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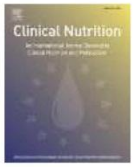

ORIGINAL ARTICLE

The impact of nutrition intervention on quality of life in pre-dialysis chronic kidney disease patients

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KEYWORDS
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Summary
Background & aims: Uraemic symptoms as a result of reduced kidney function may impact on an individual's functional and nutritional status. This study aims to investigate whether providing individualised nutritional counselling can improve nutritional status and influence quality of life in pre-dialysis chronic kidney disease patients.
Methods: Fifty-three stage IV and V pre-dialysis chronic kidney disease patients underwent assessment of nutritional status (by Patient Generated Subjective Global Assessment) and quality of life (by Kidney Disease Quality of Life™). Participants were assessed at baseline and following a 12-week randomised-controlled treatment, allocated to either individualised counselling with regular follow-up ($n = 24$) or standard care treatment (generic education only ($n = 23$)).
Results: At baseline, nutritional status was significantly correlated with all general quality of life sub-scales. There was a statistically significant mean difference in change between groups for: symptoms of kidney disease (7.1 (0.1e14.1) $p = 0.047$); cognitive functioning (14.6 (5.4e23.7) $p = 0.003$); and vitality (12.0 (4.6e19.5) $p = 0.002$) favouring intervention treatment.
Conclusions: Quality of life is related to nutritional status in pre-dialysis patients. Providing individualised nutritional counselling improves many components of quality of life, compared with standard nutrition care, in the stage prior to dialysis treatment.

Introduction

Health-related quality of life (QOL) is related to a patient's functioning, wellbeing and general health perception in physical, psychological and social domains.[1] In chronic disease, and specifically chronic kidney disease (CKD), a close relationship exists between QOL, morbidity and mortality.[2,3]

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It has been established that CKD patients experience a significantly lower QOL compared with healthy controls, which is more pronounced in the pre-dialysis phase (Stage 4 and 5), especially in the elderly.[4–6] A decline in GFR and an increase in uraemic symptoms (including fatigue, weakness, anorexia and muscular cramps) is associated with a reduced functional status and quality of life.[7]

Nutritional status has been shown to impact on QOL in dialysis patients by various nutrition assessment parameters.[8,9] Although improved nutritional management has been proposed as beneficial to the QOL of CKD patients, there has been a limited evidence base to date to support this.

This randomised controlled trial was developed to determine if providing individual nutrition counselling with regular telephone follow-up resulted in improved nutritional status and QOL, compared with standard care. The specific aims were to investigate: (1) the cross-sectional relationship between patients' QOL and nutritional status, at the onset of pre-dialysis treatment; and (2) whether individualised nutritional counselling or standard care treatment influenced the patient's QOL, and nutritional status leading up to dialysis treatment. The results reported here are part of a larger study designed to measure the effect of a nutrition intervention on body cell mass and nutritional status.

Sample and methods

The study was conducted through Royal Brisbane and Women's Hospital (RBWH) Department of Renal Medicine pre-dialysis clinic. Participants met the following criteria: adult (>18 years), glomerular filtration rate (GFR) < 30 ml/min CKD, not previously seen by a dietitian for Stage IV CKD, absence of communication or intellectual impairment inhibiting their ability to undertake the intervention and an absence of malnutrition from a cause other than CKD. Potential participants were identified upon consecutive entry into the pre-dialysis clinic, where informed consent was sought from those who met the eligibility criteria.

The CONSORT flowchart of participants in this study is provided in Fig. 1. Following the consent of 60 eligible participants, four were excluded from baseline assessment (two participants voluntarily withdrew and two transferred care to dialysis (1) and transplant (1)). Fifty-six patients underwent baseline assessment, with valid QOL assessment on 53, which is the sample used for this analysis (Male 59%; age mean (SD) 69.9 (11.9) years). Patients were randomised to receive either individual counselling with fortnightly telephone follow-up, or standard care (written material only), allocated via a computer-generated number sequence, which was concealed to the recruiting officer (see Figure 1). No participants in either group voluntarily dropped out of the study following receipt of intervention, as per CONSORT flowchart in Fig. 1.

The intervention treatment, administered by a single dietitian, experienced in renal nutrition, was undertaken over a 12 week period and aimed to optimise nutritional status and attain evidence-based dietary prescription,[10] whilst managing symptoms of reduced kidney function. The delivery of the intervention was guided by the medical nutrition therapy framework from the American Dietetic Association.[11,12] The intervention treatment group was provided with an initial individual consultation with a dietitian, and then patients were regularly monitored by telephone consultation, fortnightly for the first month, then monthly. The intervention utilised self-management principles (goal setting, menu planning, label reading and identification of foods containing protein, sodium etc, depending on requirements) and was individualised to each participant, depending on their level of kidney function, existing symptoms of kidney disease and co-morbidities.

At the time of this study, there was a lack of consistency as to what constituted standard care. In Australian practice, individualised education is not provided as standard[13] treatment for patients with severe CKD and, in this institution, involved ad hoc provision of written education material and/or one-off referral to a dietitian. Therefore, for consistency, participants in the standard care group received generic nutrition information (as provided in regular clinical practice) containing an overview of nutrition advice for chronic kidney disease and co-morbidity management. No individualised advice or monitoring was provided.

Ethical approval was granted by the Royal Brisbane and Women's Hospital and Queensland University of Technology Human Research Ethics Committees. This is Registered Trial ACTRN012606000493549.

Quality of life

Quality of life was measured by Kidney Disease Quality of Life Short Form version 1.3 (KDQOL-SF™ v1.3, ª Rand University), combining the Short Form-36 (SF-36), with a kidney disease-specific module.[14] The disease-specific part includes 43 items directed at the kidney disease (symptoms/problems, effects of kidney disease on daily life, burden of kidney disease, cognitive function, work status, sexual function, quality of social interaction, sleep). Also included are multi-item measures of social support, dialysis staff encouragement, and patient satisfaction, as well as an overall rating of health.[14] This tool required minor modification for use in pre-dialysis patients: specifically, changing the wording for satisfaction with care from ''kidney dialysis'' to ''kidney disease'' (item 23), and omitting the questions about dialysis staff encouragement and support (items 24A and 24B).

The KDQOL-SF™ v1.3 was provided to each subject prior to the baseline and follow-up assessment. The scoring spreadsheet for KDQOL-SF™ v1.3 was downloaded to Microsoft Office Excel® 2003 from the KDQOL webpage (http://gim.med.ucla.edu/kdQOL/downloads/download.html, accessed February 20, 2005). Data from individual surveys were input into this spreadsheet. Each question is precoded numerically, and then transformed into a scale of 0 to 100; the highest values reflect better QOL. QOL summary scores for each sub-scale were manually input into the main SPSS database.

Nutritional status assessment

Patient-Generated Subjective Global Assessment (PG-SGA) was used to assess nutritional status. The PG-SGA consists of

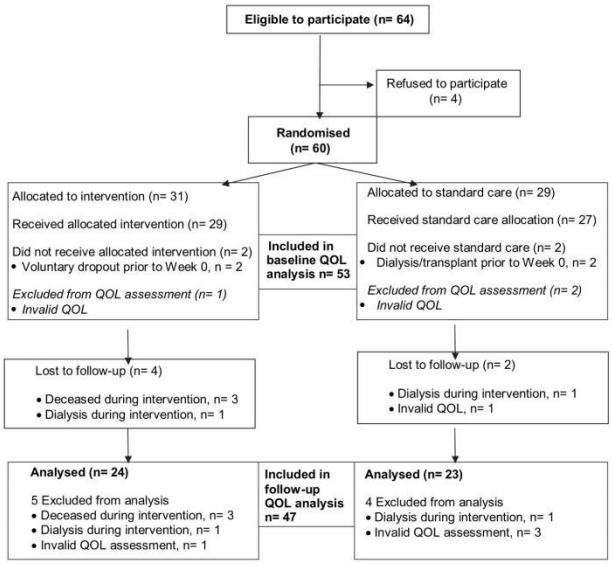

Figure 1 CONSORT flowchart of participant progression through randomised controlled trial of nutrition intervention in pre-dialysis CKD patients, evaluating quality of life.

a medical history (recent changes in weight, gastrointestinal symptoms, food intake, functional capacity, components of metabolic stress) and physical examination of fat and muscle stores.[15] The PG-SGA assessment provides an additive score from 0 up to 50 with a higher score indicating greater risk of malnutrition.[15] The PG-SGA assessment also incorporates the SGA global rating of nutritional status, categorising patients as either A (well nourished), B (moderately malnourished) or C (severely malnourished) which is well validated in CKD.[16,17]

Statistical methods

Statistical analysis was carried out using SPSS Version 13 (SPSS Inc., Chicago, IL, USA). The baseline comparison between the 18 subscales of KDQOL-SF™ were assessed for a relationship to nutritional status by SGA assessment (independent samples *t*-test) and PG-SGA score (Spearman correlation). Change variables (Week 12–Week 0) were created for the 18 KDQOL-SF™ sub-scales. The assessment of change in outcome measures by treatment group was undertaken by ANCOVA, adjusting for baseline values.

Statistical significance was set at a conventional 95% level (2-tailed). However, interpretation to the data is focused on effect size (clinical significance) as much as statistical significance. The RCT was powered to detect a significant difference in the primary outcome of body cell mass, which is published elsewhere.[18] As change in quality of life was a secondary outcome variable in the original RCT, the sample was not powered for QOL change specifically.

Clinical significance was defined using the standardised effect sizes described by Cohen.[19] This is determined by the difference of 2 means divided by the standard deviation. At baseline, this was the mean of the QOL score from well nourished minus mean from those classed as malnourished, divided by the standard deviation of the well-nourished patients. Similarly, the mean difference in change in QOL scores following the 12-week intervention period was divided by the standard deviation for change from the intervention group. The resulting effect size was evaluated against benchmarks of 0.2 for 'small' effect (equate to the minimal clinical important difference), 0.50 for 'moderate' effect and 0.8 for large effect size.[19] These benchmarks are well accepted to provide a standardised approach to evaluate a difference in QOL considered to be worthwhile or important to inform clinical practice decisions.[20]

Results

Baseline evaluation between nutritional status and QOL was conducted on the full baseline sample of 53 participants. At 12 weeks, there was complete data on 47 patients (intervention $n = 23$; standard care $n = 24$). Figure 1 identifies the flow of participants through the study. As demonstrated in Table 1, there was no significant difference between

Table 1 Baseline characteristics (mean SD) of patients with pre-dialysis CKD completing randomised treatment to Intervention (*n* 23), Standard care (*n* 24), or received allocation but lost to follow-up, or invalid QOL (*n* 9)

Variable	Intervention	Standard care	Lost to follow-up	*p* Value[a]
	n 23	*n* 24	*n* 9	
Age	71.0 12.3	68.5 12.0	72.6 8.5	0.604
Gender, Male *n* (%)	14 (60.9)	15 (62.5)	5 (55.5)	0.936[b]
GFR (ml/min)	21.9 6.3	23.4 7.9	20.6 3.4	0.525
BMI (kg/m^2)	27.4 5.3	27.0 4.9	27.0 4.7	0.965
Nutritional status, Well nourished *n* (%)	18 (81 8)	21 (87.5)	4 (60.0)	0.732[b]
Physical Health Summary (QOL)	33.8 10.2	34.7 10.0	35.8 8.9	0.909
Mental Health Summary (QOL)	48.5 11.9	45.3 12.5	41.8 113.4	0.459

[a] Assessed as difference in means between groups by analysis of covariance.
[b] Difference in proportions between groups assessed by pearson chi-square.

participants allocated to either treatment group or between the nine participants excluded from this analysis (lost to follow-up or invalid QOL assessment) for baseline variables including renal function, body mass index, nutritional status and QOL (Table 1)

Nutritional status, as determined by SGA rating and PG-SGA score, was compared with ratings of the components of the KDQOL tool (Table 2), with higher score equating to better quality of life. In the majority of the QOL components well-nourished patients had a higher mean rating than the malnourished patients (effect size > 0.5 in 12 of 18 subscales), which is considered moderately clinically significant. The components of Symptoms of kidney disease, Physical functioning, Social functioning and Role emotional were statistically significant (Table 2). The PG-SGA score demonstrated a significant negative correlation with each of the SF 36 components, relating to physical and mental health and the ratings for symptoms and effects for kidney disease and overall health from the kidney disease subscales.

Table 2 Baseline kidney disease-specific and short-form 36 quality of life components, compared with SGA rating and PG-SGA score in a sample of pre-dialysis CKD patients (*n* 53)

	Well-nourished SGA A		Malnourished SGA B		*p* Value[a]	Effect size	PG-SGA score
	n 43		*n* 10				
	Mean	SD	Mean	SD			*r*[b], *p* value
Kidney-disease components							
Symptoms of kidney disease	77.2	16.1	61.0	23.2	0.028	1.0	−0.480, <0.001
Burden of kidney disease	64.4	26.2	51.3	31.6	0.240	0.5	−0.162, 0.247
Work status	27.9	33.3	30.0	25.8	0.665	−0.1	−0.010, 0.941
Cognitive function	78.9	18.7	74.3	24.9	0.769	0.3	−0.251, 0.072
Social interactions	75.6	17.9	76.0	18.4	0.963	0.0	−0.219, 0.119
Sleep	66.2	19.4	63.3	25.4	0.891	0.1	−0.179, 0.200
Social support	75.8	26.3	81.7	12.3	0.699	−0.2	0.025, 0.863
Overall health	62.6	21.2	47.0	20.0	0.056	0.7	−0.422, 0.002
Satisfaction	73.2	22.0	74.1	20.6	0.927	0.0	−0.073, 0.615
SF-36 components							
Physical functioning	43.4	27.6	20.5	22.7	0.015	0.8	−0.458, 0.001
Role physical	32.6	38.8	12.5	31.7	0.112	0.5	−0.375, 0.006
Bodily pain	66.8	25.9	63.5	32.7	0.774	0.1	−0.304, 0.027
General health	41.5	18.1	33.5	13.6	0.331	0.4	−0.313, 0.022
Vitality	41.6	23.0	28.0	25.8	0.087	0.6	−0.345, 0.011
Social function	71.8	28.5	46.3	32.8	0.020	0.9	−0.405, 0.003
Role emotional	62.8	39.3	26.7	40.9	0.018	0.9	−0.485, <0.001
Mental health	70.8	20.9	59.6	23.2	0.138	0.5	−0.410, 0.002
Physical health component	35.9	10.2	29.9	7.9	0.107	0.6	−0.348, 0.011
Mental health component	47.7	11.7	40.0	12.6	0.069	0.7	−0.388, 0.004

SGA, Subjective Global Assessment; PG-SGA, Patient-Generated Subjective Global Assessment; SF, Short-Form.
[a] Determined by independent sample *t*-test.
[b] Determined by Spearman correlation.

The effect of the intervention on QOL is shown in Fig. 2, which summarises the change in quality of life ratings for the 10 kidney-disease; 8 SF-36 subscales from baseline to week 12 for each of the treatment groups (Fig. 2A and B); and the mean difference in change between groups (Fig. 2C and D), which include effect size (detailed on the *x*-axis). There was a clear trend for a mean increase in ratings from the intervention group with a clinically significant mean improvement in 13 of the 18 sub-scales from baseline to week 12, indicated by an effect size of 0.2 or greater in Fig. 2. There was a statistically significant difference in mean change for scores of symptoms of kidney disease (7.1 (0.1e14.1) $p \geq 0.047$); cognitive functioning (14.6 (5.4e 23.7) $p \geq 0.003$); and vitality (12.0 (4.6e19.5) $p \geq 0.002$) in favour of the intervention (Fig. 2C and D).

Over the 12-week treatment period, most of the participants maintained their baseline nutrition status according to SGA (Table 3). All of the originally malnourished subjects in the intervention group improved their nutritional status (from SGA B to A); however, there was a rise in the proportion malnourished in the standard care group from 12.5% at week 0, to 25.0% (including 1 severely malnourished, SGA C) at week 12.

Table 3 Change in Subjective Global Assessment ratings for intervention and standard care group's *n* (%) over the 12-week treatment period, in a sample of pre-dialysis CKD patients

Change in SGA[a]	Intervention ($n \geq 23$)	Standard care ($n \geq 24$)
Deteriorated	0 (0)	4 (16.7)
No change	18 (78.2)	20 (83.3)
Improved	5 (21.7)	0 (0)

SGA, Subjective Global Assessment.
[a] Difference in change in SGA was statistically significant $c^2(2) \geq 12.76$ ($p < 0.01$).

Discussion

This paper aimed firstly to show the impact of poor nutritional status on general and kidney disease-specific QOL in a sample of patients with pre-dialysis chronic kidney disease (CKD). Secondly, it aimed to show the effect of a nutrition intervention, which optimised nutritional status, on general and kidney disease-specific quality of life (QOL)

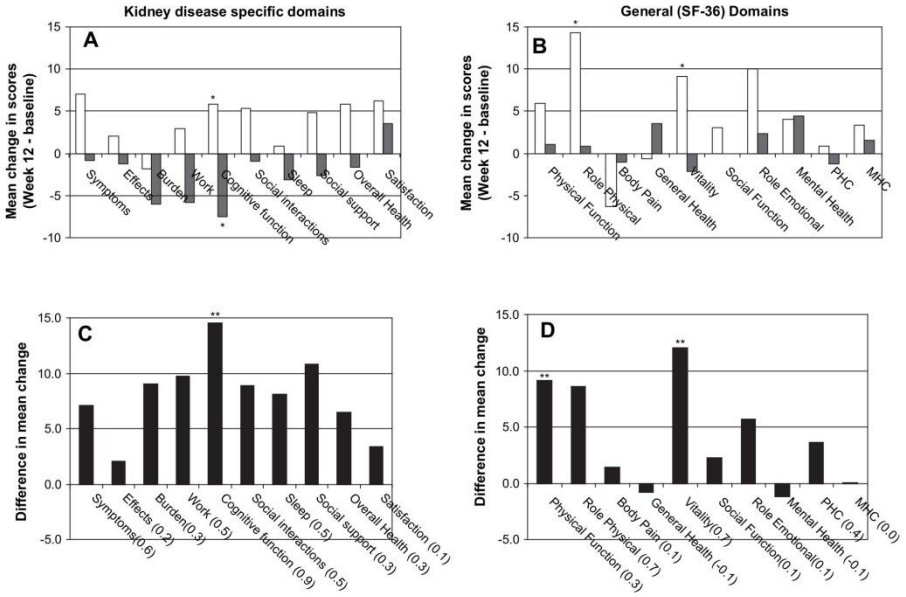

Figure 2 Change in kidney disease-specific (A) and general (SF-36) (B) quality of life subscales as a result of receiving structured intervention ($n \geq 23$) or standard care treatment ($n \geq 24$). Mean difference in change (standard care from intervention), kidney disease-specific (C) and general (D) quality of life; positive numbers equate to greater increase in intervention over change in standard care. PHC, Physical Health Component; MHC, Mental Health Component. White bars, Intervention; grey bars, Standard care; black bars, mean difference in change (effect size; Standard care — Intervention). *$p < 0.05$, Paired *t*-test; **$p < 0.05$, ANOVA (adjusting for baseline values).

components, measured by KDQOL. Previous studies in other clinical populations have observed poorer QOL outcomes in malnourished patients when compared to well-nourished.[8,9] Intervention studies have demonstrated synergistic improvement in nutritional status with improved QOL, in clinical areas such as oncology[21,22] and liver disease.[23]

Kidney–disease specific QOL

Symptoms, effects and burden of kidney disease were statistically and/or clinically lower in malnourished patients, indicating poorer QOL (Table 2). This indicates malnourished participants report greater impact form uremic symptoms, such as muscle soreness, pain, headaches, cramps, bruising, itchy skin, shortness of breath, dizziness, lack of appetite, excessive thirst, numbness in hands or feet, trouble with memory, blurred vision and nausea.[14] Symptoms, problems and effect of kidney disease also had a significant correlation with PG-SGA score indicating the sensitivity of this nutrition assessment tool to monitor changes in kidney disease symptoms directly impacting on nutritional status (Table 2). Similar associations between PG-SGA and QOL were evident in an investigation of ambulatory oncology patients receiving radiotherapy.[22]

Following the nutrition intervention period, ratings for symptoms and problems related to kidney disease was significantly reduced in participants receiving individualised intervention (Figure 2A). It is possible these improvements were afforded by concurrent improvement in nutritional status (see Table 3). Similar results have been reported in improvements in the symptoms and burden of kidney disease following parathyroidectomy in HD patients (both increased 10 points, effect size 0.8).[24]

Whilst the cognitive function sub-scale did not appear to be related to nutritional status at baseline, this component had the greatest magnitude of change between treatment groups, significantly improving in the group receiving the individualised intervention and decreasing in the standard care group. The resulting mean difference in change between the two groups was significant (14.6 (5.4e23.7) $p \mathbb{Z} 0.003$, Table 2). The trend in decreasing cognitive function scale demonstrated in the standard care may represent the gradual decline that has been associated with progressive renal function loss.[25] People with advanced stages of CKD have an increased risk of cognitive impairment, more than twice the prevalence in the age-matched population, even after adjusting for anaemia, inflammation and hyperlipidemia.[25] Improvement in cognitive function evident in the intervention group may be related to an improvement in anxiety and depressive symptoms following a supportive, individualised intervention. Depression has been also associated with decrements in sub-scales measuring quality of social interactions, social support and ratings of general health, which all significantly improved in the intervention group and remained relatively stable for ratings in standard care group during the intervention period.

General health–related QOL

Many of the health-related QOL components (from the SF-36) were strongly related to nutritional status at baseline. Malnourished patients had significantly lower rating for physical functioning and role limitations due to physical health compared with well-nourished patients at baseline (Table 2). This indicates malnutrition in pre-dialysis CKD results in decreased capacity to perform the physical requirements of life, such as attending to personal needs, walking and flexibility.

All mental health components were lower in patients identified as malnourished at baseline. Poor ratings for social interactions (Social functioning) and perceived interference of emotional problems to interactions with family and friends (Role emotional) represented a greater burden in the malnourished subjects at baseline. The clinical relevance of this relationship between malnutrition and poor mental state is demonstrated in a prospective, observational study of pre-dialysis patients where a 1-point increase in the mental health summary component related to a 4% increase in RR of death in the following 12 months.[26]

There were significant improvements in a number of the physical health components as a result of patients receiving nutritional intervention (Fig. 2). Similar improvements have been noted in studies which normalised haemotocrit and haemoglobin levels[27] and included resistance training interventions,[28] therefore individualised dietary counselling appears a comparably effective intervention for improving functional capacity.

The vitality sub-scale is sensitive to both physical and mental health issues and significantly improved in participants who received the intervention over standard care. In addition, there was a clinically significant change in the quality of social interactions and social support, over the study period in favour of the intervention treatment. It is known that CKD patients under high physiological stress in general report poorer health-related and kidney disease-specific quality of life, particularly in the psychosocial trait variables influenced by anxiety and depression.[29] It is therefore important to consider the quality of psychological care provided throughout the pre-dialysis phase, where anxiety related to prognosis and treatment options may be at their peak and multidisciplinary individual support systems may have the most benefit.

The synergistic improvement between nutrition and quality of life in CKD patients evident in this study has been recently reported in other CKD studies. Provision of daily haemodialysis,[30] exercise coaching in pre-dialysis and dialysis cohorts,[31] resistance-training[28] and use of icodextrin in peritoneal dialysis[32] all result in improvements in quality of life and markers of nutrition status. Prior to this study, there was no specific nutrition counselling interventions reporting change in quality of life in CKD. As indicated earlier, the demonstrated benefits from the intervention group in this study are likely to reflect the supportive nature of the individualised care provided, equipping patients to cope with the symptoms of their disease and reducing feelings of anxiety toward their CKD treatment.

This study was limited by the sample size which was therefore underpowered to detect statistically significant differences in several QOL sub-scales that yielded clinically significant effect sizes. Whilst the sample size is identified as a limitation of this study, it must be noted that statistical differences were apparent, and sufficient to support the aims of this study. This investigation highlights the need for

larger scale research to determine definitively the effect of nutritional counselling with regular monitoring on patient-centred outcomes, such as quality of life.

Conclusion

This study confirms pervious observations in dialysis patients that nutritional status is related to quality of life in pre-dialysis CKD. In addition, providing nutrition intervention resulted in improvement or maintenance of quality of life. It is likely that improvements in QOL were facilitated by providing an individualised, patient-centred supportive intervention, assisting patients with coping with the symptoms of their reduced kidney function and reducing anxiety associated with this stage of their disease. In addition to improvements in nutritional status, patients feeling more positive and hopeful in dealing with their kidney disease, and therefore less depressed and anxious, provided improvements in most of the kidney disease sub-scales of QOL, particularly cognitive functioning.

Conflict of interest statement

The authors have no conflict of interest to declare.

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ORIGINAL RESEARCH

Can Renal Nutrition Education Improve Adherence to a Low-Protein Diet in Patients With Stages 3 to 5 Chronic Kidney Disease?

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Objective: Low adherence is frequently observed in patients with chronic kidney disease (CKD) who are following a low-protein diet. We have evaluated whether a specific nutrition education program motivates patients with CKD who do not yet receive dialysis to reduce their protein intake and whether such a program improves adherence to a low-protein diet over and above standard dietary counseling.

Design and Methods: This was a randomized controlled clinical trial conducted at the CKD outpatient clinic at Pedro Ernesto University Hospital, Rio de Janeiro, Brazil.

Subjects: This study included adult patients with an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 who were receiving conservative treatment. Participants had received their first referrals to a renal dietitian.

Intervention: Patients were randomized to a *normal counseling* group (individualized dietary program: 0.6 to 0.75 g protein/kg/day or 0.6 to 0.8 g/kg/day for patients with diabetes and 25 to 35 kcal/kg/day with sodium restriction) or an *intense counseling* group (same dietary program plus nutrition education materials). The nutrition education material included 4 different actions to improve patient knowledge and understanding of the low-protein and low-sodium diet. Both groups were followed by means of individual monthly visits to the outpatient clinic for 4 months.

Main Outcome Measure: We looked for a change in protein intake from baseline values as well as the adherence rate, assessed as a 20% decrease of the initial protein intake (by 24-hour food recall).

Results: Eighty-nine patients completed the study (normal counseling n = 46; intense counseling n = 43). The number of patients who adhered to a low-protein diet was high but did not differ between groups (in the last visit 69% vs. 48%; $P = .48$; intense vs. normal counseling, respectively). The reduction in protein intake from baseline values was greater for the intense counseling group compared with the normal counseling group (at the last visit, −20.7 g/day [−30.9%] vs. −10.5 g/day [−15.1%], intense vs. normal counseling, respectively; $P = .04$).

Conclusion: An intense nutrition education program contributed to reducing protein intake in patients with stage 3 to 5 CKD over and above our standard dietary counseling. Nutritional education programs are effective in increasing patient adherence to protein intake recommendations.

Introduction

PROTEIN RESTRICTION IS traditionally recommended for patients with chronic kidney disease (CKD) who are not yet receiving dialysis. For adults with CKD who do not have diabetes and are not receiving dialysis (CKD stages 3-5), a protein-controlled diet providing 0.6 to 0.8 g dietary protein per kg body weight per day should be prescribed, as previously described.[1,2] The benefits of lowering the protein intake to ameliorate the metabolic disturbances that arise as a consequence of loss of renal function include better control of serum bicarbonate, phosphorus, urea nitrogen, and cholesterol levels,[3,4] as well as improved insulin sensitivity and a reduction in proteinuria.[5-9] The low-protein diet is nutritionally safe[10] and capable of improving nutritional status.[8,11]

An important pitfall in restricting dietary protein is low adherence. Some studies report that only 20% to 46% of

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patients are able to successfully adhere to a diet with 0.6 to 0.8 g of protein/kg/day.[6,11,12] The reasons for this finding are diverse and include social and economic factors (i.e., poverty, low educational level), treatment-related factors (i.e., lack of a renal dietitian and short consultations without follow up at predialysis care), and patient-related factors (i.e., limited knowledge of the reasons behind this dietary approach and of the food sources that are rich in protein; dietary dissatisfaction and lack of self-perception of success).[12,13] It is therefore relevant to work on comprehensive nutritional strategies that enable a level of adherence acceptable for the patient and capable of yielding the benefits of lowering protein intake.[12] These strategies include the prescription of dietary plans as well as the development of educational material and behavioral changes compatible with the patient's social and cultural environment.

Studies focusing on educational strategies in patients with CKD have to date been focused on the control of fluid status and phosphorus intake in patients undergoing dialysis.[14,15] Strategies used in these studies included the use of education materials (lectures, folders, posters, handouts, puzzles, and games), as well as more practical actions such as visits to restaurants, development of cooking recipes, and motivational interviewing.[14-17] These studies showed improved adherence to these complex dietary regimens.

To the best of our knowledge, no study to date has evaluated the impact of education programs in reducing protein intake and improving adherence to a low-protein diet in patients with CKD who are not yet receiving dialysis. Campbell et al.[10] reported that individualized nutrition counseling had a positive effect on overall nutritional status in conservatively treated patients, but the adherence to this regimen was not assessed. Therefore, in this study we hypothesized that a specifically designed nutrition education program would contribute to decreased protein intake and would improve adherence in patients with CKD who are not yet receiving dialysis over and above our standard dietary counseling.

Methods

This was a randomized controlled clinical trial lasting 5 ± 1.5 months (4-7 months). The local research ethical committee approved this project, and all patients provided written informed consent before their inclusion in the study. The study was conducted at the CKD outpatient clinic at Pedro Ernesto University Hospital, Rio de Janeiro, Brazil. The following enrollment criteria were applied: adult (age ≥18 years), estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2, absence of serious communication or intellectual impairment inhibiting the ability to understand the intervention, and absence of acute inflammatory disease or other comorbidities such as cancer, AIDS, and Alzheimer disease. In addition, patients were required to have had at least 1 medical appointment with the clinic's nephrologist before their enrollment in the study and none of them could have been previously seen by a renal dietitian. Figure 1 shows

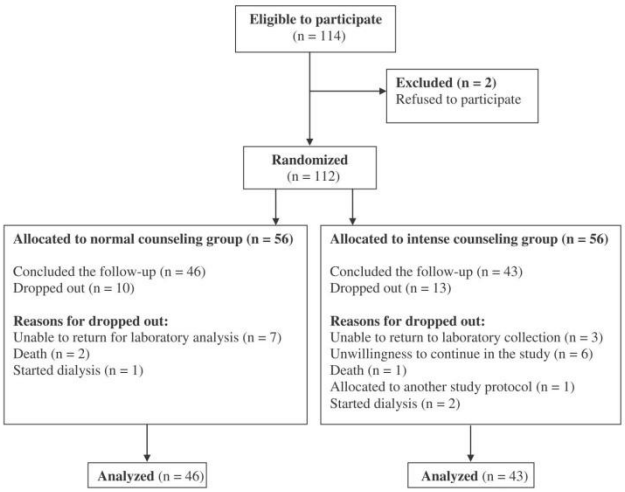

Figure 1. Flow diagram indicating selection and discontinuation of follow-up according to the randomized groups.

the flow participation as well as reasons for patients dropping out during the study. One hundred fourteen patients with CKD stages 3 to 5 were initially screened from May 2009 to January 2011. At this stage, only 2 patients refused to participate. The remaining 112 patients were randomized into 2 intervention groups: 1 receiving our dietary counseling program (*normal counseling*) and another receiving the same dietary counseling program plus a nutrition education program (*intense counseling*). A randomization list with a number sequence was generated by computer software. Patients were randomized to the intervention groups in consecutive order of admission to the study. The allocated group was concealed during the study. Of the entire sample, 23 patients left the study during the intervention—13/56 (23%) from the intense counseling group and 10/56 (18%) from the normal counseling group. No significant differences were found regarding the demographics of patients who completed the study and those who did not (data not shown).

The primary outcome of this interventional study was the reduction in protein intake (change from baseline values). In addition, adherence to a low-protein diet was defined as a reduction in protein intake of 20% or greater from baseline values. This target was based on 2 earlier studies that also addressed the issue.[6,18] Secondary outcomes were improvements in surrogates of nutritional status (such as body mass index [BMI], standard midarm muscle circumference [MAMC], and serum albumin levels) and body composition (body fat and waist circumference).

Dietary Counseling (Common for Both Intervention Groups)

The dietary counseling prescribed for both groups consisted of an individualized dietary plan that was calculated by the same experienced renal dietitian, who counseled all patients. Dietary intake was estimated by using the software Nutwin developed by the Federal University of São Paulo and that contains the US Department of Agriculture tables as a nutrient database. The energy and nutrient content of Brazilian food items were included in the software's nutrient database, according to the Brazilian food composition tables.[19] Dietary prescriptions were based on recommendations from the National Kidney Foundation Kidney Disease Outcomes Quality Initiative Nutrition Guidelines[2]: protein intake between 0.6 and 0.75 g per desirable body weight per day or 0.6 to 0.8 g/kg/day for patients with diabetes (at least 50% of the prescribed protein should be of high biological value) and energy intake of 25 to 35 kcal/kg/day, depending on the patient's nutritional status. All patients were counseled to reduce sodium intake, avoiding high-sodium foods such as canned products, commercial seasoning blends, sausages, bologna, salami, ham, parmesan cheese, and smoked products.

Nutrition Education Program (Implemented Only in the Intense Counseling Group)

This program included 4 different educational actions to improve the knowledge and understanding of the patients regarding their dietary intake. These strategies were (1) an individual class (15-20 minutes) regarding food sources of protein and sodium, reasons for reducing the intake of such food items, and the potential benefits of this therapy; (2) a hands-on session on protein-rich food by using food models and household measuring utensils to give a more real perspective of the food portion prescribed in the dietary plan and also to improve the information collected in the 24-hour food recall; (3) an education folder containing recipes to replace salt for sodium-free seasoning blends (these recipes were developed by the nutrition undergraduate students from Rio de Janeiro State University under the guidance of senior dietitians); and (4) a hands-on session using test tubes with the amount of salt content in portions of bologna, salami, sausage, ham, parmesan, and commercial seasoning blends (the salt content in the test tubes varied from 2-6 g). These tubes were used to show the contribution of these salt-rich food items to the amount of salt prescribed in the diet (5 g/d). In the monthly follow-up (4 visits), the nutrition program was reinforced.

Study Protocol

From inclusion in the study onward, patients were asked to return to the CKD outpatient clinic 4 times (every 4-6 weeks, depending on the patient's schedule) to strengthen their dietary/nutrition counseling and to assess adherence to the prescribed low-protein, low-sodium diet (Fig. 2).

At the beginning and end of the study, the demographics, laboratory measurements, full anthropometric measurements, and 24-hour food recall were recorded. Two weeks after the baseline, a phone call was made to patients in the intense counseling group to address possible doubts regarding the dietary plan. In the intermediate visits, changes in body weight and protein intake (24-hour food recall) were assessed, as described further on. For patients in the intense counseling group, information from the nutrition education program was strengthened. All included patients (regardless of the randomization group) completed the 4 follow-up visits. Those who missed the return visits were contacted to reschedule the visit to the outpatient clinic to the closest possible day of the missed visit.

Protein Intake Assessment

Protein intake was assessed with 24-hour food recall according to the US Department of Agriculture multiple pass methods[20] during each appointment (5 in total) by 3 trained renal dietitians (the same dietitian that performed the nutrition counseling plus 2 others). The software Nutwin, described earlier, was used to calculate protein intake from these food recalls.

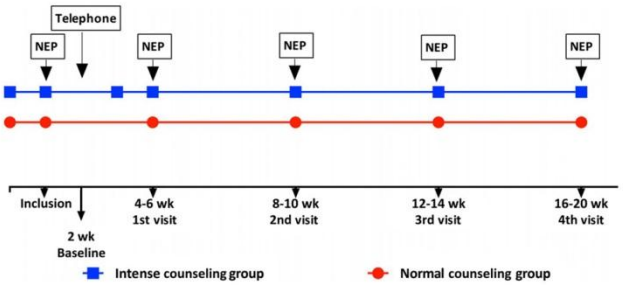

Figure 2. Study protocol. NEP, nutrition education program.

Body Composition Measurements

Anthropometric measurements were obtained in the morning by the same dietitian who counseled the patients about the nutrition program and included body weight (in kilograms), height (in meters) (body weight was measured on an electronic scale and height was measured on the vertical stadiometer from the scale–Filizola, São Paulo, Brazil), and skinfold thickness of triceps (in millimeters), biceps (in millimeters), subscapular (in millimeters) and suprailiac (in millimeters) (Lange Caliper®, Cambridge Instrument, Cambridge, MD). Arm and waist circumference was also assessed with a nonstretchable tape measure. The method described by Lohman[21] was used for measuring skinfold thickness. The skinfold thickness and arm circumference measurements were performed on the participant's right side. The waist circumference was measured over the unclothed abdomen at the umbilical level.

BMI was calculated as body weight (in kilograms) divided by height (meters squared).[22] Desirable body weight was based on the BMI depending on the patient's age. For patients younger than 60 years, we calculated the desirable body weight by multiplying the patient's height (meters squared) by 21.7 kg/m^2 (average BMI within normal limits according to the World Health Organization).[23] For patients aged 60 years or older, the average BMI within the normal limits for the elderly (24.5 kg/m^2) was used.[24] Midarm muscle circumference was calculated using the formula: arm circumference $-0.314 \times$ triceps skinfold thickness.[25] Standard percentages of triceps skinfold thickness and MAMC were obtained using the National Health and Nutrition Examination Survey percentile distribution tables adapted by Frisancho,[25] as recommended by the National Kidney Foundation Kidney Disease Outcomes Quality Initiative nutrition guidelines.[2] To classify patients with abdominal obesity, we used the sex-specific thresholds for waist circumference recommended by the World Health Organization (≥102 cm for men and ≥88 cm for women),[26] which have been applied for nondialyzed and dialyzed patients with CKD.[27,28] Body fat was assessed by the sum of the skinfold thicknesses (triceps, biceps, subscapular, and suprailiac). Body density was calculated according to the formula of Durnin and Womersley[29] and percent of body fat was then derived using Siri's equation.[30]

Laboratory Analyses

Blood samples were drawn in the morning after a 12-hour fast to measure levels of creatinine, urea, glucose, phosphorus, potassium, hemoglobin, and albumin as well as the hematocrit. These laboratory analyses were performed by using standard laboratory procedures at the laboratory of Pedro Ernesto University Hospital. GFR was estimated by using the simplified equation Modification of Diet in Renal Disease.[31]

Statistical Analysis

To estimate the sample size needed to show a significant difference after intervention, we used alpha values of .05 and beta values of .20, with a probability of positive outcome (e.g., adhering to the low-protein diet) of 65% in the intense counseling group and of 35% in the normal counseling group. After taking these values into consideration and counting a 20% dropout rate, a sample of 104 patients, equally divided into both groups, was determined as sufficient. The software Analysis of Resources for Trials, version 1.04 (StataCorp LP, College Station, TX) was used for this purpose. Data are shown as mean ± standard deviation, as median and interquartile range, or as number of patients (and percentage) as appropriate. Normality was tested by the skewness test. To evaluate whether intense counseling and normal counseling groups had similar characteristics at baseline, the independent t test or the χ^2 test was used as appropriate. To test differences between intense and normal counseling groups after intervention, a 2-way multivariate analysis of variance (MANOVA) was performed. In addition, comparisons within groups (baseline

vs. end of study) were performed by a paired *t* test. Analysis of covariance (ANCOVA) was used to evaluate changes from baseline protein intake and the proportion of patients who adhered to the diet during intervention. The presented model included correction for body weight. As a sensitivity analysis, we also controlled for baseline protein intake, age, sex, and marital status. All tests were 2-tailed at the .05 significance level. Statistical analyses were performed with SPSS 13.0 for Windows (IBM Corp, Armonk, NY), except for the ANCOVA model, which was performed with Stata, version 12 (Stata Corp LP, College Station, TX).

Results

Table 1 shows no significant differences at baseline between the 2 nutrition intervention groups regarding demographics and clinical characteristics. Regarding marital status, most subjects in both groups were married. The majority of patients were considered to have CKD stages 3 to 4, and hypertension was the main comorbidity observed.

Table 2 describes changes in anthropometric parameters during the study according to the 2 intervention groups. Our population was composed by a majority of overweight/obese subjects (70% in both groups). Abdominal obesity was observed in 67.4% and 54.3% of the patients ($P = .28$, intense counseling vs. normal counseling, respectively). Body weight and BMI decreased in both groups, whereas body fat was reduced significantly in the men in the normal counseling group and waist circumference was reduced significantly in the women in the intense counseling group. Standardized MAMC was preserved throughout the study in both groups. Comparison between intense and normal counseling groups by MANOVA showed statistical differences only for waist circumference in female patients. Regarding laboratory parameters (Table 3), serum urea levels decreased significantly in both groups, whereas serum creatinine levels and GFR were maintained. Serum albumin levels decreased in the intense counseling group, but in both groups most patients (90%) were still within desirable levels of albumin (≥3.8 g/dL). For all laboratory parameters, no statistical difference was observed between the intense and normal counseling groups.

The energy intake at baseline and at the end of follow-up in the intense counseling group was 21.9 ± 5.9 and 18.2 ± 5.9 kcal/kg desirable/day, respectively ($P = .02$) and in the normal counseling group, it was 21.5 ± 7 and 19.1 ± 5.5 kcal/kg desirable/day, respectively ($P = .21$). Data regarding protein intake during the study are shown in Table 4. Protein intake was maintained within the recommended range during the intervention, with more than 50% of the total protein intake being of high biological value in both groups (data not shown). Protein intake values as well as the percentage of adherent subjects significantly decreased in both groups.

Table 5 addresses the primary study outcome. After controlling for body weight, the gradual change in protein intake from baseline values was greater in the intense counseling group than in the normal counseling group ($P = .04$). As sensitivity analyses, we further controlled for initial protein intake as well as age, sex, and marital status, and results remained unchanged (data not shown).

Discussion

This randomized interventional study shows that a specifically designed nutrition education program aimed at reducing protein intake was effective in patients with CKD

Table 1. Baseline Demographic and Clinical Characteristics of Patients With CKD Randomly Assigned to Normal or Intense Dietary Counseling

Variable	All (n = 89)	Intense Counseling (n = 43)	Normal Counseling (n = 46)	*P* Value
Age (y)	63.4 ± 40.8	62.2 ± 12.2	64.4 ± 9.3	.34
Men (n, %)	46 (51.7)	22 (51.2)	24 (52.2)	.92
Marital status (n, %)				
Single	7 (7.9)	2 (4.7)	5 (10.9)	
Married	58 (65.2)	31 (72.1)	27 (58.7)	.52
Widower	20 (22.5)	8 (18.6)	12 (26.1)	
Divorced	4 (4.5)	2 (4.7)	2 (4.3)	
Years of study	7.1 ± 4.2	7.4 ± 4.2	6.7 ± 4.2	.46
eGFR (mL/min/1.73 m^2)	33.1 ± 12.4	32.0 ± 13.2	34.11 ± 11.7	.43
CKD stage (n, %)				
Stage 3	54 (60.7)	23 (53.5)	31 (67.4)	
Stage 4	28 (31.4)	16 (37.2)	12 (26.1)	.06
Stage 5	7 (7.9)	4 (9.3)	3 (6.5)	
Comorbidities (n, %)				
Hypertension	81 (92.0)	38 (88.4)	43 (93.5)	.40
Diabetes mellitus	38 (42.7)	15 (34.9)	23 (50.0)	.20

CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate.
Data is expressed as mean ± standard deviation or number of patients (and percentage).
Statistical differences between the 2 counseling groups were assessed by the independent *t* test or the χ^2 test as appropriate.

Table 2. Anthropometric Characteristics at Start and End of the Study According to the Different Nutritional Counseling Groups

	Intense Counseling (n = 43)		Normal Counseling (n = 46)		
Variable	Baseline	End	Baseline	End	MANOVA
Body weight (kg)	75.7 ± 16.6	72.4 ± 17.5*	74.6 ± 16.2	72.8 ± 15.9*	0.06
BMI (kg/m^2)	28.9 ± 5.6	27.7 ± 5.9*	28.3 ± 5.3	27.6 ± 5.2*	0.05
Standard MAMC (%)					
Male	94.3 ± 9.9	94.5 ± 8.8	93.3 ± 12.4	92.6 ± 12.4	0.66
Female	103.5 ± 12.6	98.35 ± 20.2	102.6 ± 13.8	103.3 ± 13.7	0.15
Body Fat (%)					
Male	31.9 ± 5.1	30.5 ± 6.4	28.8 ± 4.4	27.7 ± 5.2*	0.83
Female	38.3 ± 6.3	36.6 ± 6.5*	39.5 ± 7.4	39.6 ± 5.8	0.01
Waist circumference (cm)					
Male	102.9 ± 12.0	99.2 ± 12.0*	96.9 ± 10.2	95.7 ± 11.6	0.09
Female	95.3 ± 14.4	93.9 ± 14.8	98.3 ± 16.4	95.0 ± 14.2*	0.16

BMI, body mass index; MAMC, midarm muscle circumference; MANOVA, multivariate analysis of variance.

Results are shown as mean ± standard deviation; comparisons between groups were performed by 2-way MANOVA. Comparisons within groups were performed by a paired *t* test.

*$P < .05$ compared with baseline values.

stages 3 to 5 compared with standard dietary counseling. This study emphasizes the usefulness of dedicated education strategies to achieve patient adherence to dietary restrictions in CKD.

Since monthly visits to the outpatient clinic are not feasible in the long run in routine clinical care, educational strategies such as the one proposed here might be helpful for improving patient knowledge of food choices at the very beginning of follow-up and to keep the patient motivated to adhere to this dietary plan when visits to the outpatient clinic will have longer intervals. Our results demonstrate that an intensified nutrition educational program is effective in reducing protein intake in this patient group. These results, however, should not be interpreted against the benefits of standard dietary counseling, because both the adherence rate and the protein intake decreased. In this regard, the adherence rates of our intervention are considerably higher than those shown in previous research reporting compliance with protein-restricted diets.[6,11,12] We believe that the close contact and regular follow-up with a renal dietitian per study design was responsible for this. Because all included patients were seeing the dietitian for the first time, our results may suggest that dietary counseling is an effective and motivating approach during the first months of a new regimen.

In patients receiving dialysis, similar adherence results were found in studies that aimed to achieve better control of serum phosphate levels and fluid intake.[14,15,32] In nondialyzed patients with CKD, Flesher et al.[33] found that patients who received advice about a nutrition program (with nutrition and cooking classes and an exercise program) for 3 months had lower urinary sodium levels and better blood pressure control when compared with the control group. In addition, the rate of adherence to the low-protein diet did not differ between the nutrition program group and the control group (50% of adherent patients in both groups).[33] These results are similar to ours and suggest that nonpharmacologic interventions such as nutritional counseling or educational actions are effective in improving the adherence to a specific treatment.

Table 3. Laboratory Characteristics at Start and End of the Study According to the Different Nutritional Counseling Groups

	Intense Counseling (n = 43)		Normal Counseling (n = 46)		
Laboratory Value	Baseline	End	Baseline	End	MANOVA
Creatinine (mg/dL)	2.3 ± 0.9	2.3 ± 1.1	2.1 ± 1.0	2.3 ± 1.2	0.50
eGFR (mL/min/1.73 m^2)	32.0 ± 13.2	33.7 ± 15.6	34.1 ± 11.7	34.1 ± 13.5	0.38
Urea (mg/dL)	82.8 ± 37.5	72.1 ± 32.0*	75.5 ± 28.0	70.7 ± 26.7*	0.30
Glucose (mg/dL)	115.6 ± 48.6	107.5 ± 34.2	131.6 ± 58.6	116.6 ± 58.4*	0.48
Potassium (mEq/L)	4.8 ± 0.5	4.6 ± 0.6	4.7 ± 0.6	4.7 ± 0.4	0.13
Phosphorus (mg/dL)	4.1 ± 0.7	3.9 ± 0.8	3.9 ± 0.7	3.9 ± 0.6	0.32
Albumin (g/dL)	4.1 ± 0.3	4.0 ± 0.4*	4.2 ± 0.2	4.1 ± 0.4	0.95

eGRF, estimated glomerular filtration; MANOVA, multivariate analysis of variance.

Results are shown as mean ± standard deviation; comparisons between groups were carried out using a 2-way MANOVA. Comparisons within groups were carried out using a paired *t* test.

*$P < .05$ compared with baseline values.

Table 4. Protein Intake (by 24-Hour Food Recall) and Percentage of Patients Adherent to a Low-Protein Diet During the Study Visits and According to the Different Nutritional Counseling Groups

Variable	Intense Counseling (n = 43)	Normal Counseling (n = 46)
Protein intake (g/kg/day)*		
Baseline	0.95 (0.74; 1.15)	0.82 (0.59; 1.2)
First visit	0.79 (0.64; 0.98)	0.77 (0.62; 0.94)
Second visit	0.73 (0.57; 0.88)	0.75 (0.62; 0.91)
Third visit	0.66 (0.57; 0.78)	0.70 (0.50; 0.92)
Fourth visit	0.62 (0.45; 0.77)†	0.76 (0.61; 0.88)†
Adherence (n, %)‡		
First visit	20 (46.5)	17 (37)
Second visit	22 (51.2)	24 (52.2)
Third visit	23 (53.5)	20 (43.5)
Fourth visit	29 (69)†	22 (47.8)†

*Protein intake was analyzed as a continuous variable and shown as median (and interquartile range).

†$P < .05$ compared with baseline values.

‡Adherence to the low-protein diet is shown as number of patients (and percentage). No differences between the intervention groups was observed. Comparisons within groups were carried out using a paired *t* test or the χ^2 test as appropriate.

Another observation in our study is that nutritional status was preserved (in our study depicted by albumin levels or MAMC) throughout the intervention, sustaining the growing belief that these dietary restrictions are safe in patients with moderate to advanced CKD, as long as the energy intake is carefully monitored.[9,34,35] In our study, although the energy intake was lower than recommended for patients with CKD, it was similar to that found in other investigations in patients who are not yet receiving dialysis.[5,36] This result is probably indicative of energy underreporting, a finding commonly observed among patients with CKD with a BMI >25 kg/m^2,[36,37] such as the population of the present study. The decrease in energy intake during the follow-up is suggestive of a reduction in energy intake, but not to the absolute values reached because the reduction in the anthropometrics parameters observed did not indicate the development of protein energy wasting. This can be confirmed by the MAMC and serum albumin levels, which remained adequate throughout the intervention. Therefore lowering body weight, BMI, body fat, and waist circumference might exert further beneficial effects related to the overall metabolic status and amelioration of the low-grade inflammation,[27] since most of our patients were overweight and had abdominal obesity. It was also interesting to note that serum urea levels decreased significantly and equally in both intervention groups. We speculate that the reduction in serum urea levels occurred as a result of the reduction in protein intake, which in turn led to lower serum urea generation. Reducing serum urea levels is believed to attenuate uremic symptoms and to delay the start of dialysis, regardless of the rate of loss of kidney function.[3,37,38]

Certain limitations and strengths should be taken into consideration when interpreting these results. One strength is that the target applied to consider adherence to the low-protein diet (≥20% reduction from the initial protein intake) was not arbitrary. Rather, it was based on previous studies addressing the issue of adherence and its metabolic aspect in this regimen.[6,18] Moreover, to our knowledge, this is the first adequately powered randomized controlled trial of its kind. A limitation of our study is that we assessed the protein intake by 24-hour food recall, which may be subject to patient over- or underreporting. Because 3 dietitians performed the 24-hour food recall, a possible bias coming from different approaches and from a tendency to influence the answer to favor better adherence cannot be discarded.

To conclude, intensified educational training motivated patients and favored a reduction in their protein intake over and above our standard dietary counseling. Our study design, with close contact and regular follow-up (monthly) with a renal dietitian shows that nutritional education programs are effective in increasing the degree of adherence to protein intake recommendations.

Table 5. Change in Protein Intake (g/Day) from Baseline Values According to the Different Nutritional Counseling Groups

Visit No.	Intense Counseling (n = 43)	Normal Counseling (n = 46)	ANCOVA*
First visit	−10.3 (−15.1%)	−5.9 (−3.7%)	
Second visit	−15.1 (−20.3%)	−10.7 (−16.1%)	
Third visit	−15.7 (−22.1%)	−11.9 (−11.2%)	0.04
Fourth visit	−20.7 (−30.9%)	−10.5 (−15.1%)	

*The model included correction for body weight. Data are presented as change (delta) or percentage reduction from baseline values at each time point.

Practical Application

Because low adherence to the protein-restricted diet remains 1 of the biggest challenges when advising patients regarding the low-protein diet, the results and conclusion presented in this study will encourage and guide renal dietitians to plan the intervention of a low-protein diet.

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nutrients

MDPI

Article

Quality of Life in CKD Patients on Low-Protein Diets in a Multiple-Choice Diet System. Comparison between a French and an Italian Experience

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Abstract: Prescribing a low-protein diet (LPD) is part of the standard management of patients in advanced stages of chronic kidney disease (CKD). However, studies on the quality of life (QoL) of patients on LPDs are lacking, and the impact these diets have on their QoL is often given as a reason for not prescribing one. We, therefore, decided to assess the QoL in a cohort of CKD stage 3–5 patients followed up by a multiple-choice diet approach in an outpatient nephrology clinic in France. To do so, we used the short version of the World Health Organization's quality of life questionnaire and compared the results with a historical cohort of Italian patients. We enrolled 153 patients, managed with tailored protein restriction in Le Mans, and compared them with 128 patients on similar diets who had been followed in Turin (Italy). We found there were no significant differences in terms of age (median 73 vs. 74 years, respectively), gender, CKD stage, and comorbidities (Charlson's Comorbidity Index 7 vs. 6). French patients displayed a greater body mass index (29.0 vs. 25.4, $p < 0.001$) and prevalence of obesity (41.2 vs. 15.0%, $p < 0.001$). Baseline protein intake was over the target in France (1.2 g/kg of real body weight/day). In both cohorts, the burden of comorbidities was associated with poorer physical health perception while kidney function was inversely correlated to satisfaction with social life, independently of the type of diet. Our study suggests that the type of LPD they follow does not influence QoL in CKD patients and that a personalized approach towards protein restriction is feasible, even in elderly patients.

Keywords: low-protein diet; elderly; CKD; chronic kidney disease

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1. Introduction

The central importance of low-protein diets (LPD) in the management of chronic kidney disease (CKD) was recently underlined in the new KDOQI guidelines on nutrition in kidney diseases, which highlight the advantages of protein restriction and broaden the perimeter of action of these diets, suggesting that low-and very low-protein diets (LPD and vLPD), respectively, defined as supplying 0.6 g (moderate protein restriction) or 0.3–0.4 g of proteins per kg of ideal body weight per day, may be indicated as early as CKD stage 3 [1].

While these positions reinforce the enthusiasm of teams that have experience in using dietary management for patients with CKD, perplexities about their feasibility persist. Frequently, three points are raised: the risk of malnutrition, the difficulties encountered in obtaining compliance, and the risk of affecting a quality of life that is already threatened by a chronic disease [2,3].

Following several large trials and observational studies it has been realized that the risk of impairing nutritional status is much lower than was once thought and it is now held that, when correctly prescribed and followed, these diets do not lead to protein-energy wasting, and may even result in an improvement in nutritional status, in spite of protein reduction [4–8]. There are several reasons for this: focusing attention on energy intake may lead to the optimization of protein metabolism; a lower protein intake, in particular of proteins of animal origin, often leads to better control of acidosis and improves the calcium–phosphate balance; and attention to quality of food can limit exposure to toxic additives, including, but not limited to, inorganic phosphate [4–7].

The compliance issue is of pivotal importance. The findings have differed in trials, in which dietary treatments are usually standardized and patients cannot choose their own dietary regimen, and in observational studies, in particular when these studies were performed in settings in which patients' preferences were taken into account in defining their diet strategy [9–12]. In such settings, the model of care shifts from compliance to concordance, a term that suggests mediating between patients' wishes and preferences and physicians' best options, reaching a feasible compromise adapted to each individual [13].

Patient motivation and the presence of a patient-friendly system of care can help to optimize the effect of dietary prescriptions. Several strategies have been proposed, including educational sessions, strict follow-up, the inclusion of unrestricted meals, and the possibility of periodically changing dietary approaches to reduce diet tiredness [14].

In addition to the classic indication of CKD stages 3–5 not on dialysis, some new indications for moderately protein-restricted diets are emerging, including renewed interest in using them for incremental dialysis and high-risk pregnancies [15–17]. Furthermore, low-protein diets are occasionally employed as a rescue treatment for patients with severe proteinuria who were found to be unresponsive to specific treatment or to conventional supportive management with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers [18–21]. Conversely, normalization of protein intake (0.8 g/kg/day) is occasionally offered to patients with a very high protein intake or with a slow progression of kidney disease and advanced age [14].

In this broad, heterogeneous context, we lack studies specifically addressed to the assessment of the quality of life in CKD patients on protein-restricted diets. Although this knowledge gap was underlined in the recent Cochrane review of diet in CKD, since its publication only one large study from Italy on this question has been carried out [22–24].

In this context, we will describe the results obtained in a large French CKD cohort, encompassing mainly elderly and high-comorbidity patients. Quality of Life (QoL) was assessed in the context of an observational prospective study whose aim was to evaluate the implementation potential and the long-term impact of LPDs in the management of advanced CKD. In the setting of the study, LPDs are proposed in a flexible way, with a step-wise reduction in protein intake and are adapted to patients' preferences. The results were compared with a historical cohort of on-diet patients in Italy, followed in a setting employing the same philosophy of flexibility and adapted care [10].

2. Materials and Methods

2.1. Study Setting

This study was conducted in France, at the Centre Hospitalier le Mans (CHM), in the unit for the care of advanced kidney disease (UIRAV—(nité pour l'Insuffisance Rénale chronique AVancée) [14]. The CHM is one of the largest non-university hospitals in France, with about 1750 beds (20 for nephrology), whose nephrology unit offers care from the initial stages of kidney disease to dialysis and follow-up after transplantation (which is performed by neighboring university hospitals).

Overall, two senior nephrologists, three dieticians, one resident, and a small group of nurses work in the UIRAV. Psychological care is provided by a dedicated psychologist. Patients are followed up with outpatient visits or in day-hospital if they need intravenous treatments or complex diagnostic assessments, including at least four consultations or

imaging investigations. Conventional hospitalization in the nephrology ward is available if needed.

The UIRAV follows patients in CKD stages 4 and 5 or with progressive stage 3, up to the start of dialysis or transplantation. Whenever possible, dialysis is started with an incremental policy. Home hemodialysis and peritoneal dialysis trainings are also performed in this unit.

The results of this study are compared to those recorded in a previous study (TOPI) in a center located in Turin in Northern Italy [23]. This was a small university center with three nephrologists, and one part-time fellow dietician; its day hospital performed about 2500 hospitalizations per year.

Both the Turin and the Le Mans units were set up by the same senior nephrologist, but their socio-cultural context differs in many ways. The city of Le Mans is located in a rural area in central France, where most people have a high baseline protein intake. Conversely, in Turin, as overall in Italy, traditional Mediterranean habits favor low-protein diets. Moreover, in Italy protein-free products are available and fully reimbursed while in France they are not.

In spite of different baseline habits, the same diet policy was adopted in both settings, as patients in the Turin unit were followed up by the same senior nephrologist who later organized the unit in Le Mans.

2.2. Diet Options and General Policies

The common goal in both settings was to employ a moderately protein-restricted diet (LPD, 0.6 g/kg/day) in patients with progressive CKD stage 3, or those in stages 4 or 5 not on dialysis, in the absence of signs of protein energy wasting (PEW), alimentary disorders, or very short life expectancy (less than 3 months). This goal is usually attained in several steps, of which normalization of the protein intake is usually the first, in particular in cases with high baseline protein intake; very old patients and patients with a slowly progressive kidney disease may be managed with a normalized diet, while motivated patients, able to follow a 0.6 g/kg/day diet may attempt to further restrict their protein intake and follow a supplemented very LPD (0.3–0.4 g/kg/day).

As a first step, a dietician assesses the baseline protein intake and a nephrologist prescribes normalization or restriction of the protein intake; the prescription is individualized and is based on the patient's baseline habits and nutritional status, and the trajectory of their CKD progression, also considering proteinuria, age, comorbidity, and life expectancy.

The assessment of protein intake at baseline and over follow-up is usually based on a dietary journal reviewed by the dieticians, as discussed below.

The clinical suggestions are discussed with the patient and the main type of protein intake (mixed proteins or plant-based) is agreed on. Since, in most cases, the baseline dietary protein intake is high, a stepwise approach "French style", from normalization to restriction, described in greater detail in a previous study, is usually followed [14].

Most diets are: "traditional", based on the usual dietary patterns in the area. They usually include one vegetarian meal per day, in general a vegetable soup, containing potatoes as a source of starch, accompanied by small portions of dairy products, in keeping with traditional meals in rural France, while meat or fish, combined with bread, rice, pasta, or potatoes, are the main course in the other meal. Conversely, plant-based diets rely on carbohydrates such as potatoes, rice, bread, and pasta as their main sources of calories, and favor proteins of vegetable origin (from grains and beans). Fruits are limited only in diabetic patients; overall there are no restrictions on vegetables.

Patients are followed up to identify signs of PEW, such as reduction in body weight (unexplained by edema reduction), reduction in lean body mass (evaluated by clinical assessment integrated with bioimpedance when deemed necessary), reduction in serum albumin, prealbumin, or total proteins, in the absence of acute inflammatory events, or other clinical markers of poor nutrition, in the presence of vitamin deficits or unexplained anemia.

The LPD may require the supplementation with a mixture of amino acids and ketoacids (Kestosteril, which is available free for CKD patients in both France and Italy).

The daily dose, for moderately restricted diets, in keeping with previous experience, is 1 tablet per 8–10 kg of body weight, and can be further adjusted on the basis of albumin levels or protein losses [14]. Occasionally, diets with normal protein intake (i.e., 0.8 g/kg/day) require keto-analogue supplementation. This may be due to signs of malnutrition, or in case of nephrotic proteinuria.

Protein intake is assessed per kilogram of real body weight, and an average between real and ideal body weight is used only for patients whose body mass index (BMI) is >40 kg/m^2.

Energy intake is tailored to 30–35 kcal/kg of body weight per day in non-obese younger patients; a total of 20–25 kcal/kg of body weight per day is considered acceptable for very old patients (>80 years of age) or for obese patients. Whenever possible, obese patients are urged to increase physical activity. The start of dialysis is decided within an "intent to delay" policy based on the usual clinical and biochemical markers of blood pressure control, fluid overload, hyperparathyroidism, or any clinical element suggesting uremic toxicity (anorexia, weight loss, nausea, malnutrition, restless leg syndrome).

The Le Mans center widely employs an incremental dialysis policy; however, in this study only patients not on dialysis were enrolled, in analogy with what had been done in Turin.

The management of sodium, potassium, phosphate, bicarbonate, folic acid, iron, erythropoietin, vitamin D, and vitamin B12, is tailored to blood levels and follows the usual rules of good clinical practice [1].

2.3. Study Design, Patient Selection, Inclusion Criteria, and Long-Term Follow-Up

Participation in the study was offered to all adults (>18 years of age), with a baseline estimated glomerular filtration rate (eGFR) of <60 mL/min/1.73 m^2 (assessed by the CKD-EPI equation) [25]. Pregnant women, patients who refused to allow anonymous clinical data collection, and patients unable to give their consent were excluded from the study.

Patients were recruited from April 2018 to July 2019. Follow-up continued until December 2020 (data were censored according to mortality and dialysis start).

In Turin, the analysis took place from July to December 2014 and follow-up was concluded in February 2016.

2.4. Assessment of QoL

Quality of Life (QoL) was assessed by means of the short version of the World Health Organization's quality of life questionnaire (WHOQOL-BREF) validated for CKD patients. Patients could choose whether to complete the questionnaires at home or fill them in while waiting for their clinical visit, and in selected cases, with the help of the nephrologist or resident.

The WHOQOL-BREF, which comprises 26 items, measures four different domains (physical health, psychological health, social relationships, and environment), was analyzed per question and per domain. The analysis was compiled using the standard indications for the questionnaire: scores 1 and 2 (lower scores) and scores 4 and 5 (higher scores) were analyzed together.

2.5. Data Gathered

The following data were gathered: demographic (gender, age, country of origin), type of kidney disease, as defined by the clinical charts; type of diet (previous diets, diet at the cross-sectional analysis, at each change of type of diet and outcome on dialysis or transplantation or death at last follow-up).

Comorbidity was assessed using the Charlson Comorbidity Index (CCI, scale: 0–33) [26]. The patient's nutritional status was assessed by means of the Malnutrition-

Inflammation Score (MIS, scale: 0–30) and the Subjective Global Assessment (SGA: A, B or C) [1,27,28].

Clinical data included height, weight, body mass index (BMI), and blood pressure; laboratory data included urea, creatinine, electrolytes, albumin, total serum proteins, hemoglobin and parathyroid hormone. Data not shown in the tables, but recorded in the database, are available on request.

Energy and protein intake were assessed by a dietician using the patient's 7-day food diary or, in its absence (non-adherence, older age, etc.) based on the patient's dietary recall. Analysis of 24 h urinary urea was employed for assessment of protein intake, employing the Maroni–Mitch formula in patients able to correctly perform a 24 h urine collection [29]. However, in this population of mainly elderly patients, their dietary journal was the preferred means of assessment. In the case of a discrepancy between the two measures, the results were discussed with the senior nephrologist, and the most reliable measure was retained.

Estimated glomerular filtration rate (eGFR) was assessed using the MDRD short and the CKD Epidemiology Collaboration (CKD-EPI) formulas [25,30]. Due to its wider use, the latter was employed in the study.

2.6. Statistical Analysis

Statistical analyses were performed using SPSS Statistics version 23 (IBM Corp., Armonk, NY, USA). Quantitative data were expressed as medians (min–max) and qualitative data were presented as proportions and percentages.

The normality and homoscedasticity hypotheses were tested with the Shapiro–Wilk and Levene's tests, respectively, for continuous series. In case of normal distribution, Student's *t*-test was performed to compare two groups (e.g., Le Mans vs. Turin) and variance analysis was performed for comparisons between three or more groups; otherwise, the Wilcoxon Rank Sum Test or the Kruskal–Wallis Test were chosen.

Multiple linear regression analysis was performed employing the QoL scores for each domain as outcomes, and testing the main clinical parameters including age (dichotomized at 70), gender, eGFR (dichotomized at 15 mL/min/1.73 m^2), and CCI (dichotomized at 7).

Proportions were tested using the Chi-square test or Fisher's exact test in case of low sample size. A two-sided alpha risk was set at 5%.

2.7. Ethical Issues

The study was conducted in accordance with the Declaration of Helsinki.

In Le Mans, the study was registered with the name of Pro-Re Re-Pro ((PROtéger les REins avec un REgime bas en PROtéines): protecting the kidneys with a low protein diet), and was approved by the Ethical Committee of the University Hospital de Toulouse (Comité de Protection des Personnes (CPP)) on 7 December 2018.

The patients in the control group from Turin were enrolled in a study called PROTERENE (ridurre le PROTEine per PROTEggere il RENE): reducing proteins to protect the kidney) that was approved by the Ethics Committee of the University of Turin, Italy (*delibera* 282, 28 January 2015).

Informed consent was obtained for anonymous management of clinical data from each patient at the start of follow-up in each center. Further consent for publication was not needed for this study, dealing with overall data, not with individual cases.

3. Results

3.1. Baseline Data

The study population consisted of 153 patients referred to the UIRAV unit.

Table 1 reports the main characteristics of the population, compared to the cohort described in the Turin study (*n*: 128). There was no difference in the male–female distribution. In both cohorts, the population was elderly, with a median age of 73 in Le Mans, and 74 in

Turin. Comorbidity, evaluated by the Charlson Comorbidity Index (CCI) was likewise relatively high, with a median of 7 in Le Mans and 6 in Turin (Table 1).

Table 1. Baseline characteristics of the population, in the UIRAV unit, and in the Turin unit.

N	UIRAV—Le Mans 153	Turin—S. Luigi 128	*p*-Values
Age (years), median (min-max)	73 (23–96)	74 (20–90)	0.217
Gender, *n* (%)			
Male	100 (65.4%)	80 (62.5%)	0.619
Female	53 (34.6%)	48 (37.5%)	
BMI (kg/m^2), median (min-max)	29.0 (18.6–51.2)	25.4 (17.3–39.5)	**<0.001**
CCI, median (min-max)	7 (2–17)	6 (2–11)	**0.023**
MIS, median (min-max)	5 (1–12)	-	-
SGA, *n* (%)			
A	139 (90.8%)	-	-
B	14 (9.2%)		
C	0		
Diabetes, *n* (%)	67 (43.8%)	46 (35.9%)	0.181
Obesity (>30 kg/m^2), *n* (%)	63 (41.2%)	19 (15.0%)	**<0.001**
Kidney diseases, *n* (%)			
Glomerulonephritis + systemic	4 (2.6%)	21 (16.4%)	
Nephroangiosclerosis + diabetic	106 (69.3%)	49 (38.3%)	**<0.001**
ADPKD	6 (3.9%)	13 (10.2%)	
Others	37 (24.2%)	35 (27.3%)	
Proteinuria (g/day), median (min-max)	0.37 (0.03–10.24)	0.93 (0.01–9.65)	0.139
Proteinuria $\geq$ 3 g/day, *n* (%)	24 (15.7%)	13 (10.2%)	0.172
Creatinine, (mg/dL), median (min-max)	2.17 (0.94–8.70)	3.04 (0.66–15.66)	**<0.001**
eGFR-CKD EPI (mL/min/1.73 m^2), median(min-max)	27 (5–58)	18 (3–73)	**<0.001**
CKD stages, *n* (%)			
2	0	4 (2.6%) *	**<0.001**
3A	8 (5.2%)	6 (3.9%)	
3B	54 (35.3%)	15 (11.7%)	
4	74 (48.4%)	56 (43.8%)	
5	17 (11.1%)	47 (36.7%)	
Protein intake at Pro-Re-Re-Pro (g/kg/day), median (min-max)	0.80 (0.40–1.40)	0.50 (0.31–1.03)	**<0.001**
Protein intake at UIRAV (g/kg/day), median (min-max)	1.20 (0.65–1.70)	-	

CKD, chronic kidney disease; BMI, body mass index; CCI, Charlson Comorbidity Index; HbA1c, glycated hemoglobin; PTH, parathyroid hormone; ADPKD, autosomal dominant polycystic kidney disease; eGFR, glomerular filtration rate estimated by the CKD-EPI equation. * These patients started the diet in CKD stage 3 and continued it after improvement. Bolds highlight the significant differences.

The median CKD stage was 4, in both cohorts (Table 1). There was, however, a significant difference in the prevalence of obesity in the two cohorts (Le Mans 41.3% vs. Turin 15.0%, $p < 0.001$). Body mass index (BMI) was also significantly higher in Le Mans (median 29.0 kg/m^2 compared to 25.4 kg/m^2 in Turin, $p < 0.001$).

As a reflection of the different baseline dietary habits, protein intake at the time of quality of life evaluation was significantly higher in Le Mans than in Turin.

The median interval between the start of follow-up in the UIRAV, with the start of the diet, and the assessment of the QoL was 9 months.

It should be noted that the difference between the baseline protein intake (about 1.20 g/kg/day) and the protein intake at the time of the study was about 0.4 g/kg/day; while the pre-diet data was not available for the Italian control cohort, the median protein intake in this age group was estimated at about 1.0–1.1 kg/day in the area, thus at least partially accounting for the differences in protein intake when tested [31]. At the time of the start of care in the UIRAV the median albumin value was 3.7 g/dL (min 1.9–max 5.1) while at enrollment into the Pro-Re-Re-Pro study, nine months later, the median value was 3.8 g/dL (min 3.0–max 5.0), with a stable kidney function (median serum creatinine value at start was 2.17 mg/dl (min 0.94–max 8.70) vs. 2.18 (min 0.90–max 9.14) at enrollment into the Pro-Re-Re-Pro study)

3.2. Diet Distribution

At the time of the study, the cohort being followed in the UIRAV was almost evenly divided between normalization of protein intake, as a first step towards protein reduction, and a moderately restricted low-protein diet (Table 2).

Table 2. Diet distribution in the UIRAV patients.

	Normalization of Protein Intake (0.8 g/kg/day)		**Low-Protein Diets (≥0.6 g/kg/day)**		**All**	***p*-Values**
	Non-Supplemented	**Supplemented**	**Non-Supplemented**	**Supplemented**		**Among Diets**
N	57	8	59	29	153	
Age (years), median (min–max)	77 (23–96)	85 (61–94)	72 (37–96)	66 (33–94)	73 (23–96)	**0.029**
Age ≥ 65 years, *n* (%)	46 (80.7%)	6 (75%)	40 (67.8%)	17 (58.6%)	109 (71.2%)	0.162
Age ≥ 80 years, *n* (%)	23 (40.4%)	5 (62.5%)	12 (20.3%)	6 (20.7%)	46 (30.1%)	**0.013**
Gender, *n* (%)						0.136
Male	37 (64.9%)	6 (75%)	43 (72.9%)	14 (48.3%)	100 (65.4%)	
Female	20 (35.1%)	2 (25%)	16 (27.1%)	15 (51.7%)	53 (34.6%)	
BMI (kg/m^2), median (min–max)	28.7 (19.5 (42.7)	25.3 (18.6–50.0)	29.6 (19.0–51.2)	29.1 (21.6–41.9)	29 (18.6–51.2)	0.198
CCI, median (min–max)	7 (2–13)	8 (5–17)	7 (2–10)	7 (2–10)	7 (2–17)	0.257
CCI ≥ 7, *n* (%)	38 (66.7%)	7 (87.5%)	39 (66.1%)	16 (55.2%)	100 (65.4%)	0.374
CCI ≥ 10, *n* (%)	10 (17.5%)	3 (37.5%)	5 (8.5%)	2 (6.9%)	20 (13.1%)	0.064
Diabetes, *n* (%)	16 (28.1%)	2 (25.0%)	30 (50.8%)	19 (65.5%)	67 (43.8%)	**0.029**
HbA1c%, median (min–max)	5.86 (4.75–11.18)	5.81 (4.59–6.76)	6.15 (5.30–9.71)	6.28 (4.71–9.54)	6.01 (4.59–11.18)	0.098
PTH, median (min-max)	56 (8–281)	70 (25–408)	105 (2–986)	104 (30–962)	76 (2–986)	**0.003**
Neoplasia, *n* (%)	11 (19.3%)	2 (25.0%)	6 (10.2%)	4 (13.8%)	23 (15.0%)	0.384
Obesity, *n* (%)	19 (33.3%)	3 (37.5%)	28 (47.5%)	13 (44.8%)	63 (41.2%)	0.453
ADPKD, *n* (%)	2 (3.5%)	0	2 (3.4%)	2 (6.9%)	6 (3.9%)	0.817
Glomerulonephritis-systemic disease, *n* (%)	2 (3.5%)	1 (12.5%)	1 (1.7%)	0	4 (2.6%)	0.244
Creatinine, (mg/dL), median (min–max)	1.90 (0.94–7.05)	2.20 (1.43–3.80)	2.32 (1.46–5.72)	2.58 (1.14–8.71)	2.17 (0.94–8.71)	**0.001**
eGFR-EPI (mL/min/1.73 m^2), median (min–max) ǂ	31 (5–58)	30 (10–40)	25 (9–39)	20 (6–45)	27 (5–58)	**<0.001**
CKD stage, *n* (%)						**0.008**
3 A	7 (12.3%)	0	0	1 (3.5%)	8 (5.2%)	
3 B	26 (45.6%)	4 (50.0%)	19 (32.2%)	5 (17.2%)	54 (35.3%)	
4	19 (33.3%)	3 (37.5%)	35 (59.3%)	17 (58.6%)	74 (48.4%)	
5	5 (8.8%)	1 (12.5%)	5 (8.5%)	6 (20.7%)	17 (11.1%)	
Proteinuria (g/day), median (min–max)	0.24 (0.09–10.24)	1.70 (0.14–4.54)	0.43 (0.03–5.49)	1.44 (0.04–8.26)	0.37 (0.03–10.24)	**0.003**
Proteinuria ≥ 1 g/day, *n* (%)	12 (24.5%)	5 (71.4%)	18 (36%)	18 (62.1%)	53 (39.3%)	**0.003**
Proteinuria ≥ 3 g/day, *n* (%)	9 (18.4%)	2 (28.6%)	4 (8%)	9 (31%)	24 (15.7%)	0.062
Protein intake at Pro-Re-Re-Pro study (g/kg/day), median (min–max)	1.00 (0.50–1.40)	1.00 (0.80–1.20)	0.70 (0.40–1.20)	0.60 (0.40–1.00)	0.80 (0.40–1.40)	**<0.001**
Protein intake pre-UIRAV, (g/kg/day), median (min–max)	1.20 (0.70–1.70)	1.15 (0.90–1.40)	1.10 (0.65–1.50)	1.20 (0.80–1.50)	1.20 (0.65–1.70)	0.132
Follow-up at Pro-Re-Re-Pro (months), median (min–max)	7 (0–26)	7 (2–19)	9 (0–18)	14 (1–19)	9 (0–26)	**0.002**

Bolds highlight the significant differences.

The main clinical characteristics of the patients who started normalized or protein-restricted diets were significantly different: patients on a normal protein diet were older and had a higher comorbidity burden, while younger patients tended to be on a classic low-protein diet. Likewise, patients with lower e-GFR were more often on an LPD than on a normalized schedule. In this heterogeneous population, no difference was found on the Charlson Comorbidity Index at test.

Accordingly, no significant difference was found in the survival of patients according to the diet followed once they had been recruited in the study; the same holds true for dialysis start. Of note, patients on a normalized protein intake, associated with ketoacid and aminoacid supplementation, were older; they had higher comorbidity, a lower risk of dialysis start and a higher death rate, while the opposite is true for younger patients on supplemented LPDs. The resultant "total drop out" curve, in which the outcome was start of dialysis or death, does not show differences according to the diet at test (Supplementary Materials Figure S1a–c).

3.3. Quality of Life

There was no substantial difference in the reported quality of life according to different types of diet (normalization of the protein intake versus reduction in protein intake, with or without dietary supplements) at time of study. Older age (dichotomized at 70) and higher comorbidity (i.e., CCI $\geq$7) were associated with perception of poorer physical health perception, independently of diet (Tables 3 and 4). Conversely, patients with worse kidney function were less satisfied with their social life (Tables 3 and 4), again independently of the diet they were on.

In the multiple regression analysis, the odds of having a low QoL were not associated with any specific health determinant. Of note, the type of diet was not correlated with the risk of low QoL in any domain of QoL (Table 5).

3.4. Comparison between Settings

The comparison between the QoL scores in Le Mans and Turin confirms the lack of a significant effect of type of diet on patients' quality of life in both settings (Supplementary Table S1).

However, the setting is associated with some minor differences in results, and notably the only domain showing a significant difference is the second one (social relationships). The most important difference was observed in patients' satisfaction with their physical appearance, remarkably lower in the Italian than in the French cohort (Supplementary Materials Figure S2a–d).

Table 3. Quality of life in patients sorted according to their diet prescriptions.

	Normalization of Protein Intake (0.8 g/kg/day)		**Low Protein Diets (≥0.6 g/kg/day)**		**A**	
	Non-Supplemented	**Supplemented**	**Non-Supplemented**	**Supplemented**		***p*-Values Among Diets**
N						
Quality of life, median (min–max)						
Physical health	3.21 (2.00–4.71)	3.33 (2.83–4.00)	3.33 (2.00–4.17)	3.33 (2.29–4.33)	3.31 (2.00–4.71)	0.547
Psychological health	4.00 (2.40–5.00)	4.00 (3.50–4.50)	3.92 (2.00–5.00)	4.17 (3.00–4.67)	4.00 (2.00–5.00)	0.679
Social relationships	3.83 (1.00–5.00)	3.33 (2.67–4.33)	4.00 (1.67–5.00)	3.67 (2.00–5.00)	3.67 (1.00–5.00)	0.513
Environment	3.63 (2.63–4.75)	4.00 (3.25–4.75)	3.81 (2.38–4.75)	3.88 (2.25–4.63)	3.75 (2.25–4.75)	0.746

Bolds highlight the significant differences.

Table 4. Relationship between the main health determinants, diet and QoL.

	Physical Health	***n* = 140**			**Psychological Health**	***n* = 140**		
	Poor	**Average**	**Good**	***p*-Value**	**Poor**	**Average**	**Good**	***p*-Value**
	***n* (Row %)**	***n* (Row %)**	***n* (Row %)**		***n* (Row %)**	***n* (Row %)**	***n* (Row %)**	
N	47	75	18		7	59	75	
Diet, *n* (%)				0.593				0.197
Normal intake 0.8 g/kg/day	22 (41.5%)	24 (45.3%)	6 (11.3%)		2 (3.8%)	24 (45.3%)	27 (50.9%)	
Supplemented 0.8 g/kg/day	1 (14.3%)	5 (71.4%)	1 (14.3%)		0 (0%)	3 (42.9%)	4 (57.1%)	
LPD 0.6 g/kg/day	7 (25.9%)	15 (55.6%)	5 (18.5%)		0 (0%)	10 (37%)	17 (63%)	
LPD Supplemented 0.6 g/kg/day	17 (31.5%)	31 (57.4%)	6 (11.1%)		5 (9.3%)	22 (40.7%)	27 (50%)	
eGFR mL/min/1.73 m^2, *n* (%)				0.999				0.214
≥15	42 (33.1%)	68 (53.5%)	16 (12.6%)		5 (3.9%)	53 (41.7%)	69 (54.3%)	
<15	5 (35.7%)	7 (50%)	2 (14.3%)		2 (14.3%)	6 (42.9%)	6 (42.9%)	
Gender, *n* (%)				0.1783				**0.007**
Male	28 (29.2%)	56 (58.3%)	11 (11.5%)		3 (3.1%)	48 (50%)	45 (46.9%)	
Female	19 (42.2%)	19 (42.2%)	7 (15.6%)		4 (8.9%)	11 (24.4%)	30 (66.7%)	
Age (years), *n* (%)				**0.018**				0.459
≥70	35 (42.7%)	37 (45.1%)	9 (11%)		5 (6.1%)	37 (45.1%)	40 (48.8%)	
<70	12 (20.3%)	38 (64.4%)	9 (15.3%)		2 (3.4%)	22 (37.3%)	35 (59.3%)	
CCI, *n* (%)				**0.015**				0.089
<7	9 (18%)	33 (66%)	8 (16%)		3 (6%)	15 (30%)	32 (64%)	
≥7	38 (41.8%)	42 (46.2%)	10 (11%)		4 (4.4%)	44 (48.4%)	43 (47.3%)	
	Social relationships				**Environment**			
N	13	57	69		13	91	37	
Diet, n (%)				0.696				0.884
Normal intake 0.8 g/kg/day	5 (9.4%)	21 (39.6%)	26 (49.1%)		6 (11.3%)	35 (66%)	12 (22.6%)	
Supplemented 0.8 g/kg/day	1 (14.3%)	4 (57.1%)	2 (28.6%)		0 (0%)	4 (57.1%)	3 (42.9%)	
LPD 0.6 g/kg/day	1 (3.7%)	13 (48.1%)	12 (44.4%)		3 (11.1%)	18 (66.7%)	6 (22.2%)	
LPD Supplemented 0.6 g/kg/day	6 (11.1%)	19 (35.2%)	29 (53.7%)		4 (7.4%)	34 (63%)	16 (29.6%)	
eGFR mL/min/1.73m^2, *n* (%)				0.371				0.128
≥15	11 (8.7%)	50 (39.4%)	64 (50.4%)		11 (8.7%)	85 (66.9%)	31 (24.4%)	
<15	2 (14.3%)	7 (50%)	5 (35.7%)		2 (14.3%)	6 (42.9%)	6 (42.9%)	
Gender, *n* (%)				0.549				0.268
Male	10 (10.4%)	41 (42.7%)	44 (45.8%)		11 (11.5%)	58 (60.4%)	27 (28.1%)	
Female	3 (6.7%)	16 (35.6%)	25 (55.6%)		2 (4.4%)	33 (73.3%)	10 (22.2%)	
Age (years), *n* (%)				0.212				0.484
≥70	10 (12.2%)	29 (35.4%)	41 (50%)		6 (7.3%)	56 (68.3%)	20 (24.4%)	
<70	3 (5.1%)	28 (47.5%)	28 (47.5%)		7 (11.9%)	35 (59.3%)	17 (28.8%)	
CCI, *n* (%)				0.096				0.963
<7	3 (6%)	16 (32%)	31 (62%)		4 (8%)	33 (66%)	13 (26%)	
≥7	10 (11%)	41 (45.1%)	38 (41.8%)		9 (9.9%)	58 (63.7%)	24 (26.4%)	

Bolds highlight the significant differences.

3.5. Discussion

The fear of worsening the already impaired quality of life of patients with advanced CKD is one of the numerous barriers to the use of low-protein diets, in particular in elderly and high-comorbidity populations [1].

While there are many studies analyzing the effect of these diets on chronic kidney disease progression and metabolic interferences, as well as on mortality, there are comparatively few studies specifically addressed to LPDs' potential effect on QoL.

The only large study is a multicenter analysis carried out in Italy, where the dietary approach to CKD has a longstanding tradition. Based on traditional Mediterranean foods, CKD care in Italy favors the reduction in protein intake without traumatic changes to dietary habits. Protein-free products are available and fully reimbursed by the National Health System [23]. The four participating centers shared a multiple-choice low-protein diet approach. In this context, patients' quality of life correlated closely with the baseline conditions, in particular age and comorbidity, rather than with type and entity of dietary restriction. The presence of differences between centers indicated the possibility of a relevant modulation of QoL by cultural background and dietary habits.

Table 5. Multiple logistical regression for the outcome poor quality of life in the UIRAV cohort.

	Odds-Ratio	Lower	Higher	*p*-Values
QoL Domain 1 (Physical health)				
Age (≥70 years old)	1.698	0.667	4.326	0.267
Gender (Males vs. Females)	0.515	0.234	1.134	0.099
eGFR (<20 mL/min)	0.709	0.292	1.725	0.449
CCI (≥7)	2.578	0.943	7.045	0.065
0.6 vs. 0.8 g/kg/day of protein intake	0.750	0.352	1.598	0.456
QoL domain 2 (Psychological health)				
Age (≥70 years old)	4.705	0.467	47.417	0.189
Gender (Males vs. Females)	0.333	0.069	1.614	0.172
eGFR (<20 mL/min)	1.198	0.196	7.320	0.845
CCI (≥7)	0.314	0.040	2.444	0.269
0.6 vs. 0.8 g/kg/day of protein intake	2.110	0.372	11.974	0.399
QoL domain 3 (Social Relationships)				
Age (≥70 years old)	2.590	0.524	12.791	0.243
Gender (Males vs. Females)	1.690	0.435	6.572	0.449
eGFR (<20 mL/min)	1.491	0.412	5.400	0.543
CCI (≥7)	1.118	0.226	5.525	0.891
0.6 vs. 0.8 g/kg/day of protein intake	0.915	0.282	2.972	0.882
QoL domain 4 (Environment)				
Age (≥70 years old)	0.425	0.111	1.626	0.211
Gender (Males vs. Females)	2.480	0.513	11.984	0.259
eGFR (<20 mL/min)	0.911	0.226	3.673	0.896
CCI (≥7)	1.890	0.451	7.919	0.384
0.6 vs. 0.8 g/kg/day of protein intake	0.811	0.246	2.674	0.731

Seen from this perspective, the present study sheds further light on this issue. The unit dedicated to the care of advanced CKD in Le Mans is representative of a different setting of study, i.e., a French rural area, in which patients are used to high-protein diets, as witnessed by a baseline protein intake of 1.2 g/kg/day.

Interestingly, the units in both Le Mans and Turin were set up by the same senior nephrologist, thus allowing a comparison of results within a similar approach to tailored dietary interventions, adapted to different situations.

As previously described, the original multiple-choice diet system developed in Italy was modified to account for the dietary habits in Central France, choosing a stepwise approach, starting from normalization of protein intake, followed by progressive protein restriction, with or without keto-analogue supplementation. Patients were encouraged to discuss the strategy best suited to reaching their target with the center's dieticians [10,14]. Given that this was the approach adopted, it made it possible to evaluate the effect on QoL of being exposed to this flexible dietary "system" rather than the effect of different diets. The French cohort was comparable to the Italian one in terms of age and gender, reflecting the overall characteristics of the population with advanced CKD in Europe. However, the prevalence of obesity was significantly higher in Le Mans, as was the Charlson Comorbidity Index (Table 1). According to the REPOSI study, older age and male gender have been associated with mortality in hospitalized patients [32,33]. In this respect, our data, derived from an elderly cohort with a prevalence of men, underline the importance of a comprehensive pharmacological and nutritional approach in order to reduce mortality in advanced CKD patients starting form outpatient settings. Furthermore, in our study, about 40% of the patients were diabetic and the prevalence of proteinuria ≥1g/24 h was likewise high (Tables 1 and 2). While diabetes *per se* and the presence of proteinuria have been associated with mortality and cardiovascular disease, the entity of proteinuria modulates the progression of CKD independently from diabetes [34]. Since moderately

restricted LPDs are effective in both diabetic and non-diabetic patients, timely nutritional intervention can reduce the risk of CKD progression and related comorbidities [35]. As expected, given the known different baseline dietary habits, the protein intake at study was higher in the French cohort; however, the reduction in protein intake was also significant (about 0.4 g/kg/day from the start of combined nephrological and dietary management), and adherence was good enough to allow many patients to further reduce their protein intake over time (Table 2). A flexible attitude was also applied to the progressive changes in the diet allowing the patients to nearly or fully reach the target set; the number of diet consultations was, likewise, personalized. The median interval between the start of follow-up in the UIRAV and enrolment in the study was 9 months, which indeed corresponds to an initial adaptation time to the dietary changes prescribed.

In spite of the presence of advanced CKD, and of a high comorbidity burden, only a minority of the patients in the two settings rated their QoL as low, in each domain of the questionnaire. While physical health was described as poor by about 40% of the patients, psychological health and environment were rated as poor by only 9 to 22% of the patients. In this context, no difference was associated with the diet followed at QoL assessment (Tables 4–6).

Table 6. Multiple logistical regression for the outcome poor quality of life in Le Mans and Turin.

	Odds-Ratio	Lower	Higher	*p*-Values
QoL Domain 1 (Physical Health)				
Age (≥70 years old)	1.88	0.987	3.581	0.055
Gender (Males vs. Females)	0.361	0.199	0.654	**0.001**
eGFR (<20 mL/min)	1.082	0.59	1.986	0.799
CCI (≥7)	3.673	1.867	7.228	**<0.001**
Setting (Turin vs. Le Mans)	0.82	0.446	1.508	0.524
QoL domain 2 (Psychological)				
Age (≥70 years old)	1.525	0.722	3.22	0.268
Gender (Males vs. Females)	0.561	0.278	1.133	0.107
eGFR (<20 mL/min)	0.869	0.428	1.765	0.697
CCI (≥7)	1.536	0.738	3.199	0.251
Setting (Turin vs. Le Mans) *	10.168	4.107	25.176	**<0.001**
QoL domain 3 (Social relationships)				
Age (≥70 years old)	1.116	0.49	2.541	0.793
Gender (Males vs. Females)	1.958	0.83	4.615	0.125
eGFR (<20 mL/min)	2.141	0.98	4.676	0.056
CCI (≥7)	1.62	0.702	3.741	0.258
Setting (Turin vs. Le Mans)	1.706	0.764	3.811	0.193
QoL domain 4 (Environment)				
Age (≥70 years old)	0.266	0.101	0.697	**0.007**
Gender (Males vs. Females)	0.933	0.368	2.364	0.883
eGFR (<20 mL/min)	1.257	0.499	3.169	0.628
CCI (≥7)	3.364	1.204	9.401	**0.021**
Setting (Turin vs. Le Mans)	0.867	0.343	2.19	0.763

* Question no. 11 «Do you accept your physical appearance?», shows a different levels of acceptance of physical appearance by patients in the Le Mans and Turin cohorts, as shown in Supplementary Figure S2. The odds ratio of the setting without this question is 5.598 (2.089–15.003) for $p < 0.001$. Bolds highlight the significant differences.

The main difference in QoL in the two settings is in the social domain, and about half of this difference is in answers to the question regarding physical appearance, considered either acceptable or "not relevant" by the French cohort and "impaired" by the Italian one.

Overall, our data are in line with those recorded in elderly patients in France and Italy [36–39]. These findings, together with the lack of influence of the diet followed on the

QoL, show that low-protein diets can be safely used even for elderly and high comorbidity populations, and in settings where they have not routinely been prescribed.

Our study has several limitations: it lacks a control group with a similar level of CKD but not on a low-protein diet. This could not be avoided, given that the diet is systematically offered to all patients, and the few that refuse to at least try it and see if the results are beneficial can be expected to be clinically and psychologically different as compared with those who adhere to the program [14]. Furthermore, although the data were all gathered within a reasonably short period of time, and in settings with a similar philosophy of care, the dietary evaluation was performed by different dieticians on the basis of their experience, and the study exploits a historic cohort for comparison [10]. Finally, we did not assess the carbohydrate or fat intake at baseline in our population, which could be significant determinants of obesity and diabetes. However, the baseline dietary pattern of our population are unlikely to differ from the one described in the INCA2 survey, showing an average intake for total fat of 75.5 and 205.6 g/day for carbohydrates [38]. The strengths of the study, exploring a relatively poorly known aspect of the dietary management of CKD patients, are in the relatively large on-diet cohort enrolled and the comparison of two countries in which a similar system of care was set up.

Our results show that reducing protein intake is feasible in different settings, even for patients who, because of age and comorbidity, are often considered poor candidates for dietary management. While we believe that a flexible approach, respecting patients' preferences, as much as possible, played a major role in acceptance and perceived low intrusiveness of the diets prescribed; further comparisons with other settings and approaches on a larger scale are much needed to highlight differences and help identify the best strategies to adopt to expand the use of these important and probably underexploited dietary tools in CKD care.

4. Conclusions

In conclusion, our study, performed in a rural setting in Central France, exploring the QoL of patients with advanced CKD treated in a dedicated unit, suggests that a protein restricted diet is not associated with impairment of quality of life, and indirectly supports a personalized, stepwise approach to prescribing low-protein diets. Further multicentric studies are needed to corroborate this result in different populations with different dietary habits on a larger scale, to facilitate the implementation of the favorable results described in randomized trials and summarized in the current guidelines.

Supplementary Materials: The following are available online at https://www.mdpi.com/article/10.3390/nu13041354/s1, Table S1: Multiple logistical regression for the outcome poor quality of life in the Turin cohort, Figure S1: Survival analysis (Kaplan-Meier) for the outcome: death, dialysis and death or dialysis, Figure S2: QoL answers in different domains: comparison between settings.

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki. In Le Mans: the study was registered with the name of Pro-Re Re-Pro (PROtéger les REins avec un REgime bas en PROtéines: protecting the kidneys with a low-protein diet), and this study was approved by the Ethical Committee of the University Hospital de Toulouse (Comité de Protection des Personnes (CPP)) on 7 December 2018.The control group in Turin comes from a study called PROTERENE (ridurre le PROTEine per PROTEggere il RENE: reducing proteins to protect the kidney) that was approved by the ethics Committee of the University of Turin, Italy (delibera 282, 28 January 2015).

Informed Consent Statement: Informed consent was obtained for anonymous management of clinical datum from each patient at the start of follow-up in each center. Further consent for publication was not needed for this study, dealing with overall data, not with individual cases.

Data Availability Statement: The data presented in this study are available on request from the corresponding author.

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Low-protein diet for conservative management of chronic kidney disease: a systematic review and meta-analysis of controlled trials

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Abstract

Background Recent data pose the question whether conservative management of chronic kidney disease (CKD) by means of a low-protein diet can be a safe and effective means to avoid or defer transition to dialysis therapy without causing protein-energy wasting or cachexia. We aimed to systematically review and meta-analyse the controlled clinical trials with adequate participants in each trial, providing rigorous contemporary evidence of the impact of a low-protein diet in the management of uraemia and its complications in patients with CKD.

Methods We searched MEDLINE (PubMed) and other sources for controlled trials on CKD to compare clinical management of CKD patients under various levels of dietary protein intake or to compare restricted protein intake with other interventions. Studies with similar patients, interventions, and outcomes were included in the meta-analyses.

Results We identified 16 controlled trials of low-protein diet in CKD that met the stringent qualification criteria including having 30 or more participants. Compared with diets with protein intake of >0.8 g/kg/day, diets with restricted protein intake (<0.8 g/kg/day) were associated with higher serum bicarbonate levels, lower phosphorus levels, lower azotemia, lower rates of progression to end-stage renal disease, and a trend towards lower rates of all-cause death. In addition, very-low-protein diets (protein intake <0.4 g/kg/day) were associated with greater preservation of kidney function and reduction in the rate of progression to end-stage renal disease. Safety and adherence to a low-protein diet was not inferior to a normal protein diet, and there was no difference in the rate of malnutrition or protein-energy wasting.

Conclusions In this pooled analysis of moderate-size controlled trials, a low-protein diet appears to enhance the conservative management of non-dialysis-dependent CKD and may be considered as a potential option for CKD patients who wish to avoid or defer dialysis initiation and to slow down the progression of CKD, while the risk of protein-energy wasting and cachexia remains minimal.

Keywords Low-protein diet; Chronic kidney disease; Glomerular filtration rate; End-stage renal disease; All-cause death; Conservative management; Cachexia; Protein-energy wasting

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Introduction

Chronic kidney disease (CKD) is among the leading causes of death worldwide including emerging giant economies such as India and China.[1] Upon its development, kidney function deteriorates over time until it permanently fails. Management strategies have largely focused on slowing down progression to end-stage renal disease (ESRD), at which time, patients are invariably expected to transition to renal replacement therapy, mostly in the form of maintenance dialysis treatment.[2]

Nevertheless, recent data suggest that attempts to delay or even prevent transition to dialysis therapy may not be inappropriate,[3] including a 2009 study that showed that the initiation of dialysis was associated with a substantial and sustained decline in functional status of the elderly nursing home patients.[4] Many patients with kidney disease prefer to opt to exhaust all conservative management options for CKD, including nutritional strategies, prior to considering dialysis therapy.[5]

Century-old evidence suggests that lower dietary protein intake may help with CKD management including slowing its progression, improving albuminuria, and controlling uraemia.[6–9] However, results from the *Modification of Diet in Renal Disease* study in 1994 were inconclusive with regards to the efficacy of a low-protein diet (LPD) in slowing the rate of CKD progression.[10] Several meta-analyses that focused on the rate of CKD progression showed favourable but modest effects of an LPD.[11,12] Nevertheless, no single study has examined all clinically relevant outcomes, and fewer studies have focused on the role of an LPD in managing uraemia or other CKD complications such as mineral and bone disorders and metabolic acidosis without causing protein-energy wasting or cachexia.[13]

Protein-energy wasting characterized by a decline in body protein mass and energy reserves, including muscle and fat wasting and visceral protein pool contraction, is an underappreciated condition in early to moderate stages of CKD and a strong predictor of adverse outcomes.[14] The applicability of many nutritional interventions and their effects on outcomes in patients with moderate to advanced CKD, including those with protein-energy wasting or at high risk of its development, has not been well studied. The challenge remains as to how to reconcile low dietary protein intake—to avoid or delay dialysis initiation—with adequate nutrient intake and nutritional therapy while insuring favourable nutritional status and to avoid or correct protein-energy wasting.[13] The field lacks an up-to-date systematic review and meta-analysis study on the subject with a focus on the conservative management of CKD. There is an urgency to revisit all traditional and novel options for the non-dialytic management of patients with advanced CKD. Given these considerations and given commonalities and distinctions of the old and emerging controlled trials over the past two decades following the Modification of Diet in Renal Disease study, we aimed to conduct a comprehensive systematic review and meta-analysis study examining the effect of an LPD on the clinical management of patients with CKD.

Materials and methods

K.K.-Z., supported by other coauthors, searched MEDLINE (PubMed) and other relevant sources with no limitation in study type, language, and geographical area using the search terms including 'low protein diet', 'CKD', and 'clinical trial' as well as additional records identified through other sources including prior reviews. A field expert (K. K.-Z) identified any additional relevant studies. The studies were included if they described data from controlled trials (including randomized, self-controlled, parallel, and crossover trials) on CKD patients (excluding prevalent ESRD patients and those receiving dialysis treatment) to compare clinical outcomes across various protein intake levels (i.e. protein-free, very-low-protein, low-protein, moderate-protein, high-protein, very-high-protein, or unrestricted protein diets) or to compare a restricted protein intake with another intervention. An LPD was defined as a diet with a protein content of $<$0.8 g/kg/day. To ensure meaningful sample size in each study given our focus on the conservative management of CKD, we selected only controlled trials that included at least 30 participants to ensure selection of studies with adequate sample size and higher level of robustness[15] (*Figure* 1). The aforementioned endeavour was undertaken to both provide a comprehensive roster of relevant randomized controlled trials of LPD for CKD management, which has become Supporting Information, *Table* **S2** of a recently published *New England Journal of Medicine* review article, titled, 'Nutritional Management of Chronic Kidney Disease' by Kalantar-Zadeh and Fouque,[16] and for an additional meta-analysis project that is presented in this manuscript.

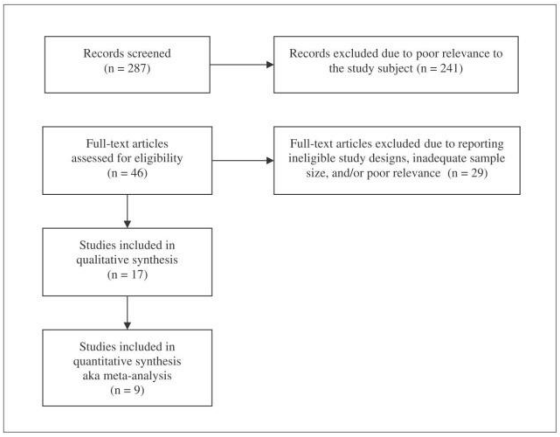
We extracted and tabulated the main characteristics and findings of the included studies as well as comments on their methodological quality and clinical significance (*Table* 1). Also, we evaluated the risk of bias using the Cochrane Collaboration's tool for assessing risk of bias (*Table* 2). We examined the effects of an LPD or very-low-protein diet (VLPD) (with or without supplementation with ketoacids or amino acids) on various outcome measures in CKD patients. The corresponding authors of the studies with incomplete results were contacted in order to request further data.

Studies with clinical homogeneity (e.g. similar patients, interventions, and outcomes) were included in meta-analyses. Statistical heterogeneity was assessed using the I^2 statistic. Summary estimates with a corresponding $I^2 \leq 50\%$ were pooled using fixed-effects meta-analysis while those with a corresponding $I^2 > 50\%$ were pooled using the random-effects model. In addition, in order to ascertain that our results were not dependent on the selected summary estimate or meta-analysis model, we completed sensitivity analyses. Statistical significance was defined as a 95% confidence interval with no overlap with the null effect value (risk difference/mean difference = 0). For statistical procedures, we used Stata 12 (StataCorp., College Station, TX, USA).

Results

Sixteen randomized controlled trials, reported in 17 articles, each with at least 30 participants, were included in our

Figure 1 Flow diagram of the study selection. See also Supporting Information, *Table* **S2** of the *New England Journal of Medicine* review article, titled, 'Nutritional Management of Chronic Kidney Disease' by Kalantar-Zadeh and Fouque.[16]



review (*Table* 1). Based on the interventions and comparisons, the included studies were divided into the following groups: (i) those comparing LPD with higher-protein diets[10,17–24]; (ii) those comparing VLPD with LPD[10,25–30]; and (iii) those involving other comparisons[31,32] (*Table* 1). As all studies were not similar in their recruited patients and/or outcome measures, not all studies in each category were meta-analysed (*Figures* 2 and 3).

Low-protein diet vs. higher-protein diets

For this comparison, LPD was defined as a protein intake of <0.8 mg/kg/day; therefore, VLPD was also considered a subgroup of LPD. Our pooled results showed that the risk of progression to ESRD was significantly lower in those who received LPD compared with those who received higher-protein diets (*Figure* 2A). In addition, the pooled results indicated a trend towards lower all-cause death in those who received LPD (*Figure* 2B).

We also meta-analysed other metabolic factors, which showed that 1 year serum bicarbonate was significantly higher in those who received LPD (*Figure* 2C). However, 1 year serum phosphorus was comparable in the two groups (*Figure* 2D). We could not meta-analyse results representing parathyroid hormone (PTH), calcium, and other metabolic factors because of their clinical and methodological heterogeneity.

In addition to the results of our meta-analysis, some results by individual studies were also informative: serum PTH was not significantly different in the two intervention groups according to the results by Cianciaruso *et al.*[19] and Ihle *et al.*[22] However, Malvy *et al.*[28] completed a longer follow-up (up to 40 months) and revealed a significantly lower PTH in those who received a lower protein intake (mean PTH: 2.71 vs. 5.91 ng/mL; $P < 0.001$). Similarly, serum calcium was not significantly different as reported by Ihle *et al.*[22] and Rosman *et al.*[23] However, it was significantly higher in the study by Malvy *et al.*[28] with a longer follow-up duration (serum calcium: 2.42 vs. 2.25 mmol/L; $P < 0.01$).

Also, Jiang *et al.*[17] showed that in peritoneal dialysis patients, those who received an LPD had better preservation of glomerular filtration rate (GFR) and residual kidney function. In addition, PTH was significantly lower in those who received ketoacid-supplemented LPD. However, serum phosphorus and calcium were not significantly different between the two intervention groups.

Very-low-protein diet vs. low-protein diet

Although the primary aim of this review was to compare LPD with higher-protein diets, we also performed meta-analyses of studies comparing VLPD with LPD. The two dietary groups were respectively defined as those with protein intakes of <0.4 and 0.4–0.8 mg/kg/day. The pooled results showed that the progression to ESRD was significantly lower (*Figure* 3A) and 1 year GFR was significantly higher (*Figure* 3C) in those who received VLPD compared with LPD. In addition, the

Table 1 Selected controlled trials (with >30 participants) that have examined the effects of an LPD or VLPD, with or without supplementation with ketoacids or amino acids, on various outcome measures in chronic kidney disease patients

Study (year)	Participants	Dietary intervention	Outcomes	Follow-Up time	Results	Comment
LPD vs. HPD Jiang *et al.*[17,18]	60 new ESRD pts on PD with RKF	LPD vs. sLPD (LPD + ketoacids) vs. HPD	RKF and nutritional markers on PD	12 months	RKF stable in sLPD group but decreased in the LPD and HPD groups.	No change from baseline on nutritional status in any of the groups during follow-up.
Cianciaruso *et al.*[19]	423 pts with CKD 4–5	Two different DPI levels 0.55 (n = 212) vs. 0.80 g/kg/day (n = 211)	CKD progression and changes in blood and urinary biomarkers	18 months	Reduced urinary excretion of urea, Na, phos in LPD. No differences in phos, albumin, PTH, bicarbonate. No changes in body composition.	Estimated DPI in low vs. high groups was 0.72 vs. 0.92 g/kg/day ($P < 0.05$). 9 vs. 13 pts in LPD vs. higher DPI stated dialysis.
MDRD study 1 Klahr *et al.*[10]	585 pts with CKD 3–4 (GFR 25–55 mL/min/ 1.73m^2)	Usual protein diet (DPI 1.3 g/kg/day) vs. LPD (0.6 g/kg/day)	CKD progression, blood pressure, proteinuria, nutrition	27 months (mean follow-up)	Projected mean GFR decline at 3 years did not differ significantly between the diet groups. Faster GFR decline in the first 4 months in the LPD group.	Two concurrent randomized controlled trials. Serum albumin increased in both sVLPD and LPD groups and did not differ between groups.
Locatelli *et al.*[20]	456 pts with CKD 3–4	LPD (0.78 g/kg/day) vs. normal DPI (0.9 g/kg/ day), both DEI > 30 cal/kg/day	*Renal survival* defined as dialysis start or doubling of serum creatinine	2 years	Borderline difference, slightly fewer pts assigned to LPD group reached the endpoint (P = 0.059).	Substantial overlap in DPI between two groups.
Williams *et al.*[21]	95 pts with CKD 4–5	LPD (0.7 g/kg/day) vs. normal diet (DPI 1.02 and 1.14 g/kg/day) and varied phos content	CKD progression rates across three groups	18 months	No differences in the reduction in creatinine clearance, dialysis initiation, or mortality among three groups.	Minor weight loss in LPD.
Ihle *et al.*[22]	72 pts with CKD 4–5	LPD (0.6 g/kg/day) vs. higher DPI (0.8 g/kg/ day)	GFR every 6 months	18 months	Stable GFR in LPD vs. loss of GFR in control group ($P < 0.05$).	LPD pts lost weight but no change in anthropometric measures or serum albumin.
Rosman *et al.*[23,24]	247 pts with CKD 3–5	0.90–0.95 (CKD 3) vs. 0.70–0.80 g/kg/day (CKD 4–5) vs. unrestricted DPI	GFR after 2 or 4 years	4 years	After 2 years significant slowing of CKD progression in LPD but only in male pts.	4 year renal survival improvement in LPD (60 vs. 30%, $P < 0.025$). PKD pts did not respond to LPD.

(*Continues*)

Table 1 (continued)

Study (year)	Participants	Dietary intervention	Outcomes	Follow-Up time	Results	Comment
VLPD vs. LPD Garneata *et al.*[25]	207 non-diabetic pts with CKD 4–5 (eGFR $_2$ <30 mL/min/1.73m^2) and proteinuria <1 g/day	LPD (0.6 g/kg/day) vs. sVLPD (vegetarian VLPD 0.3 g/kg/day with KA)	Dialysis initiation or 50% reduction in initial eGFR	15 months	Adjusted NNT (95% CI) to avoid dialysis was 22.4 (21.5–25.1) for pts with eGFR $_2$ <30 mL/min/1.73m^2 but decreased to 2.7 (2.6–3.1) for pts with eGFR $_2$ <20 mL/min/1.73m^2 in ITT analysis.	Correction of metabolic abnormalities occurred only with sVLPD. Compliance to diet was good, with no changes in nutritional measure.
Mircescu *et al.*[26]	53 non-diabetic CKD 4–5 pts (eGFR <30 mL/min/1.73m^2)	sVLPD (0.3 g/kg/day vegetable proteins) suppl. with KA vs. LPD	Transition to dialysis, eGFR, and laboratory markers	48 weeks	Less dialysis initiation with sVLPD (4 vs. 27%). Stable eGFR in sVLPD but decreased eGFR in controls.	Open-label randomized, controlled trial. Higher bicarbonate and lower phos in sVLPD group.
Prakash *et al.*[27]	34 CKD pts (mean eGFR 28 mL/min/1.73m^2)	LPD (0.6 g/kg/day) with placebo vs. sVLPD (0.3 g/kg/day with KA)	Changes in GFR and nutritional markers	9 months	Stable GFR in the sVLPD vs. worsening nutritional measures and faster GFR decline in LPD group.	Prospective, randomized, double-blind, placebo-controlled single centre trial.
Malvy *et al.*[28]	50 pts with CKD 4–5 (eGFR <20 mL/min/1.73m^2)	sVLPD (0.3 g/kg/day) with KA vs. LPD (0.65 g/kg/day)	3 mo to eGFR >5 mL/min/1.73m^2 or need for dialysis	3 years	SUN, lean body mass, and fat mass decreased in sVLPD group.	Randomized trial. No difference in renal survival, sVLPD pts lost 2.7 kg (both fat and lean body mass).
Montes-Delgado *et al.*[29]	33 pts with CKD 3–5	LPD vs. LPD suppl. with a low-protein and hypercaloric supplement	Renal function and nutritional status	6 months	Slower CKD progression in the supplemented group, with better nutritional status and higher adherence.	22 patients completed the full 6 month study.
MDRD study 2 Klahr *et al.*[10]	255 pts with CKD 4–5 (GFR 13–24 mL/min/1.73m^2)	LPD (0.6 g/kg/day) vs. sVLPD (0.3 g/kg/day with KA)	CKD progression, blood pressure, proteinuria, nutrition	27 months (mean follow-up)	sVLPD group had a marginally slower decline in GFR than LPD group (P = 0.067). Higher Ca, lower phos, alkaline phosphorus, and PTH levels in sVLPD group.	Two concurrent randomized controlled trials. Serum albumin increased in both sVLPD and LPD groups and did not differ between groups.
Lindenau *et al.*[30]	40 pts with CKD 5 (GFR <15 mL/min/1.73m^2)	LPD with calcium suppl. (n = 18) vs. sVLPD (0.4 g/kg) with KA (n = 22)	Bone and mineral markers including via bone biopsies	12 months	Decreased serum phosphorus with sVLPD, improved markers of bone breakdown in bone	CKD progression and other outcomes not assessed.

(*Continues*)

Table 1 (continued)

Study (year)	Participants	Dietary intervention	Outcomes	Follow-Up time	Results	Comment
					biopsies in sVLPD group.	
VLPD or LPD vs. other interventions						
Brunori *et al.*[31]	56 non-diabetic pts (>70 yrs old) CKD 5 (GFR 5–7 mL/min/ 1.73m^2)	sVLPD (DPI: 0.3 g/kg/ day, DEI: 35 Cal/kg/ day) with KA, vs. dialysis initiation	Survival, hospitalization, and metabolic markers.	Median time 26.5 months	Similar survival in both groups. Patients assigned to dialysis had a 50% higher degree of hospitalization.	There was a continuous benefit of LPD over time.
Teplan *et al.*[32]	105 CKD pts (GFR 22–36 mL/min/ 1.73m^2)	LPD with KA and EPO vs. LPD without KA (with/without EPO)	CKD progression rate and nutritional measures	3 years	sLPD with KA/EPO showed slower CKD progression and increased leucine, isoleucine, valine and mild decrease in proteinuria ($P < 0.01$).	Role of EPO remained unclear.

AA, amino acid; AGE, advanced glycation end products; CKD, chronic kidney disease; DEI, dietary energy intake; DPI, dietary protein intake; eGFR, estimated glomerular filtration rate; EPO, recombinant human erythropoietin; EAA, essential amino acids; ESRD, end-stage renal disease; HPD, high-protein diet; ITT, intention to treat; KA, ketoacids supplement; LPD, low-protein diet; NNT, number needed to treat; PEW, protein-energy wasting; phos, phosphorus; PKD, polycystic kidney disease; pt, patient; pts, patients; sLPD, supplemented low-protein diet; SUN, serum urea nitrogen; sVLPD, supplemented very-low-protein diet; VLPD, very-low-protein diet.

pooled results revealed trends towards lower GFR decline (*Figure* 3B) and lower 1 year serum urea (*Figure* 3D) in those who received VLPD; however, the trends were not significant. The results representing bicarbonate, phosphorus, PTH, and calcium could not be meta-analysed because of their heterogeneity.

Again, in addition to the results of our meta-analysis, we summarize some key results from the individual studies: Garneata *et al.*[25] observed higher serum bicarbonate (22.9 vs. 16.2 mEq/L, $P < 0.01$), higher serum calcium (4.4 vs. 3.9 mmol/L, $P < 0.01$), and lower serum phosphorus levels (4.4 vs. 6.2 mg/dL, $P < 0.01$) in those who received VLPD vs. LPD. Similarly, Mircescu *et al.*[26] showed higher serum bicarbonate (23.4 vs. 17.6 mg/dL), higher serum calcium (4.4 vs. 3.9 mmol/L), and lower phosphorus (4.5 vs. 6 mg/dL) in those who received VLPD compared with LPD.

Also, Lindenau *et al.*[30] reported that in patients with advanced CKD, those who received VLPD showed better control of renal osteodystrophy markers including PTH (0.6 vs. 1.53 ng/mL), osteoid surface (34.3 vs. 51.9), and bone volume (27.9 vs. 25.2); however, most differences did not reach statistical significance.

Sensitivity analyses

The results of our sensitivity analyses were comparable with the main meta-analyses, indicating that our results were not dependent upon the selected meta-analysis methods (see Supporting Information, *Figures* S1 and S2).

Other comparisons

Two included studies[31,32] compared LPD/VLPD with other interventions: Brunori *et al.*[31] completed a non-inferiority trial of supplemented VLPD vs. dialysis in elderly ESRD patients without diabetes, and they observed that the survival was not higher in those who received VLPD. In the other study, Teplan *et al.*[32] compared three interventions in CKD patients: (i) LPD supplemented with ketoacids plus human recombinant erythropoietin (EPO); (ii) non-supplemented LPD plus EPO; and (iii) non-supplemented LPD alone. They observed that patients receiving supplemented LPD plus EPO had lower GFR decline and proteinuria and better metabolic profile. None of the studied trials reported increased risk of protein-energy wasting or cachexia despite lower protein intake. There was no safety issue noted in any of the trials.

Discussion

Upon meta-analysing contemporary clinical trials of large sample size (>30 participants in each trial) that have examined an

Table 2 Risk of bias assessment in included studies

	Random sequence generation?	Allocation concealment?	Blinding of participants?[a]	Blinding of outcome assessors?	Complete outcome data?	No selective reporting?
LPD vs. higher PD						
Jiang *et al.*[17,18]	Unclear	Unclear	Unclear	Unclear	Yes	Yes
Cianciaruso *et al.*[19]	Yes	Yes	Unclear	Unclear	Yes	Yes
MDRD study 1 Klahr *et al.*[10]	Yes	Unclear	Unclear	Unclear	Yes	Yes
Locatelli *et al.*[20]	Yes	Yes	Unclear	Unclear	Yes	Yes
Williams *et al.*[21]	Yes	Unclear	Unclear	Unclear	Yes	Yes
Ihle *et al.*[22]	Yes	Unclear	Unclear	Unclear	Yes	Yes
Rosman *et al.*[23,24]	Unclear	Unclear	No	No	Yes	Yes
VLPD vs. LPD						
Garneata *et al.*[25]	Yes	Unclear	Unclear	Unclear	Yes	Yes
Mircescu *et al.*[26]	Yes	Unclear	Unclear	Unclear	Yes	Yes
Prakash *et al.*[27]	Yes	Unclear	Yes	Yes	Yes	Yes
Malvy *et al.*[28]	Unclear	Unclear	Unclear	Unclear	Yes	Yes
Montes-Delgado *et al.*[29]	Unclear	Unclear	Unclear	Unclear	Unclear	Yes
MDRD study 2 Klahr *et al.*[10]	Yes	Unclear	Unclear	Unclear	Yes	Yes
Lindenau *et al.*[30]	Unclear	Unclear	Unclear	Unclear	No	Unclear
V/LPD vs. other						
Brunori *et al.*[31]	Yes	Yes	No	No	Yes	Yes
Teplan *et al.*[32]	Unclear	Unclear	Unclear	Unclear	Unclear	Yes

[a]Blinding of participants in diet-based interventions is very difficult and almost unattainable.

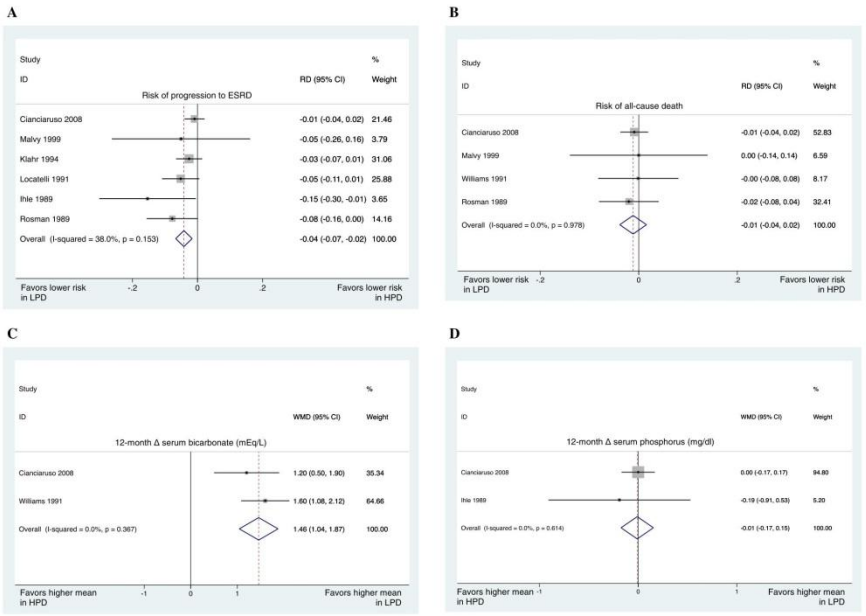
LPD for the management of CKD, we found that in comparison with diets with protein intake of >0.8 g/kg/day, diets with restricted protein intake (<0.8 g/kg/day) were associated with higher serum bicarbonate levels, lower phosphorus levels, lower rates of progression to ESRD, and a trend towards lower rates of all-cause death. In addition, VLPD (protein intake: <0.4 g/kg/day) was associated with even greater preservation of kidney function and reduction in the rate of progression to ESRD. These data may have important clinical and public health implications upon the conservative management of CKD.

For over half a century, we have regarded dialysis therapy as a life-saving intervention among patients with advanced kidney failure, in whom survival would otherwise be impossible. To that end, more dialysis and earlier dialysis initiation have been considered to more favourable patient care strategies, whereas delayed initiation or less frequent haemodialysis treatment (i.e. less than thrice-weekly haemodialysis) has been discouraged. However, emerging studies in recent years have cast doubt on the universal superiority of earlier dialysis initiation and more frequent dialysis treatments in the management of advanced CKD. A study in 2009 suggested that among nursing home residents with advanced kidney disease, initiation of dialysis was associated with a substantial and sustained decline in functional status.[4] A provocative clinical trial from Australia and New Zealand in 2010 suggested that planned early initiation of dialysis in patients with Stage 5 CKD was not associated with improved survival or other clinical outcomes.[3] These data have been supported by an increasing number of observational studies across different dialysis populations.[33] To that end, it is important to revisit the old adage of the nutritional management of CKD and re-examine whether the use of LPD can be leveraged to conservatively manage uraemic symptoms without the need for dialysis initiation. This potential application of an LPD is beyond and above its traditional use in studies that have employed it to slow progression of kidney disease. Even though the latter is of immense clinical importance, many clinicians often encounter patients in very late stages of CKD, for example, estimated GFR < 25 mL/min/1.73m^2, who wish to avoid or defer dialysis therapy by any means possible. Several individual trials[17,18,22–30,34] as well as meta-analysis studies[12,35–37] have shown the benefits of protein restriction for such conservative management of CKD patients.[38]

We found that the risk of progression to ESRD was significantly lower in the LPD compared with higher-protein diets and also found a trend towards greater survival in the former group. The 1 year serum bicarbonate level was significantly higher in those who received an LPD, which is an important metric in the treatment of CKD-associated acidosis and its deleterious effects.[39] We also found lower phosphorus levels and lower azotemia with an LPD, which are important targets for the conservative management of CKD without dialysis. The safety and adherence to an LPD was not inferior to a normal protein diet in individual studies. However, we could not meta-analyse results representing PTH, calcium, and other selected metabolic factors because of the clinical and methodological heterogeneity of the clinical trials. However, these collective results suggest that an LPD may have a potential role in the conservative management of CKD.

As a systematic review and meta-analysis study, our findings were limited by the available data regarding the role of restricted protein intake in the management of CKD patients. The included studies were heterogeneous in their

Figure 2 Low-protein diets (LPD: <0.8 g/kg/day) vs. higher-protein diets (HPD: >0.8 g/kg/day). (A) Risk of progression to end-stage renal disease was 4% lower in those who received low-protein diets. (B) The pooled results showed a trend towards a lower risk of all-cause death in those who received low-protein diets; however, the trend was not significant. (C) On average, 12 month serum bicarbonate was 1.46 mEq/L higher in those who received low-protein diets. (D) The pooled results indicated that 12 month serum phosphorus (in mg/dL) was comparable. The 'Overall' shows the results of the heterogeneity test (in all forest plots). RD, risk difference aka absolute risk reduction. WMD, weighted mean difference.



interventions, and they did not report all relevant clinical outcomes. Also, because of our limited resources, we were unable to search other electronic databases beyond PubMed. Nevertheless, we were inclusive in our data synthesis and reported on the meta-analyses of various clinical outcomes using the most up-to-date evidence, while we excluded studies with <30 participants as our key a priori selection criterion to ensure that only well-designed studies with adequate statistical powers are included. In addition, the external validity of our findings may be less certain, as the efficacy of the LPD in the controlled conditions of RCTs does not necessarily translate into its effectiveness if CKD patients are not adequately compliant to the LPD. Furthermore, we did not assess the risk of publication bias across our included studies because of the few studies pooled together in each meta-analysis. In fact, tests of publication bias, for example, Egger or Begg & Mazumdarand may generate inaccurate or misleading results if their 'sample size', that is, the number of pooled studies, is small.

In conclusion, the current evidence confirms the effect of restricted dietary protein intake on favourable metabolic surrogates of kidney function including azotemia, bone and mineral disorder, and acidosis, as well as slower kidney function loss, slower progression of CKD, and lower rates of ESRD and death. None of the studied trials reported increased risk of protein-energy wasting or cachexia despite lower protein intake, nor was there any safety issue in any of the trials. Future studies may focus on further examining the selection of appropriate patients for nutritional interventions and other approaches in the conservative management of patients with advanced CKD and investigating the role of adherence to such therapies.

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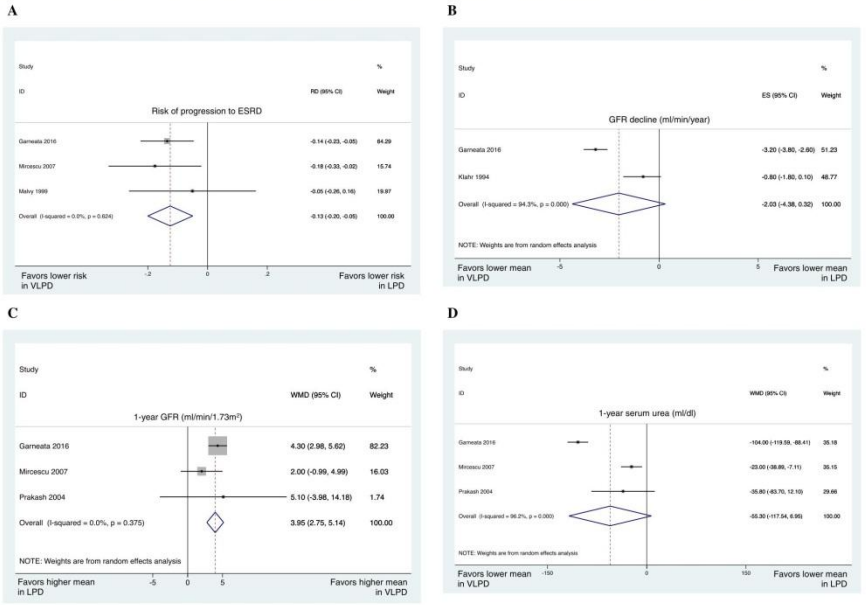
Figure 3 Very-low-protein diets (VLPD: <0.4 mg/kg/day) vs. low-protein diets (LPD: 0.4–0.8 mg/kg/day). (A) Risk of progression to end-stage renal disease was 13% lower in those who received very-low-protein diets. (B) The pooled results showed a trend towards lower glomerular filtration rate (GFR) decline (in mL/min/year) in those who received very-low-protein diets; however, the difference was not significant. The results were pooled using the random-effects model because of the observed statistical heterogeneity. (C) On average, 1 year GFR was 3.95 mL/min/1.73m^2 higher in those who received very-low-protein diets. (D) The pooled results indicated a trend towards lower 1 year serum urea (in mg/dL) in those who received very-low-protein diets. The results of Prakash[27] were based on a follow-up of 9 months. ES, estimate of effect (in this case: GFR decline).



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The authors certify that they comply with the ethical guidelines for publishing in the Journal of Cachexia, Sarcopenia and Muscle: update 2015.[40]

Online supplementary material

Additional Supporting Information may be found online in the supporting information tab for this article.

Supplemental Figure S1A. Risk of progression to end-stage renal disease in low-protein diet (≤0.6 g/kg/day) vs. higher-protein diets (>0.6 g/kg/day): **Using Random-effects model.**
Supplemental Figure S1B. Risk of progression to end-stage renal disease in low-protein diet (≤0.6 g/kg/day) vs. higher-protein diets (>0.6 g/kg/day): **Using Relative Risk.**
Supplemental Figure S1C. Risk of all-cause death in low-protein diet (≤0.6 g/kg/day) vs. higher-protein diets (>0.6 g/kg/day): **Using Relative Risk.**
Supplemental Figure S1D. 12-month serum bicarbonate (mEq/L) in low-protein diet (≤0.6 g/kg/day) vs. higher-protein diets (>0.6 g/kg/day): **Using Standardized Mean Difference.**
Supplemental Figure S1E. 12-month serum phosphorus (in mg/dl) in low-protein diet (≤0.6 g/kg/day) vs. higher-protein diets (>0.6 g/kg/day): **Using Standardized Mean Difference.**
Supplemental Figure S2A. Risk of progression to end-stage

renal disease in very low protein diet (<0.4 g/kg/day) vs. low protein diet (0.4–0.6 g/kg/day): **Using Relative Risk.**

Supplemental Figure S2B. 1-year glomerular filtration rate decline (ml/min/1.73m^2) in very low protein diet (<0.4 g/kg/day) vs. LPD (0.4–0.6 g/kg/day): **Using Standardized Mean Difference (SMD).**

Supplemental Figure S2C. 1-year serum urea (mg/dl) in VLPD (<0.4 g/kg/day) vs. LPD (0.4–0.6 g/kg/day): **Using Standardized Mean Difference (SMD).**

Supplementary Table S2. Selected controlled trials (with greater than 30 participants) that have examined the effects of low-protein or very low-protein diets (with or without supplementation with ketoacids or amino-acids) on various outcome measures in patients with chronic kidney disease.

Conflict of interest statement and disclosure

K.K.-Z. has received honoraria and/or support from Abbott, Abbvie, Alexion, Amgen, American Society of Nephrology, Astra-Zeneca, AVEO Oncology, Chugai, DaVita, Fresenius, Genentech, Haymarket Media, Hofstra Medical School, International Federation of Kidney Foundations, International Society of Hemodialysis, International Society of Renal Nutrition & Metabolism, Japanese Society of Dialysis Therapy, Hospira, Kabi, Keryx, Novartis, National Institutes of Health, National Kidney Foundation, Pfizer, Relypsa, Resverlogix, Sandoz, Sanofi, Shire, Vifor, UpToDate, and ZS-Pharma. S.-F.A., C.P.K., and C.M.R. declare that they have no conflict of interest.

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ORIGINAL RESEARCH

Improvement in Nutritional Status in Patients With Chronic Kidney Disease-4 by a Nutrition Education Program With No Impact on Renal Function and Determined by Male Sex

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Objective: Protein–energy wasting (PEW) is associated with increased morbidity and mortality and a rapid deterioration of kidney function in patients with chronic kidney disease (CKD). However, there is little information regarding the effect of nutrition intervention. The aims of this study were to evaluate the efficacy and safety of a nutrition education program (NEP) in patients with nondialysis dependent CKD (NDD-CKD), based on the diagnostic criteria for PEW proposed by the International Society of Renal Nutrition and Metabolism. The design of the study was a 6-month longitudinal, prospective, and interventional study. The study was conducted from March 2008 to September 2011 in the Nephrology Department of La Paz University Hospital in Madrid, Spain.

Subjects: A total of 160 patients with NDD-CKD started the NEP, and 128 finished it.

Intervention: The 6-month NEP consisted of designing an individualized diet plan based on the patient's initial nutritional status, and 4 nutrition education sessions.

Main Outcome Measures: Changes in nutritional status (PEW) and biochemical, anthropometric and body composition parameters.

Results: After 6 months of intervention, potassium and inflammation levels decreased, and an improved lipid profile was found. Body mass index lowered, with increased muscle mass and a stable fat mass. Men showed increased levels of albumin and prealbumin, and women showed decreased proteinuria levels. The prevalence of PEW decreased globally (27.3%-10.9%; $P = .000$), but differently in men (29.5%-6.5%; $P = .000$) and in women (25.4%-14.9%; $P = .070$), 3 of the women having worsened. Kidney function was preserved, despite increased protein intake.

Conclusion: The NEP in NDD-CKD generally improved nutritional status as measured by PEW parameters, but individual poorer results indicated the need to pay special attention to female sex and low body mass index at the start of the program.

Introduction

PROTEIN–ENERGY WASTING (PEW) is defined as "the state of decreased body pools of protein with or without fat depletion or a state of diminished functional capacity, caused at least partly by inadequate nutrient intake relative to nutrient demand and/or which is improved by nutritional repletion."[1]

Among the primary causes of PEW in patients with nondialysis-dependent chronic kidney disease (NDD-CKD) are inadequate nutrient intake due to the anorexia caused by kidney function deterioration, difficulties in adhering to dietary restrictions or to social and economic factors, and hypercatabolism caused by the disease itself or by comorbidities, oxidative stress, and acidemia.[2]

Uremic malnutrition in predialysis patients is associated with increased morbidity and mortality,[3] as well as a poorer quality of life[4] and greater deterioration of kidney function,[5] which affects the prognosis of patients on dialysis.[6]

Both the National Kidney Foundation Kidney Disease Outcomes Quality Initiative guidelines[7] and the International Society of Renal Nutrition and Metabolism (ISRNM)[8] expert committee recommend nutritional intervention during the treatment of predialysis patients. There are few studies, however, that assess the effect of nutritional intervention on these patients,[9–12] and we have not found any studies that use the ISRNM criteria to define PEW; its prognostic value in terms of survival in advanced CKD has therefore been clearly underanalyzed, despite its existence and wide acknowledge.

The potential reversing effects of early intervention on PEW are hypothesized here.

The aims of this study were to evaluate the efficacy of a nutritional education program at the predialysis stage, based

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on the diagnostic criteria for PEW proposed by ISRNM, and to assess its safety, relative to kidney function deterioration.

Methods

Study Participants

The initial number of participants in the NEP was 160, with 128 completing the study. The reasons for dropout were as follows: 14 required dialysis therapy, 8 failed to attend subsequent visits, 6 changed hospital, and 4 died. The recruitment period was from March 2008 to September 2011.

The inclusion criteria were creatinine clearance <20 mL/minute/1.73 m^2 in stages 4 and 5, not 5d (20 patients had creatinine clearances <30 mL/minute/1.73 m^2); age ≥18 years; no deterioration of cognitive abilities; and signed informed consent. Exclusion criteria were patients with active neoplasia, active infection, or severe lung disease; any patients who had begun kidney replacement therapy; or patients who had been hospitalized during the study period.

The study was approved by the Ethics Committee of La Paz University Hospital and was conducted according to the guidelines of the Declaration of Helsinki. The patients signed a written informed consent before inclusion.

Study Design

A 6-month longitudinal, prospective, and interventional study, performed on a total of 160 patients. The complete population was selected from patients in the advanced kidney disease care program at the Nephrology Department of La Paz University Hospital.

Nutrition Education Program

Selected patients were included in a nutrition education program (NEP), consisting of the design of an individualized diet plan based on the patient's initial nutritional status, attendance at 4 nutrition education sessions and nutritional assessment, and monitoring over a period of 6 months.

The intervention was administered by a single dietitian, aimed at providing a personalized dietary prescription (including energy [25-35 kcal/kg/day] and protein [0.75-1.0 g/kg/day]).[7]

In the nutrition education sessions, the patients were addressed over protein and energy intake, content of phosphorus and potassium in foods, cooking techniques, and a fourth issue chosen according to the patient's specific needs; for example, content of fat, cholesterol, or sucrose in foods. We also elaborated a dietary plan after obtaining information from a 3-day dietary record. We used photographic albums as material support to estimate portions size or to explain patients how to read and understand food labels.

Thirty-two patients (25%) required specific nutritional support (oral supplementation).

During the program, the patients continued with their usual medical treatment.

Clinical data were collected at the beginning of the NEP.

Laboratory Parameters

Preprandial blood samples were collected: albumin, prealbumin, creatinine clearance, serum creatinine, serum potassium, serum phosphorus, C-reactive protein, total lymphocyte count, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglycerides. Also collected were 24-hour urine variables: diuresis volume and proteinuria levels. The analysis of biochemical parameters was performed according to the standardized method used in the Biochemistry Unit Laboratory of La Paz University Hospital.

Normalized protein nitrogen appearance (nPNA) was calculated using the formula proposed by the National Kidney Foundation.[7]

Anthropometrics and Body Composition

Anthropometric measurements were performed using standard techniques following the recommended international regulations (World Health Organization, 1976). These measurements were taken with the patients in underwear and barefoot. Weight was measured using a single frequency body composition analyzer (TANITA BC-420 MA; Biológica Tecnología Médica S.L., Barcelona, Spain). Height was measured using a measuring rod with pinpoint accuracy (range: 80-200 cm). The mid-arm circumference (MAC) was measured using a stretchable measuring tape. The tricipital skinfold (TSF) was measured using a Holtain caliper with a jaw-width of 20 cm and sensitivity of 0.2. The mid-arm muscle circumference (MAMC) was calculated, in centimeters, as follows: $MAMC = MAC - (3.14 \times TSF)$.

Body mass index (BMI) was calculated on the basis of the weight and height measurements (weight [kilogram]/height^2).[7]

Measures of body composition included bioimpedance analysis (BIA-101; Akern Systems, Florence, Italy) at 50 kHz.

Dietary Intake

The overall dietary intake of each patient was recorded in a food intake record for 3 consecutive days, listing all food intake (including hydration); 1 of these days was on a weekend. The caloric and nutritional value of the diet was quantified using DietSOURCE®3.0 nutritional software. The values obtained were compared with current recommendations in the Kidney Disease Outcomes Quality Initiative guidelines.[7]

Nutrition Assessment

The nutritional assessment was performed according to PEW criteria proposed by the ISRNM.[1]

To determine nutritional status according to ISRMN criteria, the patient must have met 1 criterion out of 3 in the 4 categories that determine the presence of PEW, maintaining it over a period of 2 months:

- Biochemical category: <3.8 g/dL; prealbumin <30 mg/dL body mass; cholesterol <100 mg/dL without lipid-lowering medication (in our case, this criterion was not used, given that a total of 147 patients consumed such medication).
- Body mass category: BMI <23 kg/m^2; unintentional 5% weight loss over the last 3 months or of 10% over the last 6 months.
- Muscle mass category: Loss of 10% of MAMC muscle mass in relation to percentile 50.
- Intake category: Protein catabolism rate (nPNA) < 0.6 g; energy intake <25 kcal/kg adjusted to weight/day.

Adherence

Adherence was assessed on completion of the intervention, using a score of 0 to 10 based on the compliance with the guidelines and the effort invested. We asked: "*How would you score the effort invested to 0- 10?*" and, "*How would you score the compliance of the recommendations to 0-10?*". A visual analog scale was used as material support.

Statistical Analysis

Qualitative variables are described using absolute frequencies and percentages; for quantitative variables, the mean and standard deviations (X ± SD) are used.

The comparison of qualitative variables between 2 groups was performed using the chi-squared test, test and/or Fisher's exact test, depending on the data distribution. Wilcoxon test (quantitative variables) and McNemar test (qualitative variables) were performed to compare differences between the beginning and the end of the program in each individual. The comparison of quantitative variables between 2 groups was performed using the Mann–Whitney U test or Student's *t*-test, depending on the data distribution.

All the statistical tests were bilateral, with a significance level of 0.05. Statistical analysis was performed using the SPSS 17.0 statistics program.

Results

General Characteristics of the Population

A total of 128 patients with a mean age of 67 ± 14.8 years, 52.3% ($n = 67$) women, completed the NEP. The primary etiology of CKD was diabetes mellitus (54 patients; 42.2%); 4 patients (3.1%) had type I diabetes, followed by nephroangiosclerosis (21 patients; 16.4%), glomerulonephritis (16 patients; 12.5%), polycystic kidney disease (14 patients; 10.9%), unknown etiologies (12 patients; 9.4%), and other (11 patients; 8.6%). General characteristics of the studied population are summarized in Table 1.

Laboratory Parameters Follow-up

At completion, the NEP process was associated with a mild increase in kidney function (creatinine clearance 17.4 ± 3.9 vs. 19.5 ± 6.4 mL/minute; $P < .001$) and decreased levels of urea (136.6 ± 45.1 vs. 133.6 ± 41.2 mg/dL; $P = .048$ mg/dL), nPNA (1.3 ± 0.4 vs. 0.3 ± 1.2 g/kg/day; $P < .001$), and proteinuria at the limit of significance (1.7 ± 2.1 vs. 1.6 ± 2.0 g/24 hours; $P = .060$). Serum potassium (4.8 ± 0.6 vs. 4.6 ± 0.5; $P = .040$) also decreased. The lipid profile showed minor global changes (decreased total cholesterol and low-density lipoprotein cholesterol).

Table 2 shows the follow-up of kidney, metabolic, and inflammation parameters separated by sex; kidney function in both men and women remained stable, with a slight upward trend, and with stable proteinuria levels. Serum potassium and polymerase chain reaction (PCR) levels decreased.

Regarding biochemical parameters related to nutritional status, increases in albumin and prealbumin values were observed in men, whereas increases in total lymphocyte count were observed in women.

Anthropometric and Body Composition Parameter Follow-up

BMI significantly dropped (27.6 ± 5.0 vs. 27.1 ± 4.3; $P = .001$), whereas body composition improved. Muscle mass increased (38.7 ± 9.4 vs. 40.3 ± 9.0; $P = .001$), fat mass remained stable, and the distribution of body fluid

Table 1. Comorbidities and Pharmacological Treatment in the Studied Patients

Comorbidities		Pharmacologic Treatment	
CHF or unresolved ischemia	41 (32%)	Antihypertensive antiproteinuric medication (ACE inhibitors, ARBs, or selective renin inhibitors)	99 (77.3%)
Peripheral arterial disease	40 (31.2%)	Other antihypertensive	77 (66.1%)
Functionally severe physical sequelae	5 (3.9%)	Hypolipidemic agents	99 (77.3%)
Cerebrovascular accident	10 (7.8%)	Phosphate binders	14 (10.9%)
COPD	8 (6.2%)	Potassium binders	16 (12.4%)
DM	54 (42.2%)	Insulin	31 (24.6%)

ACE inhibitors, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptors blockers; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus.
Values are presented as percentages.

Table 2. Kidney, Metabolic, and Inflammation Parameters by Sex

Variable	Men 61 (47.7%)			Women 67 (52.3%)		
	Month 0	Month 6	*P*	Month 0	Month 6	*P*
Albumin (g/dL)	3.5 ± 0.5	3.7 ± 0.4	**.040**	3.5 ± 0.4	3.6 ± 0.3	.146
Prealbumin (mg/dL)	30.0 ± 7	32.1 ± 6.2	**.040**	29.9 ± 6.2	30.7 ± 5.6	.309
Creatinine (mg/dL)	4.0 ± 1.2	3.8 ± 1.3	**.014**	3.5 ± 0.9	3.3 ± 1	.110
ClCr (mL/min)	18.4 ± 3.4	21.1 ± 6.4	**.020**	16.4 ± 4.0	17.8 ± 6	**.013**
Urea (mg/dL)	137.2 ± 49.8	131.1 ± 42.5	.732	136 ± 40.7	136.0 ± 40.1	.956
Volume diuresis (mL/d)	2462.4 ± 632.5	2445.7 ± 710.4	.543	2142.1 ± 682.3	2179.4 ± 711.4	.174
Proteinuria (g/24 h)	1.9 ± 1.7	1.9 ± 1.7	.373	1.5 ± 2.4	1.3 ± 2.2	**.039**
nPNA (g/kg/d)	1.3 ± 0.3	1.1 ± 0.2	**.023**	1.3 ± 0.3	1.2 ± 0.3	**.001**
Potassium (meq/L)	4.8 ± 0.6	4.6 ± 0.5	**.038**	4.8 ± 0.6	4.6 ± 0.4	**.007**
Phosphorous (mg/dL)	4.0 ± 1.0	3.9 ± 0.8	.294	4 ± 0.8	3.9 ± 0.6	.239
CRP (mg/L)	5.0 ± 8.2	3.5 ± 3.9	**.040**	4.4 ± 5.3	3.4 ± 3.9	**.004**
Total lymphocyte count (lymph/cc)	1745.9 ± 718.4	1732.3 ± 675.5	.454	1636 ± 491.8	1965.7 ± 238.3	**.013**
Cholesterol (mg/dL)	172 ± 48.5	157.5 ± 36.0	**.009**	184.2 ± 43,6	180.8 ± 38	.625
LDL-C (mg/dL)	107.4 ± 34.6	100.1 ± 23.9	**.049**	116.8 ± 33.1	110 ± 31.6	**.044**
HDL-C (mg/dL)	45.6 ± 13.6	44.0 ± 13.6	.065	53.2 ± 13.7	53 ± 12.5	.790
TG (mg/dL)	136.6 ± 52.5	121.4 ± 31.8	**.046**	138.2 ± 66.3	126.8 ± 48.4	**.040**

ClCr, creatinine clearance; CRP, C-reactive protein; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; nPNA, normalized protein nitrogen appearance; TG, triglycerides.

Values are presented as mean ± standard error of the mean. *P* was calculated by Wilcoxon test. Significant differences are highlighted in bold.

improved with a reduction in the Na/K exchange ratio (1.2 ± 0.3 vs. 1.1 ± 0.2; $P = .045$).

Table 3 shows the follow-up of the anthropometric and body composition parameters by sex. BMI dropped, and muscle mass increased in men. Women showed a slight drop in body weight, maintaining stable body composition. A reduction in extracellular water and an increase in intracellular water were observed in both the men and the women.

PEW Outcome

The NEP contributed toward a significant improvement in nutritional status by reducing the number of patients in a PEW state from 35 patients (27.3%) to 14 (10.9%) ($P = .001$). Nineteen patients (59.7%) with PEW required oral supplementation.

An improvement in the unintentional weight loss criteria was observed; at the start of the program, 59 patients (46.15%) met these criteria, whereas none of them met it

Table 3. Anthropometric and Body Composition Parameters by Sex

Variable	Men 61 (47.7%)			Women 67 (52.3%)		
	Month 0	Month 6	*P*	Month 0	Month 6	*P*
Weight (kg)	77.3 ± 10.7	75.5 ± 9.5	**.010**	65 ± 13.4	64.4 ± 11.7	**.017**
Height (m)	167.2 ± 6.4			153.9 ± 7.3		
BMI (kg/m^2)	27.7 ± 3.7	27.0 ± 3.1	**.010**	27.5 ± 5.9	27.3 ± 5.3	.134
TSF (mm)	15.5 ± 5.9	15.2 ± 5.8	**.043**	22 ± 7.3	21.7 ± 7.1	.053
MAMC (mm^2)	23.9 ± 3.7	24 ± 3.7	.459	22.3 ± 4.2	22.5 ± 3.9	.236
Resistance (Ω)	463.6 ± 57.1	484.1 ± 64.6	**.019**	543 ± 88	543.2 ± 85.7	.680
Reactance (Ω)	41.8 ± 12.3	45.6 ± 11.7	**.019**	41.7 ± 10.5	44.5 ± 9.1	**.029**
Phase angle (°)	5.2 ± 1.3	5.4 ± 1.2	**.040**	4.4 ± 1	4.7 ± 0.8	**.003**
Exchange Na/K	1.2 ± 0.3	1.1 ± 0.2	.612	1.3 ± 0.3	1.2 ± 0.2	**.010**
Body cell mass (%)	45.5 ± 8.1	46.4 ± 6.5	.330	43.2 ± 8.5	46.8 ± 7.9	**.040**
Total body water (%)	57 ± 6.1	56 ± 5.4	**.045**	51.1 ± 7.4	50 ± 6.6	.830
Extracellular water (%)	50.1 ± 6.7	48.7 ± 6.1	**.006**	55.2 ± 6.3	52.5 ± 4.2	**.002**
Intracellular water (%)	49.9 ± 6.7	51.2 ± 6.0	**.018**	44.7 ± 6.2	47.9 ± 4.4	**.001**
Fat mass (%)	27.4 ± 8.7	27.6 ± 8.9	.626	35.8 ± 9.2	36.6 ± 8.8	.681
Fat-free mass (%)	71.8 ± 10.6	72.8 ± 8.2	.910	64.2 ± 9.2	63.5 ± 8.9	.670
Muscle mass (%)	41.6 ± 8.5	43.2 ± 7.4	**.043**	36 ± 9.7	37.7 ± 9.7	**.001**
Body cellular mass index	8.7 ± 2.3	8.9 ± 2.1	.118	7.1 ± 1.9	7.7 ± 2.1	**.003**

BMI, body mass index; MAMC, mid-arm muscle circumference; TSF, tricipital skinfold.

Values are presented as mean ± standard error of the mean. *P* was calculated by Wilcoxon test. Significant differences are highlighted in bold.

on program completion. The same was the case with the nPNA criteria <0.6 (6.3% vs. 0%).

Table 4 shows the evolution of the protein energy wasting state by sex. We found significant differences between the response to nutritional intervention between men and women. Men improved their nutritional status significantly, with only 4 men (6.5%) of 18 (29.5%) having remained in the PEW state. On the contrary, 10 women (14.9%) remained in PEW status (dropping from 17 [25.4%]). The nutritional state actually worsened in 3 of these women after intervention (Fig. 1).

The common criteria of the 4 men at the start of the NEP who remained in a PEW state were older age (78.5 ± 7.1 vs. 69.1 ± 10.6; $P = .045$), lower serum albumin levels (2.8 ± 0.3 vs. 3.3 ± 0.32; $P = .016$), BMI (23.2 ± 1.1 vs. 26.2 ± 2.7; $P = .002$), and body cellular mass index (6.5 ± 2.1 vs. 8.2 ± 2.1; $P = .045$). When we removed the BMI variable from the PEW criteria, only 1 man and 3 women remained in this state, with one of them actually worsening.

Adherence

The analysis of adherence variables showed differences in effort score regarding nutritional intervention by sex (men 8.0 ± 1.3 vs. women 7.1 ± 3.1; $P = .030$), but not in terms of compliance (men 6.7 ± 1.5 vs. women 6.7 ± 2.0; NS).

Characteristics of Women Who Improved Their Nutritional Status

Although we began with a global analysis of results, the different behavior of women in relation to the intervention requires a separate analysis.

We evaluated the female patients demonstrating an improved nutritional status if they did not have PEW at any point during the intervention.

The women classified as having improved their nutritional status maintained their levels of albumin and prealbumin and showed a slight increase in kidney function with a slight reduction in inflammation, measured by C-reactive protein (CRP). As for anthropometric and body composition parameters, BMI dropped and body composition improved. This was determined by a fat deposit reduction with muscle mass increase. Total body water remained stable, with an improvement in the distribution of body fluid, a reduction in extracellular water, and an increase in intracellular water and phase angle.

Comparison of Women in PEW State to Women Who Improved After Nutritional Intervention

Of the 67 women in the study, 10 (14.9%) overcame the wasting state, 7 (10.4%) remained in it, and 3 (4.5%) entered it at the end of the NEP.

Table 4. Protein–Energy Criteria (PEW) Criteria According to Sex

	Men 61 (47.7%)			Women 67 (52.3%)		
Protein–Energy Wasting (PEW) Criteria	Month 0	Month 6	*P*	Month 0	Month 6	*P*
(A) Serum chemistry						
Albumin <3.8 g/dL	40 (65.5%)	36 (59%)	.454	47 (70.1%)	45 (67.1%)	.854
Prealbumin <30 mg/dL (*N* = 102)	15 (24.5%)	11 (18%)	**.049**	19 (28.3%)	17 (25.4%)	.754
Patients meeting the biochemistry category	42 (68.8%)	41 (67.2%)	.900	49 (73.1%)	48 (71.6%)	.900
(B) Body weight and fat (body mass)						
BMI <23 kg/m^2	8 (13.1%)	6 (9.8%)	.625	19 (28.3%)	17 (25.4%)*	.625
Unintentional weight loss: 5% over 3 mo or 10% over 6 mo.	28 (45.9%)	0 (0%)	**.000**	31 (46.2%)	0 (0%)	**.000**
Fat mass <10%	2 (3.2%)	2 (3.2%)	1.000	1 (0.1%)	1 (0.1%)	1.000
Patients meeting body mass category	30 (49.1%)	6 (9.8%)	**.000**	33 (49.2%)	17 (25.4%)	**.000**
(C) Muscle mass						
MAMC: reduction >10% in relation to 50th percentile	25 (41%)	23 (36.7%)	.800	23 (34.3%)	24 (35.8%)	1.000
Reduced muscle mass: 5% over 3 mo	–	0 (0%)		–	0 (0%)	
Patients meeting the muscle mass category	25 (41%)	23 (36.7%)	.754	23 (40.3%)	24 (35.8%)	1.000
(D) Dietary intake						
nPNA <0.6	2 (3.2%)	0 (0%)	**.000**	6 (8.9%)	0 (0%)	**.000**
Unintentional low dietary energy intake <25 kcal/kg/d for 2 mo	22 (36.1%)	18 (29.5%)	.557	18 (26.8%)	17 (25.3%)	1.000
Patients meeting the protein intake category	22 (36.1%)	18 (29.5%)	.090	18 (26.8%)	17 (25.37%)	1.000
PEW	18 (29.5%)	4 (6.5%)	**.000**	17 (25.4%)	10 (14.9%)	.070
PEW (without BMI)	18 (29.5%)	1 (1.6%)	**.000**	14 (20.9%)	3 (4.3%)	**.001**

BMI, body mass index; MAMC, mid-arm muscle circumference; nPNA, normalized protein nitrogen appearance.
Values are presented as percentages. *P* was calculated by McNemar test. Significant differences are highlighted in bold.
*Significant differences at 6 months between women and men.

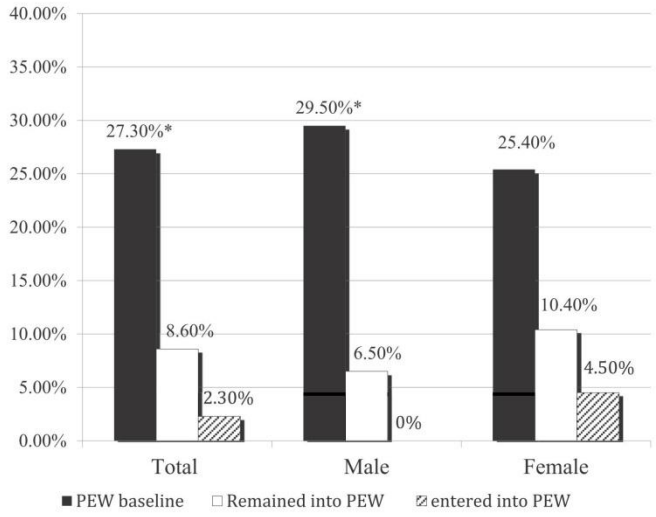

Figure 1. Protein–energy wasting evolution by sex. Percentage of subjects, total and by sex, with PEW at baseline and at the end of the nutrition intervention, and the subjects who entered into PEW during the intervention. *P* was calculated by the chi-squared test. *Statistically significant differences ($P < .05$) between baseline and the end of nutritional intervention.

Table 5 shows the variables that underwent a significant modification or that were approaching limits of significance in the 10 women who showed a reversed PEW state compared with those who maintained or entered into it.

The group of women who failed to reverse or who worsened their nutritional status showed a significantly lower BMI at starting NEP, with no other difference detected in baseline. After the program, a slight increase in kidney function and prealbumin levels were detected, along with a reduction in proteinuria, nPNA, and PCR levels.

Those who improved their nutritional status increased their levels of albumin and prealbumin, with no other biochemical variable change.

Among the anthropometric variables, weight increased in both groups, although significant differences were reached only when wasting status was reversed, with an improved distribution of body fluids. We did not find differences in the other variables analyzed.

The 3 women whose nutritional status worsened had a lower BMI (22.9 ± 4.4 kg/m^2) adjusted for age (65.4 ± 7.3 years), depletion of muscle mass at baseline, as well as low food intake over time in their dietary histories. No values changed after the intervention except energy and protein intake, which dropped.

Discussion

Few studies have investigated nutritional status in patients with NDD-CKD, although its importance is recognized. In our study, we found a malnutrition prevalence of 27.3%, which is higher than the 11% of this population found in Norway[13] and lower than the 63.7% found in Brazil,[14] although both studies use different scales to define the disorder.

There are also few studies evaluating the effect of nutritional intervention before commencing dialysis, with none using ISRNM criteria to define PEW, and their sample size and demographics being clearly different. Campbell et al.[4] performed a 4-month study on a control group of 27 patients who only received written material and on an intervention group of 24 who received individual nutritional education. The control group increased the proportion of patients with malnutrition measured by a subjective global assessment scale from 11% to 22%, whereas all the patients in the intervention group diagnosed with malnutrition (20.8%) reversed their situation. Concordantly, our study did show a reduction in patients with PEW, but we unexpectedly found that nutritional status actually worsened in 3 patients.

Table 5. Characteristics of Women Who Reverse and Do Not Reverse the Wasting Situation

	Women Who Reverse 10 (14.9%)			Women Who Do Not Reverse 10 (14.9%)		
Variable	Month 0	Month 6	*P*	Month 0	Month 6	*P*
Albumin (g/dL)	3.3 ± 0.3	3.6 ± 0.4	**.007**	3.5 ± 0.4	3.6 ± 0.3	.990
Prealbumin (mg/dL)	28.4 ± 6.6	29.5 ± 4.7	**.049**	26.6 ± 5.2	30.9 ± 6.2	**.020**
ClCr (mL/min)	14.0 ± 4.4	15.8 ± 6.0	.320	16.3 ± 4.5	17.0 ± 6.4	**.049**
Proteinuria (g/24 h)	1.2 ± 0.9	1.1 ± 1.9	.635	1.2 ± 0.8	0.6 ± 0.4	**.020**
nPNA (g/kg/día)	1.3 ± 0.5	1.2 ± 0.3	.530	1.3 ± 0.	1.1 ± 0.3	**.010**
CRP (mg/L)	3.4 ± 3.7	3.0 ± 3.4	.990	5.7 ± 6.7	3.1 ± 2.5	**.049**
Weight (kg)	56.9 ± 7.6	58.1 ± 7.7	.050	51.8 ± 11.2	53.1 ± 10.8	.090
BMI (kg/m^2)	24.2 ± 3.2*	24.8 ± 3.6	**.038**	21.0 ± 2.9*	21.5 ± 2.6	.092
MUAC (mm^2)	19.9 ± 3.3	20.8 ± 3.2	.06	18.2 ± 1.1	18.6 ± 0.9	.065
Reactance (Ω)	36 ± 12.6	42.5 ± 9.0	.06	32.0 ± 2.6	37.3 ± 1.5	.289
Phase angle (°)	3.7 ± 0.9	4.5 ± 0.9	.06	3.5 ± 0.5	3.8 ± 0.3	.120
Body cell mass (%)	37.8 ± 8.3	46.4 ± 7.7	.06	34.9 ± 2.1	37.6 ± 2.5	.108
Total body water (%)	55.7 ± 2.7	54.4 ± 4.0	.06	58.4 ± 8.4	55.1 ± 9.12	.179
Extracellular water (%)	60.5 ± 7.8	54.6 ± 6.3	.06	59.7 ± 4.9	55.8 ± 2.1	.108
Intracellular water (%)	39.4 ± 7.8	45.4 ± 6.3	.06	40.3 ± 4.9	44.3 ± 2.1	.108
Muscle mass (%)	36.6 ± 5.3	40.4 ± 7.8	.06	34.8 ± 5.1	37.4 ± 4.6	.108
Body cellular mass index	6.0 ± 0.8	7.2 ± 0.9	.06	5.3 ± 0.6	6.0 ± 1.0	.317

BMI, body mass index; ClCr, creatinine clearance; CRP, C-reactive protein; MAMC, mid-arm muscle circumference; nPNA, normalized protein nitrogen appearance.

Values are presented as mean ± standard error of the mean. *P* was calculated by Wilcoxon test. Significant differences are highlighted in bold.

*Differences at baseline between women who reverse and not reverse at baseline, *P* was calculated by Student's t-test.

In another study[10] involving 11 patients with creatinine clearance below 25 mL/minute/m^2 under 6 months of nutritional intervention, the number of malnourished patients dropped from 3 to 1 using the subjective global assessment scale.

Despite the PEW criteria having been widely used in studies on dialysis patients, we found only one study assessing the efficacy of nutritional education compared with oral supplementation. In that series, malnutrition was diagnosed by albumin values <3.5 g/dL and found that the number of malnourished patients fell significantly from 57.4% to 31.3% ($P < .05$) in the nutritional education group. Although it does not assess the PEW state, our study concurs regarding the improvement in albumin levels.[15]

Even if part of the results in our study may be effect of the oral supplementation, we consider that the function of an NEP is not only detecting malnutrition and patients with high risk for malnutrition but also explains how to take supplementation.

As indicated in the literature, differences in sex have an important influence on CKD outcomes.[16] Our study has found that after the intervention, male patients improved their nutritional status significantly, whereas women failed to improve and their nutritional status even worsened. This finding is contrary to the data of Campbell et al.,[4] which showed better results in women because of better adherence to dietary guidelines; nevertheless, our data on adherence have not yielded differences by sex. We believe, in agreement with Westland et al.,[13] that female sex is a risk factor associated with PEW.

In the PEW analysis of improvement, with the exception of the BMI <23 kg/m^2, it is remarkable that only 4 of 32 patients who started in a situation of wasting actually maintained it, therefore suggesting a low BMI as a chronicity of PEW status, indicating a requirement for earlier nutritional intervention. BMI can be influenced by several factors, such as water overload, age, inflammation, and others[17]; we believe, however, that these factors did not influence our affected population group because a normal hydration state and no age influence were detected. One of the common characteristics of the 10 women who completed the study and who remained in a PEW situation was the lower BMI they showed at the start of the study, a fact that highlights the importance of the starting point in any nutritional intervention. The 3 women whose nutritional status worsened also presented a low BMI for their age[18] and low levels of muscle and fat mass, with adequate intake and normal biochemical levels. Consequently, although not includable in the PEW criteria, they showed caloric malnutrition criteria[19] and were examples of the difference between malnutrition and PEW.[20,21]

On the other hand, the 4 men who completed the NEP in a state of PEW presented significantly lower levels of albumin, BMI, and body cellular mass index at the outset than the patients whose nutritional status improved. Defining features of elderly related frailty[22] were observed in these patients, coexisting with wasting, which represents an additional difficulty in improving nutritional status.[23] As a result, we consider that women with caloric malnutrition and men with elderly frailty characteristics are, as have been identified by other authors, groups at risk of PEW,[13] which

strongly supports the recommendation of personalization and adaptation of any nutritional support.[2,7]

The literature has endorsed the use of restricted protein diets as a renoprotective measure, ensuring that this will not entail negative effects on nutritional status.[24,25]

We participate in the current open debate on this issue and consider that renal function and nutritional status are determining factors in its use.

One of the limitations of the study is the length of the intervention period. We have observed an improvement in most of the parameters analyzed—many of which at the limit of significance—suggesting that a longer intervention period would have had a greater influence on nutritional status. In addition, an increase in sample size would have enabled us to perform a multivariate analysis.

In conclusion, our study demonstrates the efficacy and safety of a PEN in patients with CKD-NDD by improving the nutritional status measured by PEW parameters and indicates the need to pay special attention to maintaining kidney function, female sex, and low BMI for personalizing more effective nutrition interventions.

Practical Application

The application of individualized nutrition education programs in nondialysis-dependent chronic kidney disease might decrease the levels of malnutrition and the complications from nutritional status on subsequent dialysis.

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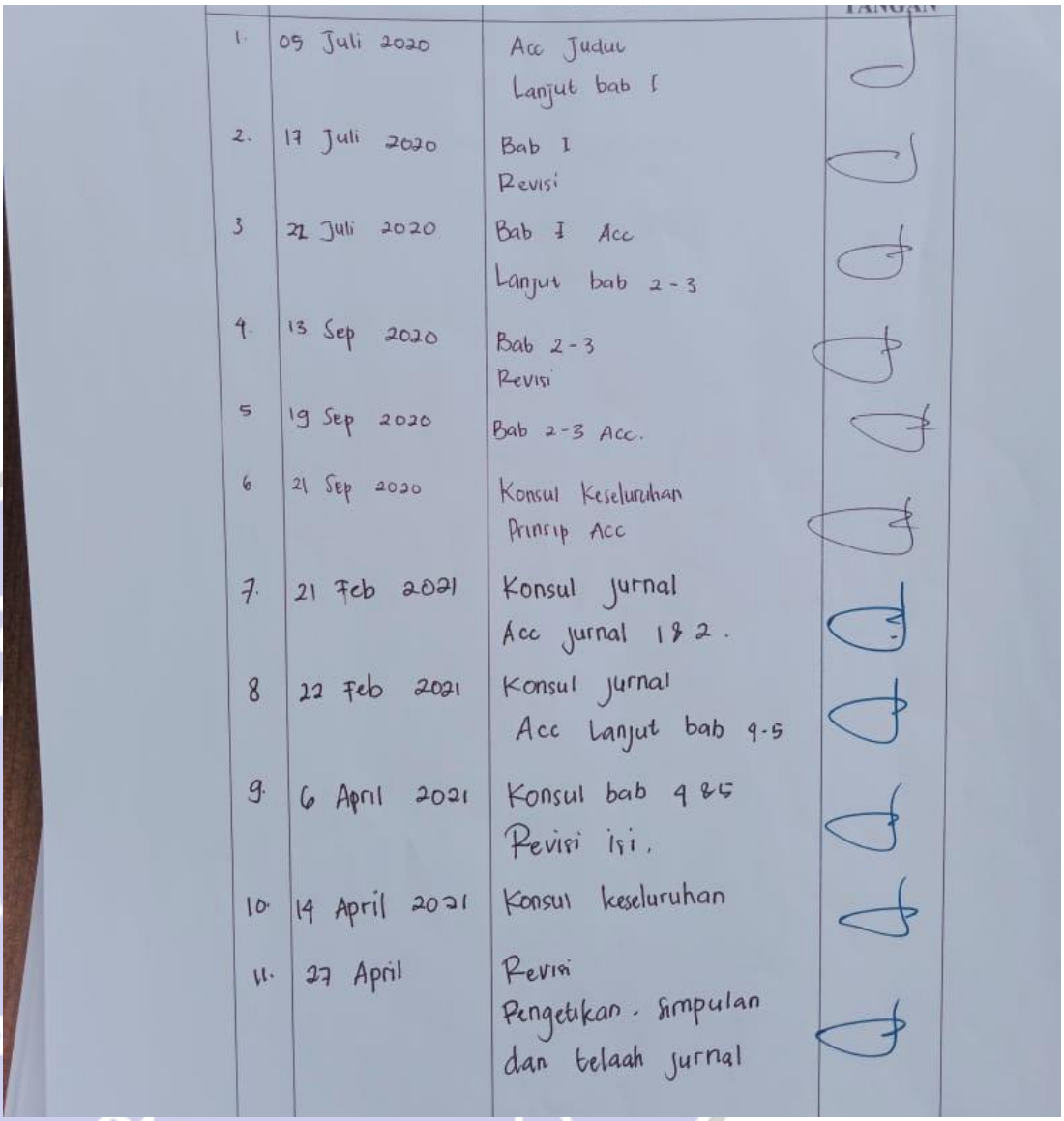
Lampiran 2



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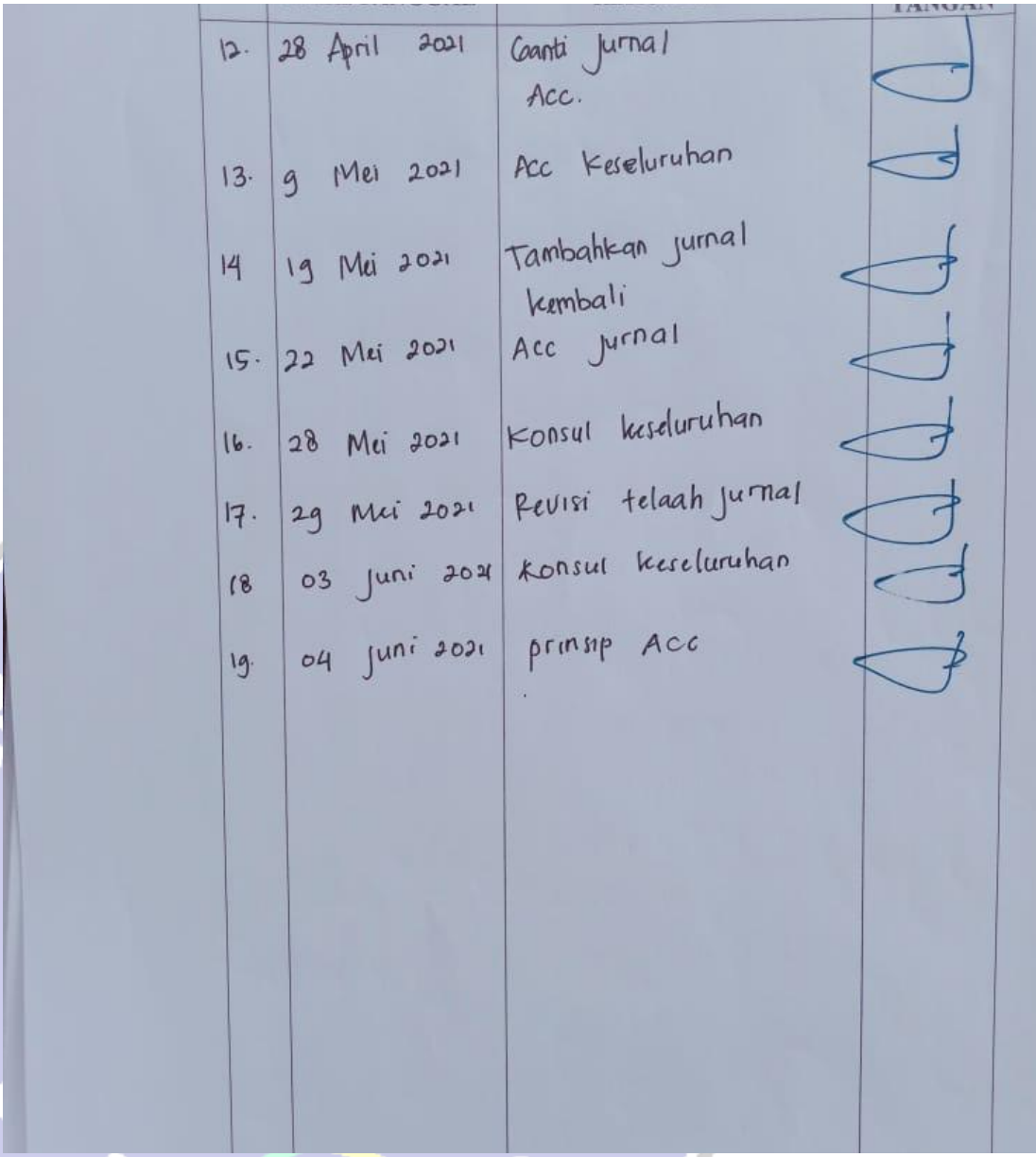

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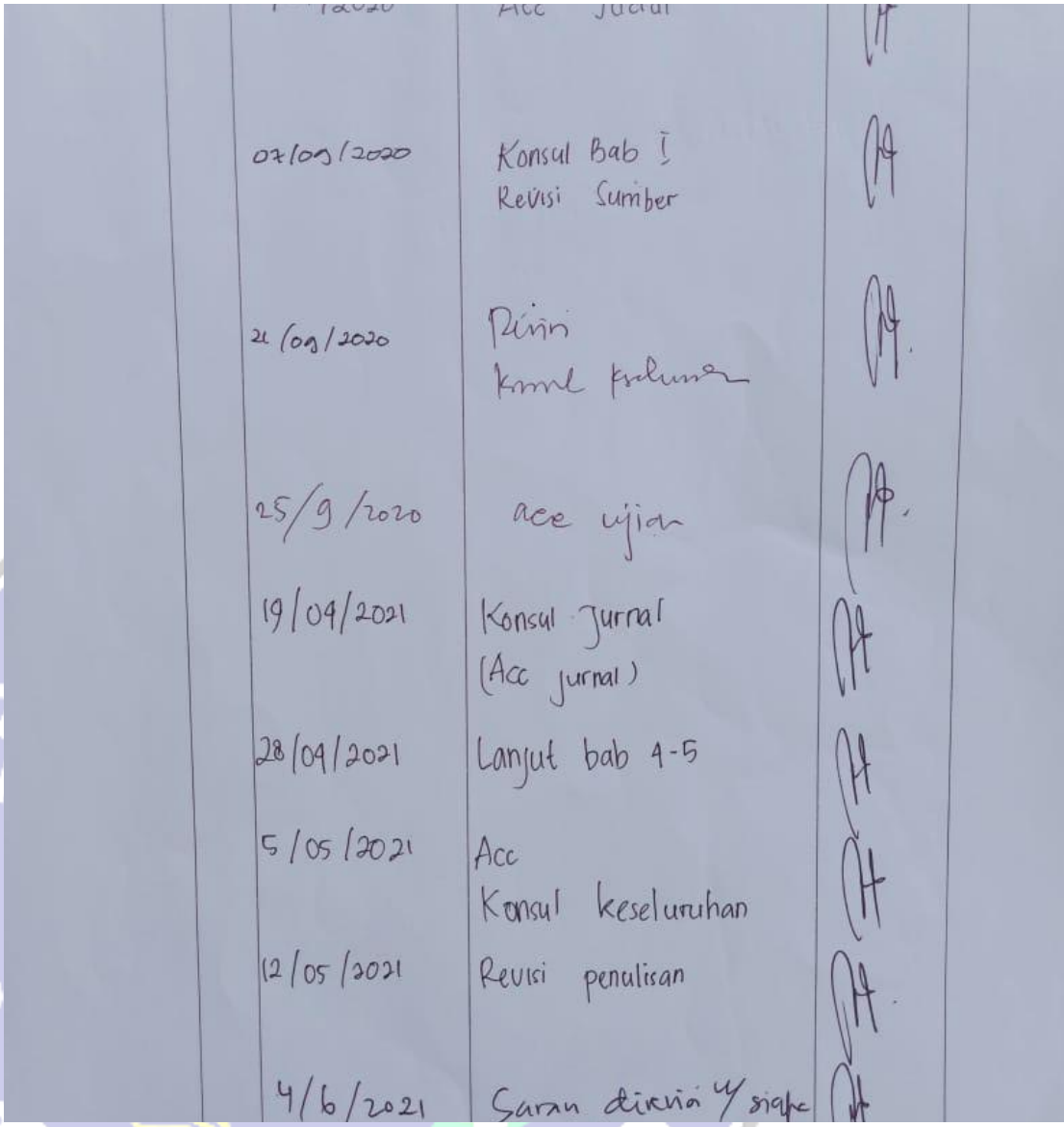

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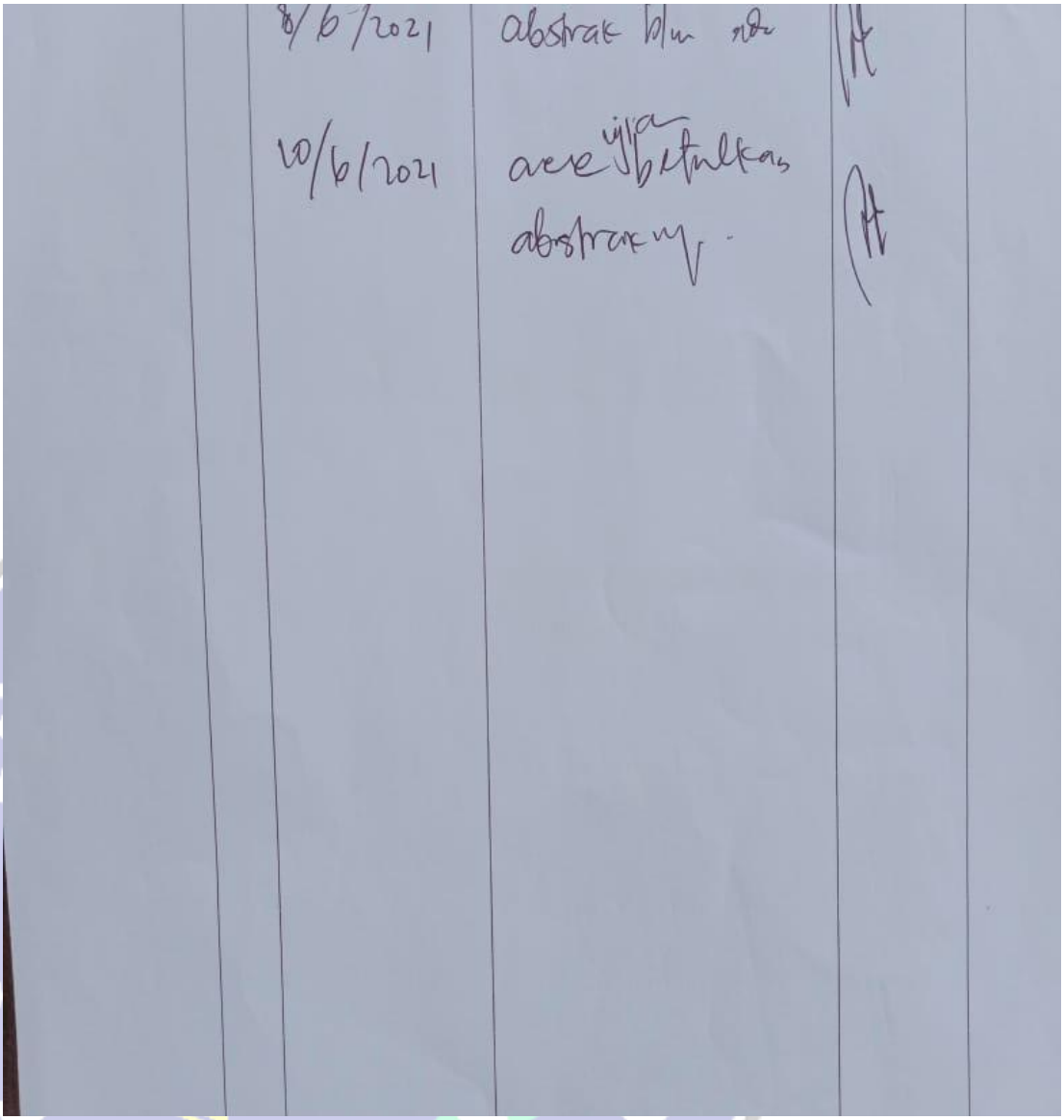
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