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Role of Low-protein diets in CKD

Review of the international literature

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  Piccoli GB, Nazha M, Capizzi I et al. Nutrients 2016, 8, 758; doi:10.3390/nu8120758

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Dietary protein intake and chronic kidney disease

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Curr Opin Clin Nutr Metab Care 2017, 20:77-85

ABSTRACT

Purpose of review

High-protein intake may lead to increased intraglomerular pressure and glomerular hyperfiltration. This can cause damage to glomerular structure leading to or aggravating chronic kidney disease (CKD). Hence, a low-protein diet (LPD) of 0.6–0.8 g/kg/day is often recommended for the management of CKD. We reviewed the effect of protein intake on incidence and progression of CKD and the role of LPD in the CKD management.

Recent findings

Actual dietary protein consumption in CKD patients remains substantially higher than the recommendations for LPD. Notwithstanding the inconclusive results of the "Modification of Diet in Renal Disease" (MDRD) study, the largest randomized controlled trial to examine protein restriction in CKD, several prior and subsequent studies and meta-analyses appear to support the role of LPD on retarding progression of CKD and delaying initiation of maintenance dialysis therapy. LPD can also be used **to control metabolic derangements** in CKD. Supplemented LPD with essential amino acids or their ketoanalogs may be used for incremental transition to dialysis especially on nondialysis days. The LPD management in lieu of dialysis therapy can **reduce costs, enhance psychological adaptation, and preserve residual renal function** upon transition to dialysis. Adherence and adequate protein and energy intake should be ensured to avoid protein-energy wasting.

Summary

A balanced and individualized dietary approach based on LPD should be elaborated with **periodic dietitian counseling** and surveillance to optimize management of CKD, to assure adequate protein and energy intake, and to avoid or correct protein-energy wasting.

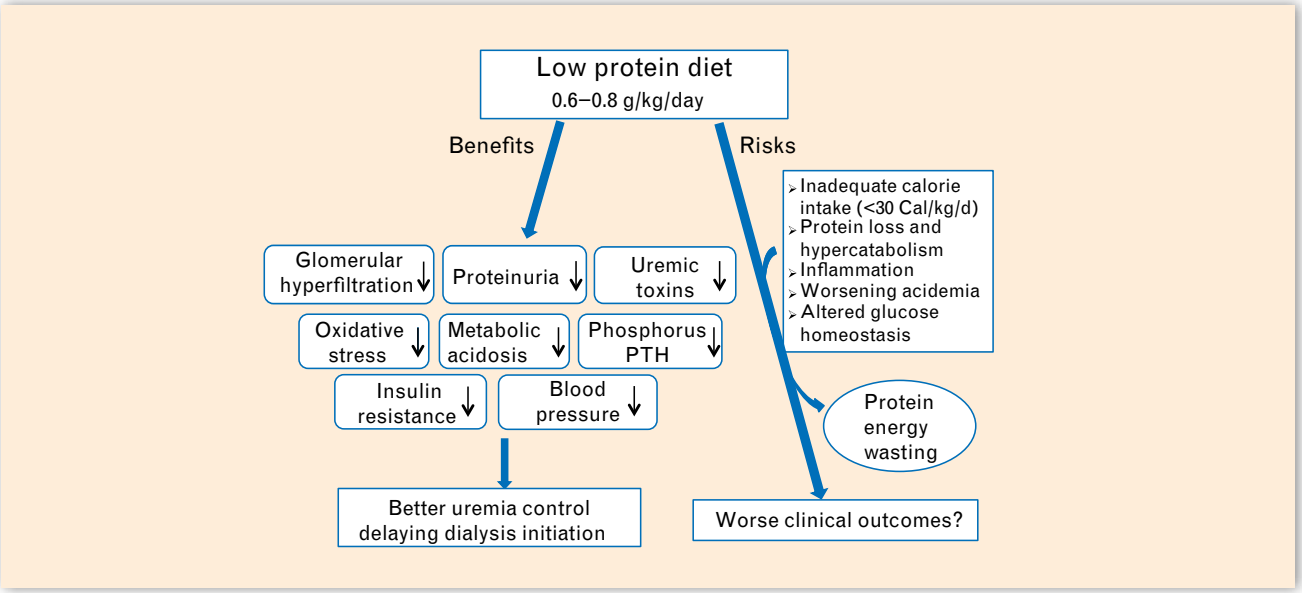

Figure 1.
Diagram of the role of low-protein diet in the management of chronic kidney disease. PTH, parathyroid hormone.
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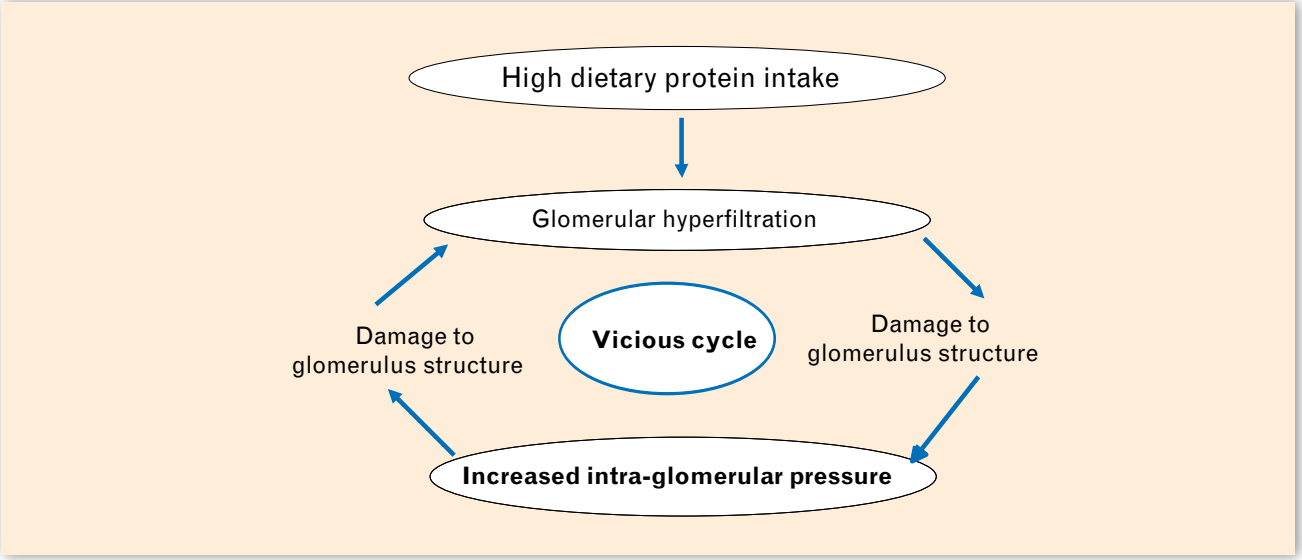

Figure 2.
Effect of high dietary protein intake on kidney.

CONCLUSIONS

- **There is enough evidence to suggest that LPD retards the rate of progression of CKD.**
- **LPD may facilitate the targeted delay of the start of dialysis and can be used to adopt incremental or infrequent dialysis.**
- **Patient adherence to LPD is mandatory to achieve its renoprotective goal.**
- **Education, good patient–physician communication, and monitoring by well-trained dietitians would favor adherence through improved knowledge of the importance of diet.**
- **Better information about a patient's preference and continuous effort to find new solutions for better tolerability would be essential for successful dietary treatment.**
- **However, an inadequate energy intake may lead to protein-energy wasting (PEW) and in dialysis patients, proper amount of protein intake should be ensured.**

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The role of low protein diet in ameliorating proteinuria and deferring dialysis initiation: what is old and what is new

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Panminerva Med. 2016 Oct 19. [Epub ahead of print]

ABSTRACT

In the management of patients with chronic kidney diseases (CKD), a low-protein diet usually refers to a diet with **protein intake of 0.6 to 0.8 grams** per kilogram of body weight per day (g/kg/day) and should include **at least 50% high-biologic-value protein**. It may be supplemented with essential acids or nitrogen-free ketoanalogues if <0.6 g/kg/d. Low-protein diet can reduce proteinuria especially in non-diabetic CKD patients. In hypoalbuminemic patients it may lead to an increase in serum albumin level.

By lowering proteinuria, decreasing nitrogen waste products, ameliorating metabolic burden, mitigating oxidative stress and acidosis, and lowering phosphorus burden, a low-protein diet can help delay dialysis start in advanced CKD.

Low-protein diet is safe, since most CKD patients can maintain nitrogen balance by mechanisms of decreasing amino acid oxidation and protein degradation in addition to increased utilization of amino acids for protein synthesis. We suggest a dietary protein intake below 1.0 g/kg/day when estimated glomerular filtration rate (eGFR) falls below 60 ml/min/1.73m^2 or when there is solitary kidney or proteinuria at any level of GFR.

Protein intake should be reduced progressively based on severity and progression of CKD and patient's nutritional status with a target of 0.6-0.8 g/kg/d in most patients with eGFR <45 ml/min/1.73m^2.

The **risk of protein-energy wasting can be overcome** by careful attention to quantity and quality of the ingested proteins, sufficient energy intake of 30-35 Kcal/kg/d, and use of **dietary supplements**. Long-term observations and individualized approaches are needed to further demonstrate the benefits and safety of low-protein diet.

Table 1 Proposed advantages and disadvantages surrounding the use of low-protein diets in patients with chronic kidney disease. Future research is needed to guide individualized therapy and confirm long-term benefits of low-protein diets in this patient population.

Advantages	Disadvantages
Adequate adaptation to a reduction in protein intake	Risk of inducing or worsening PEW and consequent poor outcomes
Decrease load on remaining nephrons	
Improve insulin resistance	Requires considerable motivation and discipline on patient's part
Reduce oxidant stress	
Ameliorate proteinuria	Resource-intensive (need for trained dietitian)
Reduce PTH levels and improve lipid profile	
Additive effect of ACE inhibitors	
Decrease likelihood of patients death or delay initiation of dialysis by 40%	Cost of properly composed diet
Favorable number needed to treat (one patients saved from death or initiation of dialysis every year for every 18 patients maintained on a LPD)	

Note: PEW, protein-energy wasting; PTH, parathyroid hormone; ACE inhibitors, Angiotensin-converting-enzyme inhibitors; LPD, low-protein diet.

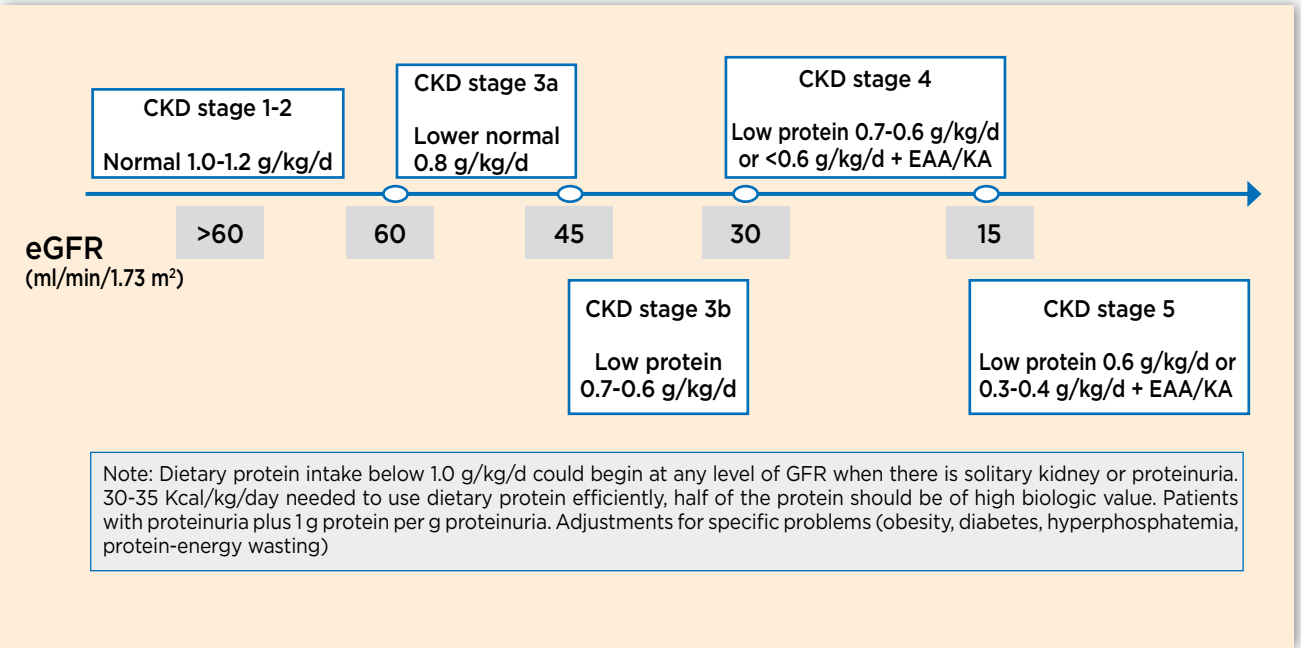

Figure 1.
Dietary protein requirements in stable, non-nephrotic and non-catabolic CKD patients

CONCLUSIONS

- **In the literature there are several *evidence*-based demonstrations of the possible role low protein diets (LPDs) may play in reducing urinary protein losses and in delaying the start of dialysis therapy among most forms of CKD.**
- **The risk of malnutrition and protein-energy wasting (PEW) can be alleviated by ensuring adequate quantity and quality of ingested proteins and with careful attention to energy intake.**
- **Potential strategies to achieve these goals include supplementing diet with essential nutrients or supplements that are specifically designed for CKD patients.**
- **Future studies are needed to confirm the effectiveness and safety of these strategies at improving long-term patient outcomes.**

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Low-protein diets for chronic kidney disease patients: the Italian experience

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BMC Nephrology 2016; 17:77

ABSTRACT

Background: Nutritional treatment has always represented a major feature of CKD management. Over the decades, the use of nutritional treatment in CKD patients has been marked by several goals. The first of these include the attainment of metabolic and fluid control together with the prevention and correction of signs, symptoms and complications of advanced CKD.
The aim of this first stage is the **prevention of malnutrition and a delay in the commencement of dialysis**. Subsequently, nutritional manipulations have also been applied in association with other therapeutic interventions in an attempt to control several cardiovascular risk factors associated with CKD and to improve the patient's overall outcome. Over time and in reference to multiple aims, the modalities of nutritional treatment have been focused not only on protein intake but also on other nutrients.

Discussion: This paper describes the pathophysiological basis and rationale of nutritional treatment in CKD and also provides a report on extensive experience in the field of renal diets in Italy, with special attention given to approaches in clinical practice and management.

Summary: Italian nephrologists have a longstanding tradition in implementing low protein diets in the treatment of CKD patients, with the principle objective of alleviating uremic symptoms, improving nutritional status and also a possibility of slowing down the progression of CKD or delaying the start of dialysis. A renewed interest in this field is based on the aim of implementing a **wider nutritional therapy** other than only reducing the protein intake, paying careful attention to factors such as energy intake, the quality of proteins and phosphate and sodium intakes, making today's **low-protein diet program** much more ambitious than previous. The motivation was the reduction in progression of renal insufficiency through **reduction of proteinuria**, a better **control of blood pressur**e values and also through **correction of metabolic acidosis**. One major goal of the flexible and innovative Italian approach to the low-protein diet in CKD patients is the **improvement of patient adherence**, a crucial factor in the successful implementation of a low-protein diet program.

Table 1 Dietary composition of low-protein diets for CKD patients

	Normal diet	LPD	Vegan	VLPD
Nutrients				
Energy requirement	normal	high	high	high
Protein, g/Kg/d	0.8	0.6	0.7	0.3-0.4
Prevalent origin of proteins	Mixed	Animal	Plant	Plant
Phosphate, mg/d	700-800	500-600	500-600	300-400
Sodium, mmol/d	100	100	100	100
Supplements				
Free-protein products use	Optional	Yes	No	Yes
EAA + KA	No	Optional	Optional	Yes
Calcium, g/d	Optional	0.5-1.0	0.5-1.0	0.5-1.0
B12 Vitamin	No	Optional	Yes	Yes
Iron	No	Optional	Yes	Yes

EAA essential aminoacids, *KA* ketoacids

Table 2 Criteria suggested for the nutritional monitoring of patients with CKD in conservative treatment. Most nutritional variables should be obtained every 3 months

Category	Nutritional variable	Additionally useful variables
Biochemical markers	Albumin < 3,8 g/dL Total cholesterol < 100 mg/dL	Transferrin, prealbumin Inflammatory markers: CRP, Total lymphocyte count or percentage
Body mass	BMI < 23 Kg/m^2 Unintentional weight-loss > 5% in 3 months or > 10% in 6 months Reduced fat mass < 10%	Bioelectrical Impedance Analysis
Muscle mass	Reduction of muscle mass by 5% in 3 months or 10% in 6 months Reduced AMA by 10% as compared to the 50th percentile of the reference population	DEXA (6 months interval) CT and/or MRI (6 months interval) Measurements of muscle strength and function (for example handgrip, 6 min walking test)
Nutritional intake	Unintentional DPI < 0.6 g/kg/day for at least 2 months Unintentional DEI < 25 kcal/kg/day for at least 2 months	Appetite assessment questionnaires Food frequency and dietary recall questionnaires Measuring energy expenditure by indirect calorimetry Protein catabolic rate (PCR)
Nutritional scoring system	Subjective Global Assessment (SGA) Malnutrition-inflammation Score (MIS)	

AMA arm muscle area, *BMI* body mass index, *CRP* C-reactive protein, *CT* computed tomography, *DEI* dietary energy intake, *DEXA* dual energy X-ray absorptiometry, *DPI* dietary protein intake, *MRI* magnetic resonance

CONCLUSIONS

- **Dietary protein and phosphorus restriction, together with salt reduction, while maintaining an adequate energy intake is the mainstay of the nutritional treatment for CKD patients.**
- **In order to maximize benefits whilst minimizing the risks, as well as to maintain patient adherence to dietary recommendations, nutritional therapy must be adapted to patient clinical and extra-clinical needs.**
- **The current, innovative approach of Italian nephrologists is not only reducing the protein intake of CKD patients but also implementing a wider and more correct nutritional therapy of a population that is increasing in age, with comorbidities, including cardiovascular diseases, diabetes and hypertension.**
- **The major characteristic of this approach is to pay particular attention to energy intake and to quality of proteins, achieved by using new protein-free foods of greatly improved quality and palatability. The phosphate and salt intake is also carefully considered.**
- **The main goal of this approach adapted to individual patient needs is to obtain patient adherence, which is mandatory for achieving the successful implementation of a low protein diet program.**

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North American experience with low protein diet for non-dialysis-dependent chronic kidney disease

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BMC Nephrology (2016); 17:90

ABSTRACT

Whereas in **many parts of the world a low protein** diet (LPD, 0.6-0.8 g/kg/day) **is routinely prescribed** for the management of patients with non-dialysis-dependent chronic kidney disease (CKD), this practice is infrequent in North America. The historical underpinnings related to LPD in the USA including the non-conclusive results of the Modification of Diet in Renal Disease Study may have played a role.

Overall trends to initiate dialysis earlier in the course of CKD in the US allowed less time for LPD prescription. The usual dietary intake in the US includes high dietary protein content, which is in sharp contradistinction to that of a LPD.

The fear of engendering or worsening protein-energy wasting may be an important handicap as suggested by a pilot survey of **US nephrologists**; nevertheless, there is also potential **interest and enthusiasm in gaining further insight regarding LPD's utility** in both research and in practice.

Racial/ethnic disparities in the US and patients' adherence are additional challenges. Adherence should be monitored by well-trained dietitians by means of both dietary assessment techniques and 24-h urine collections to estimate dietary protein intake using urinary urea nitrogen (UUN).

While keto-analogues are not currently available in the USA, there are other oral **nutritional supplements** for the provision of high-biologic-value proteins along with dietary energy intake of 30–35 Cal/kg/day available.

Different treatment strategies related to dietary intake may help circumvent the protein-energy wasting apprehension and offer novel conservative approaches for CKD management in North America.

Table 1 Pilot survey of nephrologists from the Veterans Administration health system (based on 16 preliminary sets of responses)

Question 1: Do you recommend or practice LPD?		Question 2: Will you be interested in implementing and managing LPD?		Question 3: How to suggest implement LPD more effectively?	
Never	13%	No	25%	Dedicated dietitian involvement needed	44%
Rarely	56%	Maybe	56%	Need to improve patient adherence and education	19%
Sometimes	25%	Yes	19%	Monitor protein intake including by 24-h urine	19%
Frequently	6%			Do not favor LPD	13%
				Prioritize amino-acid and other supplements	6%

Exact questions that were asked: Question 1: Do you recommend or implement Low Protein Diet (LPD) for conservative management of patients with moderate to advanced CKD, e.g. limiting daily dietary protein intake to 0.6-0.8 gram/kg/day? Question 2. Will you be interested in implementing and managing Low Protein Diet (LPD) for conservative management of CKD patients? Question 3. How do you suggest nephrologists can help implement more effectively Low Protein Diet (LPD) protocols for management of CKD patients?

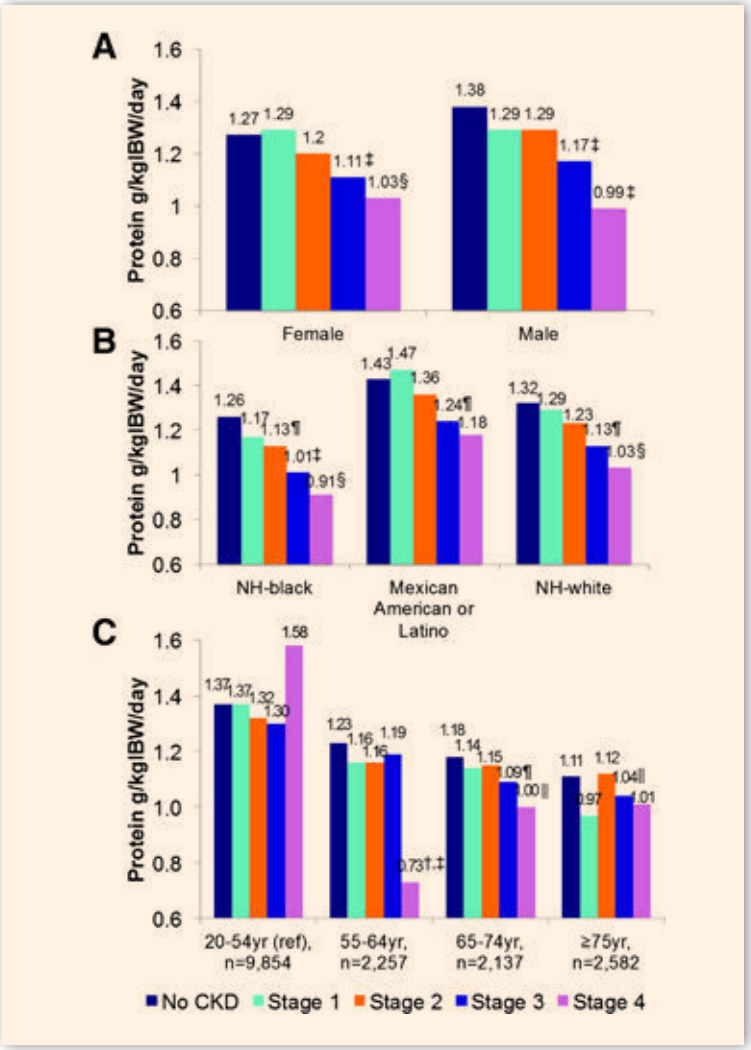

Figure 1.
Estimated DPI in the USA across gender, race, and age accounting for stages of CKD: normalized to protein in g/kgIBW/d, for adults in the USA depicted for (**a**) sex, (**b**) race or ethnicity, and (**c**) age group. No evidence of CKD (No CKD), stage 1 CKD (eGFR, ≥90ml/min with kidney damage), stage 2 CKD (eGFR 60–89ml/min with kidney damage), stage 3 CKD (eGFR 30–59ml/min), or stage 4 CKD (eGFR <30 ml/min without dialysis). P<0.0001, *P<0.0001, †P<0.05, ‡P<0.0001, §P<0.001, ||P<0.01, ¶P<0.05, NH=non-Hispanic. *Adapted from secondary NHANES data analyses by Morre et al. (with permission).*

CONCLUSIONS

- **The implementation of the LPD practice in North America is hampered by several barriers, including concerns about induction and aggravation of protein-energy wasting (PEW) as suggested by a survey of US nephrologists.**
- **PEW is a powerful predictor of poor outcomes and death risk for CKD patients that can be improved by assuring adequate protein and energy intake.**
- **Supplementing diet with substitutes that are manufactured to guarantee high biologic value (HBV) proteins and adequate energy intake may result in preservation of kidney function and nutritional status as well as improvement in PEW and uremia.**
- **Authors prudently favor the expansion of the LPD practice in North America, suggesting further studies evaluating this approach.**

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Patient survival and costs on moderately restricted low-protein diets in advanced CKD: equivalent survival at lower costs?

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ABSTRACT

The indications for delaying the start of dialysis have revived interest in low-protein diets (LPDs).

In this observational prospective study, we enrolled all patients with chronic kidney disease (CKD) who followed a moderately restricted LPD in 2007–2015 in a nephrology unit in Italy: 449 patients, 847 years of observation.

At the start of the diet, the median glomerular filtration rate (GFR) was 20 mL/min, the median age was 70, the median Charlson Index was 7.

Standardized mortality rates for the "on-diet" population were significantly lower than for patients on dialysis [United States Renal Data System (USRDS): 0.44 (0.36–0.54); Italian Dialysis Registry: 0.73 (0.59–0.88); French Dialysis Registry 0.70 (0.57–0.85)].

Considering only the follow-up at low GFR (≤15 mL/min), survival remained significantly higher than in the USRDS, and was equivalent to the Italian and French registries, with an advantage in younger patients. Below the e-GFR of 15 mL/min, **50% of the patients reached a dialysis-free follow-up of ≥2 years**; 25% have been dialysis-free for five years.

Considering an average yearly cost of about 50,000 Euros for dialysis and 1200 Euros for the diet, and different hypotheses of "spared" dialysis years, **treating 100 patients on a moderately restricted LPD would allow saving one to four million Euros**.

Therefore, our study suggests that in patients with advanced CKD, moderately restricted LPDs may allow prolonging dialysis-free follow-up with comparable survival to dialysis at a lower cost.

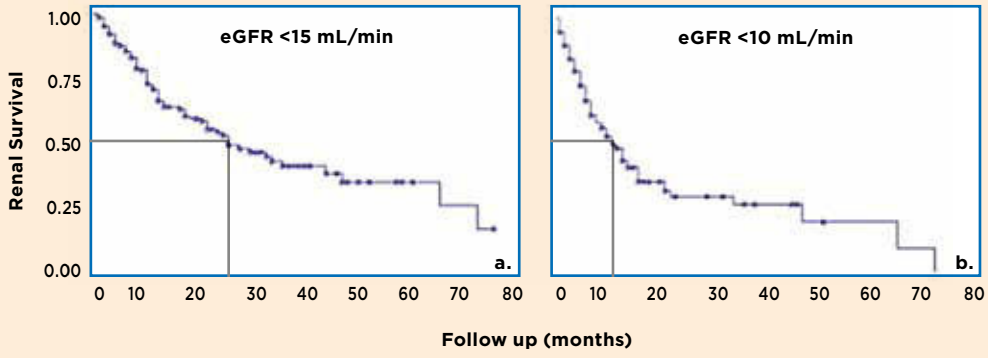

Figure 1.
Dialysis-free follow-up after the first finding of an e-GFR at or below 15 mL/min and 10 mL/min. Half of patients were able to continue a dialysis-free follow-up for at least two years, 25% for about four. About half of the patients who reached an e-GFR <10 mL/min were dialysis-free one year later.

Table 1 Standardized mortality rates (SMR), all LPDs together: 240 patients who reached an e-GFR < 15 mL/min and 148 patients who reached an e-GFR < 10 mL/min (follow-up after the first finding of reduced e-GFR).

	e-GFR < 15 (mL/min)	e-GFR < 10 (mL/min)
Follow-up (years)	384.83	204.75
Observed deaths	64	29
Expected deaths (USRDS)	104.43	50.00
RR (CI) (USRDS)	0.61 (0.47–0.78)	0.58 (0.39–0.83)
Expected deaths (Italian Reg.)	63.79	30.16
RR (CI) (Italian Reg.)	1.00 (0.77–1.28)	0.96 (0.64–1.38)
Expected deaths (French Reg.)	67.85	31.51
RR (CI) (French Reg.)	0.94 (0.73–1.21)	0.92 (0.62–1.32)
<65 years		
Follow-up (years)	127.83	80.42
Observed deaths	6	4
Expected deaths (USRDS)	18.04	11.65
RR (CI) (USRDS)	0.33 (0.12–0.72)	0.34 (0.09–0.88)
Expected deaths (Italian Reg.)	9.33	6.05
RR (CI) (Italian Reg.)	0.64 (0.24–1.40)	0.66 (0.18–1.69)
Expected deaths (French Reg.)	8.62	5.63
RR (CI) (French Reg.)	0.70 (0.26–1.52)	0.71 (0.62–1.32)
≥65 years		
Follow-up (years)	262.00	124.33
Observed deaths	58	25
Expected deaths (USRDS)	86.39	38.35
RR (CI) (USRDS)	0.67 (0.51–0.87)	0.65 (0.42–0.96)
Expected deaths (Italian Reg.)	54.46	24.11
RR (CI) (Italian Reg.)	1.06 (0.81–1.38)	1.04 (0.67–1.53)
Expected deaths (French Reg.)	59.23	25.88
RR (CI) (French Reg.)	0.98 (0.74–1.27)	0.97 (0.63–1.43)

CONCLUSIONS

- **Low-protein diets (LPDs) are still underutilized for a number of reasons, including concerns about impaired survival and of a carry-over effect increasing the risk of death in patients who were previously on a diet.**
- **Each patient enrolled in this study could choose between various moderately restricted LPD options and change them over time.**
- **The main finding of this study is that mortality rates of patients on dialysis-free follow-up were similar to or lower than the USRDS and the Italian and French dialysis registries.**
- **This advantage was higher in younger patients; the absence of evidence of a difference considering the first year of follow-up after the start of dialysis allows the investigators to rule out a carry-over effect of the diet.**
- **The potential for delaying the start of dialysis, may be indirectly shown by the patient-years of observation recorded after the first time the e-GFR dropped to or below 15 mL/min, equivalent to "early dialysis start", or 10 mL/min, equivalent to "late dialysis start".**
- **These observations would appear to support this flexible and personalized approach to moderately restricted LPD as a means of safely retarding dialysis.**

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