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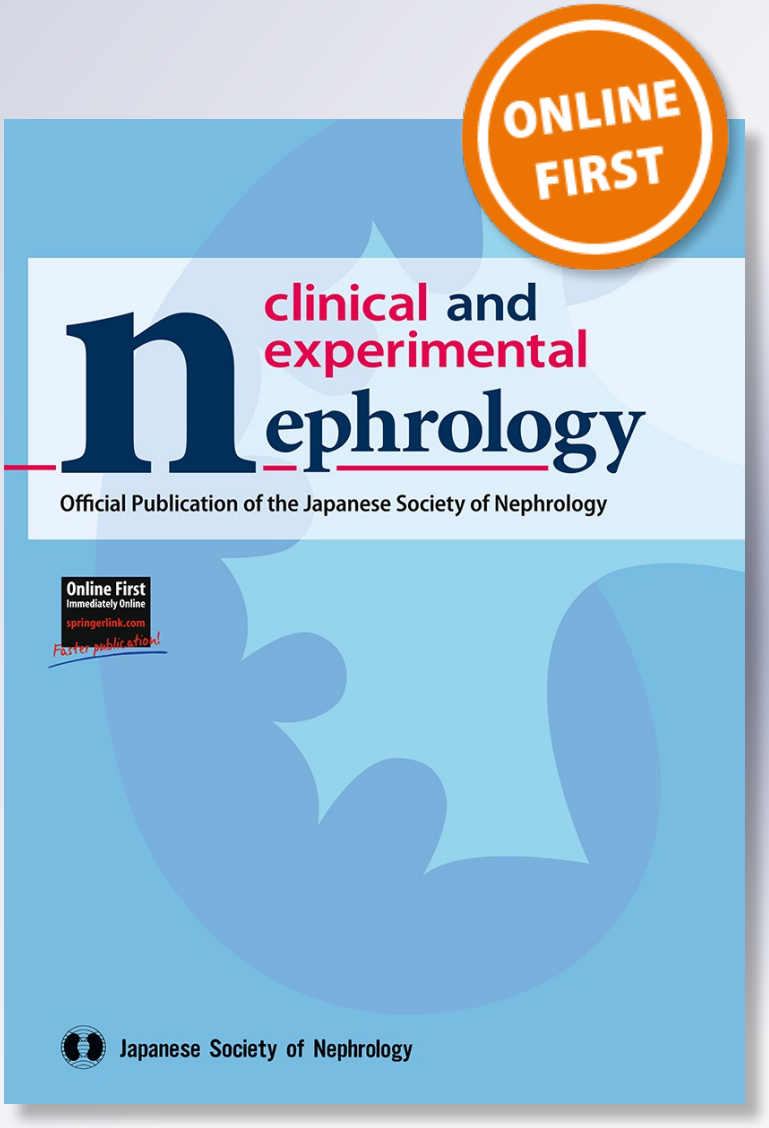

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REVIEW ARTICLE

Nutritional treatment in chronic kidney disease: the concept of nephroprotection

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Abstract Low-protein diets have been advocated for many decades as the cornerstone in the treatment of chronic kidney disease. Initially, the low intake of protein was used to reduce uremic symptoms; thereafter, albeit controversial, evidences suggested that dietary protein restriction can also slow the rate of progression of renal failure and the time until end-stage renal disease. This reviews focuses on the dietary factors and their influence on the loss of renal function and on the evidences in the literature supporting a nephroprotective role of the low-protein diet.

Keywords Chronic kidney disease · Glomerular filtration rate · Low-protein diet · Protein intake

Introduction

Chronic kidney disease (CKD) is a common disorder and its prevalence is increasing worldwide. Early diagnosis could permit early intervention not only to slow the progression to end stage renal disease (ESRD), but also to reduce the risks of cardiovascular (CV) events and death that are associated with CKD. Effective strategies are available to slow the progression of CKD and reduce CV risk. In this context, a central role is certainly played by nutritional dietary treatment.

The use of a low-protein diet in treating CKD is still a matter of debate. Despite a universal agreement on the amount of protein intake to prescribe in patients with advanced CKD does not exist, dietary restriction of proteins and sodium still remains a cornerstone in the treatment of CKD. Initially, in the early 1960s, the low intake of protein was used to reduce uremic symptoms [1]. Later, experimental studies hypothesized that high protein load could cause hyperfiltration and, as a result, the worsening of renal function [2], and the low-protein diet became widely used in the belief that it could slow down the progression of chronic renal failure.

Despite controversy still exists about the potential beneficial effect of reduction in dietary protein on the course and rate of progression of loss of renal function, most studies and clinical practice suggest that lowering protein intake allows to correct several metabolic complications of renal failure: in particular, the reduced protein intake is able to reduce the alimentary load of phosphate, hydrogen ions and sodium, ameliorating the hyperphosphatemia, secondary hyperparathyroidism, acid–base balance control and hypertension [3].

Although high-degree scientific evidence is lacking, the interest in the use of the low-protein diet in clinical practice increased, and the historical aims for a use of dietetic therapy in CKD, that was handling of uremic symptoms, has changed, highlighting the role of low-protein diet in the more general topic of nephroprotection.

Dietary factors and influence on the loss of renal function

Several dietary factors related to the protein intake can affect the loss of function and the severity of kidney disease. When examining dietary constituents that directly influence the severity of kidney disease, it is important to remember that higher-protein diets are also generally

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Table 1 The influence of diet on the progression of renal insufficiency

1. Changes in the measurement of the rate of loss of kidney function [20]
(a) An acute change in dietary protein causes a parallel change in measured glomerular filtration rate (GFR)
2. Creatinine production changes with dietary protein [20]
(a) An increase or decrease in protein intake reciprocally change serum creatinine or eGFR
(b) The new steady state after changing the diet occurs in ~4 months
3. Protein-associated dietary factors affecting progression of CKD
(a) Salt and hypertension [4–6, 41]
(b) Uric acid and hypertension/inflammation [7–9]
(c) Phosphates and kidney injury [10–12, 28, 29]
4. Direct effects of protein intake and progression of CKD
(a) Net acid load and aldosterone/hypertrophy [18–21, 24, 25]
(b) Albuminuria/proteinuria via hyperfiltration [13, 17–23]
(c) Protein-derived nephrotoxins (e.g., indoxyl sulfate) [26, 27]

higher in the content of sodium, uric acid precursors and phosphorus (Table 1).

In particular, the dietary salt influences blood pressure (BP) [4, 5]: a randomized trial compared the short-term effects of dietary salt restriction added to angiotensin-converting enzyme inhibitors (ACEi) and/or angiotensin receptor blockers (ARBs), on proteinuria and BP in CKD stage 1–2 patients; reduction of salt intake to 6 g/day enhances the urinary protein e BP lowering effect of either ACEi and ARBs [6].

Another dietary influence on the degree of kidney damage is uric acid production: high-protein diet is associated with an increase in the risk of raising serum uric acid and the development of gout [7], and these associations are magnified in CKD patients. In experimental models of CKD, a high serum uric acid raises BP and is associated with more intense vascular inflammation [8]. In patients with hypertension, reducing the serum uric acid level with allopurinol can lower BP independently of antihypertensive medications [9].

A third diet-related factor that adversely affects kidney function is a high serum phosphorus concentration: when kidney function is impaired and the diet is rich in protein, serum phosphorus increases to raise the risk of developing secondary hyperparathyroidism [10]. Based upon cumulated data Lau [11] expressed the "precipitation-calcification hypothesis" as the main mechanism of renal damage by phosphorus. According to this hypothesis, the filtered load of phosphorus per renal tubule increases, as a consequence of increased blood phosphate level and increased single nephron GFR, leading to an increased tubular lumen phosphorus burden and concomitant transepithelial phosphate traffic. Sodium, phosphorus and uric acid are also associated with enhanced cardiovascular mortality in CKD [12].

In 1982, Brenner and colleagues [13] proposed that the progression of kidney damage in CKD is directly linked to an increase in glomerular hemodynamics or "hyperfiltration"; the mechanism is similar to the adaptive response that occurs to compensate for the loss of renal mass [14]. For the first time, they showed experimentally that hemodynamic changes associated with kidney damage were reduced by restricting dietary protein [13, 15, 16].

Excess of dietary proteins also increases proteinuria, a surrogate marker for progression of renal disease [17]. The mechanism for increasing proteinuria includes hyperfiltration, but acid can also play a role because a high-protein diet contains precursors of sulfates and phosphates, which increase the release of aldosterone [18–20]. In the presence of proteinuria, increased dietary protein alters glomerular permselectivity [16], increasing urinary albumin loss [21–23] and resulting in a decrease in serum albumin concentration among patients with nephrotic syndrome [23].

Additionally, dietary protein also delivers an increased acid load per nephron providing a non-hemodynamic mechanism promoting renal injury through the induction of endothelin and aldosterone in response to increased nephron ammonia generation [21]. Acid loading may also promote progression of renal disease by increasing the degree of renal hypertrophy [24, 25]. Dietary factors most directly increase the risk of uremic toxin-induced damage to the kidney. Most nitrogen-containing toxins generated by the metabolism of amino acids accumulate because of impaired excretion [26, 27].

Clinical effects of a low-protein diet

The beneficial clinical effects of the protein-restricted diets are largely due to their lower content of sodium, uric acid precursors, potassium and phosphorus.

Phosphorus, which plays a crucial role in the progression of renal disease, has been shown to be an independent risk factor for death in hemodialysis patients. Thus, reducing the phosphorus intake by decreasing dietary proteins may slow the progression of renal disease and may reduce the levels of both phosphorus and parathyroid hormone [28]. It has been evidenced that even a slight actual reduction of protein intake of 0.2 g/kg of body weight per day is sufficient to achieve a significant metabolic improvement of hyperphosphatemia and hyperparathyroidism [3]. Finally, reduced phosphorus intake and serum phosphorus levels can also enhance the effects of a low-protein diet on proteinuria and, likely, CKD progression to renal death [29]. Hypocalcemia is typically associated with CKD. It is due to the reduced intestinal

absorption of calcium and the spontaneously reduced protein intake that occur in patients with progressive renal disorders. Activated vitamin D and calcium supplements should be administered to patients who are following low-protein diets to prevent secondary hyperparathyroidism; the doses should be correlated with actual renal function and protein intake.

It has been shown that the reduction of protein intake in CKD improves the lipid profile by reducing the levels of cholesterol, triglycerides and also lowering lipoprotein AI and the Apo-AI:Apo-B ratio [30]. In the same way, after 3 months of low-protein diet, the insulin sensitivity of patients improved and their fasting serum level, need for daily insulin, blood glucose production were reduced [31].

During the MDRD study, moreover, serum bicarbonate levels increased markedly in both stage 3 and 4 CKD intervention cohorts in association with a reduction in protein intake of 0.2 g/kg body weight/day [32]. A 2007 study by Bellizzi and co-workers [33] showed that BP control improved markedly in patients with CKD on a very low protein diet supplemented with ketoanalogs, while there was no change in the two groups of patients whose protein intake were not modified. The decrease of protein intake of about 30 % was associated with a 28 % drop in sodium intake. Finally, many studies have confirmed that low protein diets have a favorable effect on the rate of urinary protein excretion, and a linear relationship between reduction in dietary protein intake and decrease in proteinuria has been reported in a number of clinical trials [34].

Clearly, success with a protein-restricted diet depends on providing the requirements of different nutrient while regularly assessing nutritional adequacy to avoid malnutrition. The minimal amount of calories required by patients with uncomplicated CKD is 30–35 kcal/kg/day [35].

Protein restriction and progression of renal insufficiency: evidence of the literature

Several evidences in the literature indicate that restricting dietary protein might limit damage and prevent the loss of kidney function (Table 2). As early as the 1930s, Chanutin and colleagues [36, 37] demonstrated that restricting dietary protein protected rat models of CKD against progressive kidney damage: specifically, they found that restricting dietary protein reduced histologic damage and BP while improving the survival of rats with CKD [13, 15, 16]. These experimental results were consistent with

Table 2 Characteristics of studies examining effects of protein-restricted diets

Study (references)	Number of participants	Interventions	Results
Maschio [38]	83	LPD (0.6 g/kg/day) vs unrestricted diet	Slower loss of renal function with LPD
Rosman [41]	247	Protein-restricted diet (0.90–0.95 g/kg/day for GFR 30–60 mL/min; 0.70–0.80 g/kg/day for GFR 10–30 mL/min) vs unrestricted diet	50 % reduction of renal death with protein-restricted diet
Ihle [42]	72	Protein-restricted diet (0.4 g/kg/day) vs unrestricted diet	Reduction of progression to dialysis with protein-restricted diet
Williams [45]	95	LPD (0.6 g/kg/day) vs unrestricted diet	No difference in renal disease progression
NCDS [46]	456	1.0 vs 0.6 g/kg/day	Renal survival slightly increased with 0.6 g/kg/day
Malvy [28]	50	LPD (0.6 g/kg/day) vs VLPD (0.3 g/kg/day) + ketoacids	No difference in renal survival
MDRD [47]	585	Study A: 0.6 vs 1.4 g/kg/day (GFR 25–55 mL/min)	Study A: no difference in GFR decline
		Study B: 0.3 + ketoacids vs 0.6 g/kg/day (GFR 13–24 mL/min)	Study B: GFR decline slower with 0.3 g/kg/day
Menon [50]	255	LPD (0.6 g/kg/day) vs VLPD (0.3 g/kg/day)	VLPD increases risk of death
Cianciaruso [3]	423	Moderate protein diet (0.8 g/kg/day) vs LPD (0.6 g/kg/day)	Better metabolic control with LPD
Cianciaruso [53]	423	Moderate protein diet (0.8 g/kg/day) vs LPD (0.6 g/kg/day)	No difference in risk of death and dialysis initiation
Bellizzi [54]	9610	VLPD (0.3–0.4 g/kg/day) + ketoacids vs no VLPD	Longer survival with VLPD in younger patients (<70 years) and in those without CV disease

LPD low-protein diet, *GFR* glomerular filtration rate, *NCDS* national cooperative dialysis study, *VLPD* very low-protein diet, *MDRD* modification of diet in renal disease, *CV* cardiovascular

reports about small numbers of patients with CKD who benefited from dietary protein restriction [38, 39]. The benefits of protein restriction concern both glomerular hemodynamic and other non hemodynamic processes. Low-protein diets reduce the single nephron GFR, especially by reducing glomerular hypertension that occurs with the loss of functioning nephrons. Moreover, protein restriction decreases profibrotic cytokines, reduces glomerular and tubular growth and can limit plasmatic renin activity.

One of the earliest trials examining the effects of a low-protein diet on the progression of CKD was reported by Maschio et al. [38]. They compared three groups of patients. Groups I and II had initial serum creatinine values (Scr) of 1.6–2.7 and 2.9–5.4 mg/dl, respectively. Both groups were prescribed a diet containing 0.6 g of predominantly high-quality protein per kg, 40 kcal energy intake per kg, 650 mg of phosphorus and 1.0–1.5 g of calcium daily. Group III (initial Scr, 1.6–4.7 mg/dl) consumed an unrestricted diet and served as the control group. Progression was assessed by evaluating changes in Scr. Notably, the loss of renal function in groups I and II was far slower than in group III. In 1989, these same researchers reported results from 390 patients treated with a low-protein diet for 54 ± 28 months [40]. They found that 57 % of the patients had stable Scr values, 11 % had slower deterioration (defined as a decrease in the decline of Scr −1 at a rate exceeding −0.02 but less than −0.04 dl/mg per month), while 32 % had more rapid loss of kidney function (≥0.04 dl/mg per month).

These data were confirmed by Rosman et al. [41] that reported results from 247 patients after 2 or 4 years of protein-restricted diets. Actual protein intake was 0.90–0.95 g/kg/day in patients with GFR values between 30 and 60 mL/min and 0.7–0.8 g/kg/day when GFR values were between 10 and 30 mL/min. Control patients had an unrestricted diet. After 4 years, renal death was markedly improved in those assigned to the more restricted dietary protein (60 vs 30 %, $p < 0.025$), with a good compliance to the diet and no malnutrition signs.

Moreover, Ihle et al. [42] studied 72 Australian patients with advanced CKD for 18 months (initial GFR <15 ml/min) that were randomly assigned to an unrestricted diet or to 0.4 g protein/kg/day. The outcome was evaluated from measurements of GFR. On average, there was no loss of GFR in the low-protein diet group, and fewer patients progressed to dialysis when compared with the unrestricted diet group ($p < 0.005$). Again, patients in low-protein diet reduced their weight, without anthropometric changes or variations in albumin levels. However, it is noteworthy that the conclusion that nutritional status did not deteriorate with protein restriction could be premature, since further more accurate exams may be needed to evaluate the presence of sarcopenia, whose occurrence is increased by the protein restriction [43, 44].

Williams and colleagues [45] studied 95 British patients with CKD for 18 months after randomly assigning them to receive a diet of 0.6 g protein/kg/day and unrestricted dietary protein; a third group received no dietary protein or phosphate restriction. The authors found no differences in the rate of loss of creatinine clearance or in the beginning of dialysis therapy.

The Northern Italian Cooperative Study Group evaluated 456 CKD stage 3–4 patients, assigned for 2 years to a control diet of 1.0 g protein/kg/day or to a diet containing 0.6 g protein/kg/day. The results indicated that "renal survival" was only slightly different; fewer patients in the low-protein diet group reached the predetermined endpoint ($p = 0.059$) [46].

Malvy et al. [28] studied a different diet: restriction to 0.3 g protein/kg/day plus a supplement of ketoacid precursors of essential amino acids (Ketosteril, 0.17 g/kg/day). The control patients were prescribed 0.65 g protein/kg/day. Fifty patients with CKD stage 4–5 (creatinine clearance ≤20 mL/min) were included in the study and they were evaluated for differences in the progression to dialysis or to a creatinine clearance <5 mL/min/1.73 m^2. It was concluded that renal survival was not different between the two groups.

The largest study to date is the modification of diet in renal disease (MDRD) study that examined more than 800 randomly assigned patients for an average of 2.2 years. In this study were evaluated both the effects of diet and the strict control of BP in four groups of patients with CKD stage 3–4 (Study A) or only with CKD stage 4 (Study B). In Study A (GFR 25–55 mL/min/1.73 m^2), the prescribed diets consisted of 1.4 g protein/kg/day compared with 0.6 g protein/kg/day. In Study B (GFR 13–24 mL/min/1.73 m^2), patients were prescribed a diet with 0.6 g protein/kg/day or 0.3 g protein/kg/day plus a ketoacid supplement. No difference in the overall rates of GFR decline was detected in the two Study A groups. The low-protein diet was associated with a faster decline in GFR initially; this was attributed to hemodynamic changes rather than to progressive kidney damage. In Study B, the loss of GFR was somewhat slower in patients prescribed the 0.3 g protein/kg/day diet plus ketoacids than in patients prescribed the diet containing 0.60 g protein/kg/day ($p = 0.07$). The secondary analyses demonstrated that if the rate of loss of GFR is analyzed according to actual protein intake, the outcome was positive because the rate of decline in GFR was strongly related to actual protein intake ($p = 0.011$) as was the number of patients progressing to dialysis or death ($p = 0.001$) [47]. Specifically, reducing dietary protein by 0.2 g protein/kg/day slowed the loss of GFR by 1.15 mL/min/year and reduced renal death by 49 %. Moreover, it

significantly increased bicarbonataemia and reduced blood urea nitrogen and phosphorus.

Shortcomings of the MDRD study have been identified [48, 49]. In the first four months of Study A, a sharp decrease in GFR in the protein-restricted group was related to physiologic reduction in glomerular hemodynamics. Subsequently, the loss of GFR was slowed. Moreover, patients were randomly treated with angiotensin-converting enzyme inhibitors; finally, the duration of the MDRD study was only 2.2 years. A recent long-term follow-up of MDRD patients examining the effect of a very low-protein diet on the development of kidney failure and death showed that assignment to a very low-protein diet did not delay progression to kidney failure, but appeared to increase the risk of death [50].

On the other hand, the study published by Di Iorio et al. [51] evaluated the effect on the requirement of erythropoietin (Epo) in a group of 10 patients, randomly assigned to a ketoanalogues supplemented diet (0.3 g protein/kg/day) vs the use of a diet with a protein intake of 0.6 g/kg/day. The decreased need for EPO could be explained by the reduction of parathormone levels likely due to the modest phosphorus intake with the very low-protein diet, and to the chelating effects on phosphorus of the calcium salts content in the mixture of ketoanalogs.

Recently, a prospective randomized controlled trial (RCT) of Brunori et al. [52] evaluated the efficacy of ketonalog-supplemented diet in elderly patients (>70 years) with CKD stage 5; 112 patients were randomized to two groups: one started dialysis with GFR 5–7 ml/min, while the second started a supplemented diet. The patients in the diet group had started dialysis an average of 10 months after the beginning of the diet; moreover, in this population, morbidity was significantly lower than in patients that started dialysis. Good control of uremic symptoms with this type of diet has allowed to postpone the beginning of dialytic therapy that was started with GFR values of 4.3 ml/min, a value that is lower than what is suggested by current guidelines.

Finally, Cianciaruso et al. [3, 53] compared in a RCT the effects of two diets with different protein content (low- vs moderate protein diet, protein intake 0.55 vs 0.80 g/kg/day) in 423 patients with CKD stages 4–5. During the 18 months of the trial, in patients assigned to the low-protein diet, nine progressed to dialysis or had a doubling of the serum creatinine [3, 53]. Their study represented the first evidence that in CKD patients a protein intake of 0.55 g/kg/day, compared with a 0.8 g/kg/day, guarantees a better metabolic control and a reduced need of drugs, without a substantial risk of malnutrition [3]. However, the low-protein diet did not decrease the risk of death or dialysis therapy initiation compared with the moderate-protein diet [53]. On the contrary, Bellizzi et al. [54] have recently showed that very low-protein diet is associated with longer survival in younger (<70 years) CKD patients and in those without cardiovascular disease.

To increase the number of subjects studied when analyzing protein-restricted diets and progression to kidney failure, a series of meta-analyses have been conducted. The criterion analyzed in RCTs was renal death. The analyses were chosen to reduce biases and to increase the robustness of conclusions. To carry out the meta-analysis, were used the data of 1494 patients (753 in protein-restricted dietary groups and 741 control patients assigned to a higher dietary protein) representative of the entire population reported in previous studies [55]. It was found that there was a 39 % reduction in renal death ($p < 0.001$).

In 2006, were published the results of cochrane meta-analysis which showed that 16 patients should be treated with a low-protein diet (NNT = number needed to treat) to "rescue" a patient per year from the beginning of dialysis and renal death (NNT range: 2–56). This result is better than that reported in the study on the effectiveness of statins in the study 4S (NNT = 30) or in the study of primary prevention WOSCPS (West of Scotland Coronary Prevention study) (NNT = 111) [56].

Fouque and Laville [57] performed a meta-analysis of ten clinical trials, including a total of 2000 randomly assigned non diabetic patients. They concluded that the risk of renal death among patients with stage 3 CKD consuming either a protein intake of 0.6 versus 1.1 g/kg/day was 0.68 [range 0.55–0.84 ($p < 0.001$)].

Conclusions

There is general agreement on the effect of dietary protein restriction on reducing the rate of loss of GFR among most forms of renal injury in humans [58, 59]. There are several potentially injurious pathways that have been well established whereby diets containing high levels of protein should facilitate renal injury [14, 21]. Dietary protein restriction reduces the histological damage and slows the progression of renal disease in experimental animals. Therefore, although high-degree evidence is lacking, it is recommended to start a nutritional treatment in the early stages of CKD.

Conflict of interest The authors declare no conflict of interest

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