4 g/kg/day) compared with an LPD (0.58–0.65 g/kg/day) (eight studies) or normal protein diet (two studies) in patients affected by CKD Stages 4–5 (RR = 0.64; CI 0.49–0.85), the meta-analysis did not show the same effect

comparing LPD (0.55–0.6 g/kg/day) with a normal protein diet (0.8–1 g/kg/day). Indeed, the last comparison was conducted in patients with CKD in stages 3a and 3b using nine studies and only one study considered subjects affected by CKD Stage 4. The same meta-analysis did not show beneficial effects of VLPD or LPD on eGFR and mortality and had a low level of certainty about the risk of malnutrition. In contrast with these results, we found a beneficial effect of the LPD compared with the UPD, but our patients all had eGFR levels <20 mL/min/1.73 m<sup>2</sup> b.s. Thus, we probably avoided bias from including the earliest, moderate stages of CKD at lower risk of progression towards ESKD. Regarding the risk of malnutrition that remains an open field of investigation to date [27], in our experience, BMI remained stable with a reduced protein diet, and it decreased in the UPD group at the end of follow-up despite the starting BMI not being different between the three groups. UPD patients also had higher spontaneous protein intake. Furthermore, the percentage of patients with an albumin concentration <3.7 g/dL was lower in the UPD and CPD groups than in the LPD group. These results indicated the importance of patient adherence with protein restriction and emphasized that it cannot be ensured without regular follow-up performed by a skilled dietitian. This issue affects not only the dietary protein and caloric intake but also appropriate salt consumption.

Patient adherence has been an important issue for previous studies, some of which even showed an adverse effect of LPD on renal survival (0.55 g/kg/day) compared with CPD (0.8 g/kg/day) [34], but the real daily protein intake of LPD patients was higher than that prescribed. Nevertheless, LPD is associated paradoxically with increased risk of hospitalization and mortality [35] if not matched with adequate energy intake, and deficiency leads to sarcopenia and frailty. Frailty is defined as unintentional weight loss, subjective physical exhaustion, measured muscle weakness, slow walking, low physical activity [36] and low levels of albumin (<3.8 g/dL), prealbumin (<30 g/dL) and total cholesterol (<100 mg/dL) [37].

The main causes of frailty are advanced age, reduced appetite, alterations in taste, loss of teeth, uraemic toxicity, metabolic acidosis and poor physical activity, but it can also be caused by intentional dietary protein restriction. In our study, we did not assess muscle mass directly or with strength tests. Nevertheless, we found stable BMI and albumin serum concentrations in patients receiving nutrition therapy at the end of follow-up.

These data are not surprising because other experimental findings show that the transition from a daily dietary protein content of 1.1 to 0.45 g/kg/day supplemented with keto-analogues increases muscle protein recycling up to 86% [38], and reduced protein content transitioning from 0.55 to 0.45 g/kg/day reduces protein catabolism assessed as oxidative deamination of leucine [39].

Nevertheless, malnutrition can be avoided and muscle trophism can be maintained provided adequate energy support and physical activity [40] are guaranteed. In fact, there is an inverse relationship between the amount of dietary calories and muscle mass in individuals with severe CKD assuming 0.55–0.6 g/kg/day of protein randomly assigned to receive a daily caloric intake of 45, 35, 25 or 15 kcal/kg [41]. This finding justifies an advised caloric intake of 30–35 kcal/kg/day with an LPD or very LPD.

This caloric intake is a difficult target to reach but some important considerations are necessary:

- i. Energy needs are reduced from 8% to 20% with a sedentary lifestyle (Human Energy Requirements. Report of a joint FAO/WHO/ONU expert consultation 2001. [www.fao.org](http://www.fao.org)).
- ii. Energy needs decrease by 7–10 kcal/year after the age of 30 years [Dietary reference intakes for energy, carbohydrate, fibre, fat, fatty acids, cholesterol, protein, and amino acids (Macronutrients) National Academic Press 2005].
- iii. Physical activity energy expenditure is reduced in CKD patients [42].

Therefore, energy needs in CKD should be individualized based on basal metabolism and usual physical activity, which could be determined with simple equations for CKD individuals [43].

Our analysis has several limitations because it is retrospective, not controlled and not randomized. Furthermore, there are biases in the assessment of renal function with eGFR rather than calculated GFR, which is perhaps more accurate because indirectly evaluates muscle mass through urine creatinine. Ideal body weight could have been underestimated by the Keys formula, and there was not an evaluation of muscle mass. However, the key strength of this study is that these results confirm the suggestions noted in the guidelines despite not coming from a trial specially designed for this purpose. In our opinion, a well-designed nutritional therapy should not be viewed simply as a conservative approach for severe CKD,

because it has the greater possibility of a pre-emptive kidney transplant and is a useful adjunct tool to dialysis therapy in frail elderly patients [44, 45] that preserves residual renal function [46].

## CONCLUSIONS

Based on our experience, we can say that nutritional therapy should not be considered a second choice approach for CKD in agreement with recent Italian statements [29], and should be used across nephrology wards. The last, but not least, important aspect is patient quality of life and cost, but there is insufficient data on these aspects. These are important issues that must certainly be investigated in further studies.

## CONFLICT OF INTEREST STATEMENT

None declared. The results presented in this paper have not been published previously in whole or part, except in abstract format.

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