J Nephrol (2017) 30:743–754
DOI 10.1007/s40620-017-0435-5

REVIEW

Diet and enteral nutrition in patients with chronic kidney disease not on dialysis: a review focusing on fat, fiber and protein intake

Alice Sabatino[1] · Giuseppe Regolisti[1] · Ilaria Gandolfini[2] · Marco Delsante[2] · Filippo Fani[1] · Maria Cristina Gregorini[3] · Enrico Fiaccadori[1,2]

Received: 28 April 2017 / Accepted: 24 August 2017 / Published online: 7 September 2017

Abstract The clinical data available on dietary requirements of patients with chronic kidney disease (CKD) not on dialysis are limited and largely inconclusive in terms of the renal, cardiovascular and nutritional outcomes achievable through dietary modifications. Restriction of protein intake during the early stages of CKD may in fact slow its progression, but at the same time this approach may also lead to protein-energy wasting, if energy intake is not adequate and properly monitored. Unfortunately, compliance to dietary recommendations is traditionally low in this patient population. A switch from saturated to mono- and polyunsaturated fats is generally recognized as advantageous for cardiac health; however, the benefits in term of renal function are largely unknown. Similarly, the association between dietary fiber intake and kidney disease is largely unknown. In fact, while there is evidence on the positive health effects of dietary fibers in the general population, nutritional guidelines for CKD lack formal recommendations concerning fiber intake. This paper reviews data and evidence from clinical trials and meta-analyses on renal and cardiovascular outcomes related to modifications in protein, fat and fiber intake. Suggestions for maintaining nutritional status through patient-oriented dietary patterns and enteral supplementation in CKD patients on conservative therapy are also presented.

✉ Enrico Fiaccadori
enrico.fiaccadori@unipr.it

[1] Department of Medicine and Surgery, University of Parma, Via Gramsci 14, 43100 Parma, Italy

[2] Postgraduate School of Nephrology, University of Parma, Parma, Italy

[3] Nephrology and Dialysis Unit, Santa Maria Nuova Hospital, Reggio Emilia, Italy

Keywords Chronic kidney disease · Conservative treatment · Enteral nutrition · Nutritional support · Protein energy wasting · Renal diet

Introduction

Dietary factors are not considered to be directly involved in kidney damage, even though dietary habits may significantly influence obesity, diabetes and hypertension, all of them well known risk factors for chronic kidney disease (CKD) [1]. However, even notwithstanding that the prevalence of the early stages of CKD is far greater than the prevalence of end-stage renal disease (ESRD) and stage 5 CKD, and the prevalence of CKD stages 2 to 4 has significantly increased in recent years, more emphasis has been placed by research on investigating the effects of dietary modification during renal replacement therapy (RRT) than on slowing the progression of CKD through dietary interventions in non-dialysis-dependent CKD.

A proper nutritional approach in patients with early stage CKD may significantly improve metabolic alterations, such as metabolic acidosis and hyperphosphatemia/secondary hyperparathyroidism, also positively addressing some of the modifiable risks for CKD progression, including hypertension, proteinuria and hyperglycemia [2, 3].

Worsening of renal function and progression of CKD stage is related to a progressive reduction of nutritional intake as a consequence of taste abnormalities, loss of appetite (anorexia), uremic toxin accumulation, dysregulation of gastrointestinal homeostatic mechanisms, altered blood concentration of appetite regulators and deranged hypothalamic output [2, 3]. Frequently, patients spontaneously restrict their protein and energy intake as a natural response to symptoms caused by uremia, setting the stage for

protein-energy wasting (PEW) [2, 3]. The right amount of protein for patients with CKD on conservative treatment has been discussed in depth in the past, and it is generally agreed that controlled dietary protein restriction may have a positive effect on urinary protein losses and CKD progression [2, 3]. However, little is known about the renal and nutritional effects of different types of dietary fats and dietary fibers. Saturated fats have been strongly linked to cardiovascular disease (CVD) in the general population, and it is well known that n-3 polyunsaturated fatty acids (n-3 PUFAs) and fish oils may reduce the risk of cardiovascular events [4]. Moreover, fiber intake, usually reduced in the diet of CKD patients, may improve bowel function, also reducing blood urea levels and uremic toxin concentrations [5].

In this review we discuss the role of fat, fibers and protein in the diet of CKD patients on conservative treatment, as well as the role of enteral nutrition and supplements in providing nutritional support for patients with PEW. Also, we briefly discuss the role of carbohydrates and the effects of protein-free foods on the diet of CKD patients with diabetes mellitus.

Methods

An extensive review of the English language literature was performed to identify all relevant articles describing the epidemiology, pathogenesis, nutritional intervention and outcome of PEW in non-dialyzed CKD patients. To this end, we searched PubMed, EMBASE™, CINHAL, Web of Science and Cochrane databases for relevant articles. Related search terms were used as follows: "chronic kidney disease", "calorie", "carbohydrates", "compliance", "diabetes mellitus", "diabetic nephropathy", "dietary fiber", "dietary fat", "energy", "enteral nutrition", "guidelines", "inflammation", "intestinal microbiota", "malnutrition", "low-protein diet", "omega-3 fatty acids", "oral supplementation", "proteins", "protein energy wasting", "protein-free foods", "very low protein diet". Medical subject heading terms were used to enhance electronic searches. Additional studies of interest were identified by hand searches of bibliographies. Studies that involved patients <18 years of age, case reports, or conference proceedings were excluded. The search was last updated on June 20, 2017.

Fat intake

CKD is typically characterized by derangements of lipoprotein metabolism, resulting in abnormalities of the serum lipid profile, including reduced high-density lipoprotein (HDL) and increased triglyceride levels [6]. Hence, dyslipidemia is inherent in the CKD population, and while pharmacologic interventions may reduce serum lipids, also replacing saturated with polyunsaturated fats may modulate hyperlipidemia and positively impact renal outcomes. In pre-dialysis patients, a significantly accelerated decline in renal function was associated with serum low-density lipoprotein (LDL) levels >2.50 mmol/l, an increase in serum triglyceride levels and a HDL/LDL ratio <0.4 [7]. Similarly, either lower or higher total cholesterol and increased LDL were associated with renal function decline in CKD stages 3 to 5 [8].

Modification of fat intake and recommendations

The Mediterranean and other similar diets that have a high content of polyunsaturated fatty acids (PUFA) and a low content of saturated fats have been touted as beneficial in preventing ischemic heart disease, as well as reducing overall morbidity and mortality [9]. In pre-dialysis patients, a Mediterranean diet improved dyslipidemia and provided protection against lipid peroxidation and inflammation [10], and a greater adherence to this diet independently predicted survival in CKD patients (glomerular filtration rate, GFR <60 ml/min/1.73 m^2) [11]. In healthy elderly subjects, higher intakes of PUFA were associated with a lower age-related decline in estimated (e)GFR [12], and in a cohort of 2600 adults the likelihood of having CKD (GFR <60 ml/min/1.73 m^2) was significantly reduced when a diet rich in n-3 PUFA was consumed [13]. Similar results were found in another cohort of 5316 adults [14], again suggesting a renal protective effect of n-3 PUFA rich diets.

There are no randomized trials on the modification of dietary fat intake in the CKD population and on its effect on renal outcomes, cardiovascular disease and inflammation. The Kidney Disease Improving Global Outcomes (KDIGO) guidelines recommend therapeutic lifestyle changes (TLC) in the presence of important hypertriglyceridemia [15], while earlier guidelines were more focused on prevention [16–19] (Table 1). The KDIGO Work Group on CKD suggested that, in the management of risk factors such as dyslipidemia, patients with CKD should be considered to be in the highest risk category, i.e. equivalent to that of patients with known coronary heart disease [15]. In general, substituting high-fat animal derived foods with lean meat, poultry, fish and low-fat dairy products will have little adverse effect on serum potassium and phosphorus of CKD patients on conservative treatment. However, attention should be paid in recommending the consumption of nuts, some sources of vegetable proteins (soy and beans) and certain sources of soluble fiber since this may have a role in the development of hyperkalemia, especially in later stages of CKD [20]. Several guidelines recommend 2–3 servings of fatty-fish per week to increase n-3 fatty acid (FA) intake [20]. Limited data show beneficial effects of supplementation of n-3 FA on proteinuria, and consequently on the progression of the

Table 1 Daily dietary fat recommendations in non-dialyzed chronic kidney disease

Guideline	Recommendation
KDIGO Clinical Practice Guideline for Lipid Management in Chronic Kidney Disease [15]	High serum triglyceride levels: low fat intake (<15% of total calories), reduced monosaccharide and disaccharide intake, reduced total amount of dietary carbohydrates, fish oils to replace some long-chain triglycerides
ESPEN Guidelines on Enteral Nutrition: Adult Renal Failure [16]	Normal distribution between lipid and carbohydrate (30 and 55–60%, respectively); emphasis on unsaturated fatty acids For hypercholesterolemia: ≤30% of energy as fat, saturated fatty acids <10% of total calories, monounsaturated fatty acid > 10%, dietary cholesterol intake <300 mg/day
Australian and New Zealand Renal Guidelines Taskforce [17]	Stage 3–4: fat intake <30% of daily energy intake, saturated fat intake <10% of daily energy intake Stage 5: saturated fats <7%, polyunsaturated fat ≤10%, mono-unsaturated fat ≤20% of daily energy intake
Australian KHA-CARI Guidelines [18]	Mediterranean-style diet to reduce dyslipidemia and protect against lipid peroxidation and inflammation
Diabetic patients with chronic kidney disease	
KDOQI Clinical Practice Guidelines and Clinical Practice Recommendations for Diabetes and Chronic Kidney Disease [19]	30% fat: 5% saturated, 5% omega-6, 10% omega-3, 10% omega-9

renal disease [21–25]. A markedly reduced risk of sudden cardiac death during the first year of dialysis, which usually is characterized by a very high cardiovascular mortality risk, was associated with the presence of higher levels of long-chain n-3 PUFA docosapentaenoic acid (DPA), but not eicosapentaenoic acid (EPA) or docosahexaenoic acid (DHA) [26]. Randomized controlled trials investigating the beneficial effects of n-3 PUFA supplementation on cardiovascular risk found a reduction in triglyceride levels in the intervention group [27–29].

A reduction in inflammation may contribute to slowing the progression of CKD. The n-3 PUFAs EPA and DHA act through multiple interconnected mechanisms to reduce production of inflammatory eicosanoids and cytokines, while enhancing production of counter-inflammatory and modulatory substances such as resolvins and protectins. In this way, n-3 PUFA act to oppose the pro-inflammatory actions of saturated fatty acids and n-6 PUFA [30]. While a high intake of n-6 PUFAs, especially arachidonic acid, could contribute to inflammatory processes and possibly predispose to, or exacerbate, inflammatory diseases, long-chain n-3 PUFAs supplementation may promote an anti-inflammatory action [30]. A prospective observational study on hemodialysis patients found an association between higher dietary n-6 to n-3 PUFA ratio with both worsening inflammation over time and a trend towards higher mortality risk [31]. Available randomized trials studying the effects of n-3 PUFA supplementation on inflammatory markers are scarce, but promising [32, 33]. In these studies, n-3 PUFA supplementation in non-dialyzed CKD patients was associated with a reduced pro-inflammatory adipose tissue gene expression [32], and significantly reduced the increase in interleukin (IL)-1β, an important mediator of the inflammatory response [33].

Dietary fiber

Health benefits of dietary fiber

Based on consistent data, the American Dietetic Association concluded that dietary fiber intake from whole foods or supplements may lower blood pressure, improve serum lipid levels, and reduce indicators of inflammation [34]. An inverse association between both total dietary fiber and insoluble fiber with cardiovascular disease was demonstrated in a systematic review [35], and fiber intakes of 12 to 33 g/days from whole foods or up to 42.5 g/days from supplements were associated with protective cardiovascular effects [34].

Dietary fiber and renal outcomes

At the present time, the only way to reduce uremic solutes levels in ESRD is by RRT. However, recent data suggest that also dietary interventions could have, at least partially, a similar effect by a different mechanism, i.e. by reducing the intestinal generation of these molecules [36]. Dietary fiber may reduce serum urea levels, due to increased intestinal nitrogen excretion. A diet lacking in fiber, by contrast, could increase the intestinal production of uremic molecules, such as p-cresol, indoxyl-sulphate, trimethylamine-N-oxide (TMAO), secondary to increased proteolytic activities by protein fermenting bacteria [36].

The effect of dietary fiber on serum urea and creatinine in CKD has been recently evaluated in a meta-analysis [5]. In the primary pooled analysis of 173 patients (of which 74 were on hemodialysis), dietary fiber was shown to significantly reduce blood urea nitrogen (BUN) levels; serum creatinine was significantly reduced in the overall analysis. The authors found a significant dose–response effect of fiber intake in reducing serum creatinine concentration. A shift in nitrogen excretion from the urinary route to the digestive route, with a significant decrease in serum urea concentration, was reported with fermentable carbohydrate supplementation in a small group of patients started on dialysis [37].

Decreasing the ratio of acid-forming to alkali-forming proteins may be kidney-protective. In a study comparing the effects of reduced dietary acid load with added oral $NaHCO_3$ or alkali-forming fruits and vegetables on urine parameters of CKD patients stage 1 or 2 [38], the fruits and vegetables regimen comparably improved renal function in stage 2, but not in stage 1 CKD patients. Furthermore, dietary acid load reduction by a fruits and vegetables diet (but not by sodium bicarbonate) was accompanied by a significant decrease in systolic blood pressure (BP), and by a significant decrease in body weight in both groups. No significant increase in serum potassium levels was observed in patients on fruits and vegetables regimen. Using a similar study design, stable eGFR values and lower levels of urinary markers of kidney injury have been reported after one year of fruits and vegetables or sodium bicarbonate in CKD stage 4 patients [39].

Despite the known healthy value of dietary fiber, whole grain foods, legumes, fruits and vegetables are often restricted in more advanced stages of CKD, in order to prevent or correct hyperkalemia and hyperphosphatemia. Dietary fiber may also improve bowel movements: in a small interventional study, 16 patients with stage 3 to 5 CKD consumed fiber-added (23 g/days) cereal, cookies and snack bars for 4 weeks. The addition of fiber provided a significant increase in stool frequency as compared to the pre-intervention period and significantly decreased total cholesterol with an improved total cholesterol to HDL ratio [40].

An inverse relationship has been proposed between dietary fiber and systemic inflammation. The analysis of dietary fiber intake and mortality in a subset population of the National Health and Nutrition Examination Survey (NHANES) III with and without CKD showed that for each 10 g/day increase in total fiber intake, the odds of elevated serum C-reactive protein (CRP) levels decreased by 38 and 11% respectively [41]. Moreover, while total fiber intake was not significantly associated with mortality rate changes in the normal population, it was inversely related to mortality risk in CKD, thus suggesting a stronger role of dietary fiber in lowering inflammation in patients with CKD as a potential mechanism for the lower mortality in CKD versus non-CKD populations.

Dietary fiber intake in non-dialyzed CKD patients

Few clinical trials have reported on dietary fiber intake or have evaluated the optimal daily fiber requirements in non-dialyzed CKD patients. A study on 113 CKD patients assessed dietary fiber intake using a 4-day dietary journal [42] and showed that 80% of patients underreported their food intake, which could have influenced the observed intake of fibers. Indeed, in the total sample, mean fiber intake was lower than recommended (26–38 g/day of fibers in adults >18 years old) but it was within the recommended range in valid reporters (19.8 ± 8.9 g/day for all patients versus 28.0 ± 10.2 for valid reporters) [42]. In another study [41], 56.4% of CKD patients reported a fiber intake of <14.5 g/day (mean 9.6 ± 3.7) and 43.6% an intake ≥14.6 g/day (mean 22.7 ± 7.7).

Recommendations for dietary fiber intake

Few professional guidelines provide a reference to fiber intake for patients with CKD. Recommendations for fiber intake are summarized in Table 2. The KDIGO Clinical Practice Guidelines for Diabetes and CKD recommended that 40–45% of calories from carbohydrates should come from whole grains, fruits and vegetables [43] and the Kidney Disease Outcomes Quality Initiative (KDOQI) Guidelines on Dyslipidemia recommend 20–30 g/day of fiber [44]. The European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines emphasized the inclusion of fiber-rich foods in the diet [16] and the Australian Kidney Health Australia - Caring for Australasians with Renal Impairment

Table 2 Recommendations for dietary fiber intake

Guideline	Fiber intake recommendations
KDIGO Clinical Practice Guidelines for Diabetes and CKD [43]	40–45% of calories from carbohydrates should come from whole grains
KDOQI Guidelines on Dyslipidemia in CKD [44]	20–30 g of fiber
ESPEN [16]	Inclusion of fiber-rich foods in the diet
Australian KHA-CARI [18]	Balanced diet, rich in fruits and vegetables

CKD chronic kidney disease

(KHA-CARI) guidelines recommended a balanced diet, rich in fruits and vegetables [18].

Proteins

The positive clinical effects of a low protein diet are not only related to the control of uremic symptoms, reduction in proteinuria and hyperfiltration, but also to its lower sodium, inorganic acid and phosphorus content. No other topic in the realm of managing pre-dialysis CKD patients has been as widely and controversially discussed as when to initiate protein restrictions and with how much protein. Despite controversy over risk versus benefit, professional guidelines generally advocate a low protein diet (LPD; 0.6–0.8 g protein/kg/day) for CKD stages 3 and 4 (Table 3) [2, 16, 18–20, 45–48]. As renal function declines, so does spontaneous protein intake [49], with increased risk of PEW. Unsupervised LPD may lead to PEW which is associated with poor outcomes in terms of future morbid events, progression of renal disease and mortality in pre-dialysis CKD patients [50].

Protein intake and CKD outcomes

Favorable renal outcomes have been reported with LPD. Some guidelines go further and recommend very-low protein diets (VLPD, 0.3 g/kg/day) for patients with eGFR <25 ml/min/1.73 m^2 [16, 45], while the NICE guideline does not recommend giving less than 0.6 g/kg/day of protein for any GFR level. Available data show that in patients with moderate-to-advanced CKD, VLPD supplemented with ketoacids may improve several metabolic abnormalities, including net urea generation (by decreased amino acids degradation and urea synthesis), hyperphosphatemia, metabolic acidosis, hyper-parathyroidism and dyslipidemia [51–53], also contributing to a better control of proteinuria, blood pressure and hemoglobin [54–57], without compromising nutritional status [58, 59]. Although this dietary treatment does not reduce the decline in GFR, it delays the beginning of dialysis by 1–2 years by helping to manage symptoms [60–62]. Despite inconclusive data regarding the role of LPDs in slowing down CKD progression, the main role of this type of diet in more advanced stages of CKD is to control metabolic abnormalities of CKD. Even a slight reduction in protein intake of 0.2 g/kg/day may significantly improve the uremic state, metabolic acidosis and hyperphosphatemia [63]. Indeed, the protein prescription of 0.6 g/kg/day compared with a 0.8 g/kg/day protein diet allows a better control of hyperparathyroidism and metabolic acidosis, even if adherence to the diet is incomplete [64].

The NKF-KDOQI guidelines on hypertension and antihypertensive agents in CKD [44] recommend that patients with a GFR >60 ml/min/1.73 m^2 should follow the Dietary Approaches to Stop Hypertension (DASH) diet [65–67]. The DASH diet emphasizes fruits, vegetables, and low-fat dairy products, includes whole grains, poultry, fish, and nuts, and contains only small amounts of red meats, sweets, and sugar-containing beverages; it has decreased amounts of total and saturated fat and cholesterol and moderate amounts of proteins. The magnitude of blood pressure reduction in the hypertensive subgroup was 8–10 mm Hg lower in those

Table 3 Daily dietary protein recommendations in nondialyzed patients with chronic kidney disease

Guideline	Protein intake recommendation
ESPEN Guidelines on Enteral Nutrition: Adult Renal Failure [16, 45]	0.55–0.6 g protein (2/3 HBV)/kg/day if GFR is 25–70 ml/min 0.55–0.6 g/kg/day (2/3 HBV) or ~0.3 g/kg/day supplemented with EAA or EAA/KA if GFR is <25 ml/min
NKF/KDOQI Clinical practice guidelines for nutrition in chronic renal failure [46]	0.60 g/kg/day, carefully designed, if GFR <25 ml/min ≤0.75 g/kg/day if adherence an issue ≥50% of protein of HBV
Australian KHA-CARI Guidelines [18]	0.75–1.0 g/kg/day for all patients
International Society of Renal Nutrition and Metabolism [2]	Stage 3–5: 0.6 and 0.8 g/kg/day in the absence of signs of malnutrition, ≥50% of protein of HBV, +1.0 g/kg/day in the presence of illness
National Institute for Health and Care Excellence [47]	Do not offer low-protein diets (dietary protein intake less than 0.6–0.8 g/kg/day) to people with CKD
NKF/KDOQI Guidelines on Hypertension and Antihypertensive Agents in CKD [48]	Stages 1–2: 1.4 g/kg/day (~18% of calories) Stages 3–4: 0.6–0.8 g/kg/day (~10% of calories)
Diabetic patients with chronic kidney disease	
KDOQI Clinical Practice Guidelines and Clinical Practice Recommendations for Diabetes and Chronic Kidney Disease [19]	0.8 g protein/kg/day and ≤20% of total Kcal
Canadian Diabetes Association guidelines [20]	0.8 g protein/kg/day Avoidance of intakes >1.3 g protein/kg/day

EAA essential amino acids, *GFR* glomerular filtration rate, *HBV* high biological value, *KA* keto analogues, *NKF/KDOQI* National Kidney Foundation-Kidney Disease Outcomes Quality Initiative Guidelines

who consumed the DASH diet compared to the control diet [67], and was similar to the reduction obtained by pharmacological therapy in other trials. However, unrestricted protein intake in the face of a decreased number of functioning nephrons may lead to increase in glomerular capillary pressure, resulting in single-nephron hyperfiltration [68]. These hemodynamic changes may contribute to glomerulosclerosis. This results in a further reduction of functioning nephrons, setting up a vicious cycle which culminates in ESRD. In fact, a 32% relative risk reduction in renal death in favor of a LPD over a higher protein intake was identified in a meta-analysis of 2000 patients [69]. In otherwise healthy females, those with mildly reduced renal function (eGFR >55 but <80 ml/min per 1.73 m^2) had a significant reduction in eGFR per each 10-g increase in protein intake over an 11-year period compared to women with normal renal function [70]. To avoid hyperfiltration and the worsening of proteinuria, a normalization of the diet based on current guidelines for the general population (0.8 g/kg/day) should be implemented in the early stages of CKD. High protein intake was also associated with worsening GFR compared to moderate and low protein intake in non-dialyzed stage 3 to 5 CKD patients [71].

The problem of simultaneously adhering to a LPD and achieving calorie requirements is common in patients with CKD, despite availability of professional nutritional counseling. Supplementation with essential amino acids allows the intake of lower quality protein, better palatability, and a broader choice of foods [72]. Other forms of supplementation of LPDs are based on the use of special protein-free foods. Today these products are usually available as pasta, cookies, bread and flour but also as precooked soups and desserts and represent a very valuable resource for optimal low-protein dietary management of CKD, allowing high energy intake with no phosphate, protein and a lower sodium burden.

Recommendations for dietary protein intake

Differences in study inclusion criteria, outcome measurements, type of protein ingested as well as issues in dietary adherence make it difficult to draw firm conclusions on the association between protein intake and clinical outcomes [73]. Despite the available clinical evidence suggesting that LPD, if closely monitored, is not only not harmful but in many cases can be beneficial for CKD patients, still some guidelines do not recommend LPD for the conservative treatment of CKD [18, 47] because of the risk of malnutrition. However, literature data show that, provided there is an adequate energy intake, malnutrition should not be a problem [58, 59]. Actually, a recent consensus from Italy addressed this concern, suggesting that LPD with adequate caloric intake should be implemented in stage 3–5 CKD patients in order to maintain a satisfactory nutritional status and to delay renal replacement therapy start [74]. Several guidelines recommend at least 50% of the ingested protein to be of high biologic value, or contain a high percentage of essential amino acids to ensure net neutral nitrogen balance [73]. Recommendations on dietary intake of protein are summarized in Table 3.

Considerations on carbohydrate intake in CKD

Excess fructose consumption, such as that found in table sugar (sucrose) or sugar sweetened beverages, is considered to promote features of metabolic syndrome, including insulin resistance, dyslipidemia, and hypertension - factors that are also associated with an increased risk of CKD [75, 76]. Also, fructose metabolism promotes uric acid production, another factor related to CKD onset and progression [75, 77, 78]. Other experimental studies also suggest that fructose metabolism may have a direct role in kidney injury by increasing the production of reactive oxygen species (ROS) and chemokines [79, 80]. Dietary fructose is very prevalent in the diet due to excess use of added sugar, industrialized pre-cooked meals, and soft drinks, and represents another modifiable dietary factor that could prevent or delay CKD progression.

A systematic review of controlled feeding trials found that uric acid production was increased only when fructose was given as 35% excess energy to non-diabetic participants, but not when fructose was used to isocalorically substitute other carbohydrate sources [81]. This suggests that the negative effect of fructose on serum uric acid only occurs when it is given as excess energy intake of energy requirements. Few studies have investigated fructose consumption in patients with CKD [82]. In this pilot study, a diet with a restricted content of fructose for 6 weeks (12 g/day in comparison to 60 g/day that was their normal diet) found no effects on GFR, proteinuria, serum or urinary uric acid. However, a significant reduction in inflammatory markers such as high-sensitivity (hs)CRP and intercellular adhesion molecule (ICAM)-1 was found, suggesting that reducing dietary fructose in moderate CKD may have some positive effect on the inflammatory status of patients. Further controlled trials are required to ascertain the relationship between dietary fructose intake and serum uric acid levels, and whether there is a safe level of fructose consumption.

Diabetic patients with CKD

Diet and lifestyle modifications are the core of diabetes mellitus (DM) care. An optimal nutritional approach is able to keep blood glucose within acceptable ranges, helps the management of blood lipids, may control body weight and reduce the incidence and progression of DM associated vascular complications, including CKD. One important

characteristic of diabetic nephropathy is the presence of proteinuria, and for those patients the restriction of sodium and protein should be considered a routine approach [83, 84].

Available guidelines still do not recommend conventional LPDs (0.6 g protein/kg/day) for diabetic patients with CKD [20] (Table 3), since the benefits of LPD for diabetic nephropathic patients have long been debated [85]. A recent study in 74 older adults with type 2 diabetes mellitus (T2DM) and moderate CKD (stages 3b and 4) demonstrated that the adherence to a LPD regimen slowed CKD progression by 42% [84]. In addition, this beneficial effect was also associated to improvement of oxidative stress, inflammation and proteinuria with no negative effect on blood glucose levels and nutritional status [84]. Furthermore, a significant improvement in GFR with a LPD was concluded from a meta-analysis of 13 studies including 779 diabetic CKD patients [83].

In contrast, according to a Cochrane review, reducing protein intake in patients with T1DM or T2DM for at least four months appears to slightly slow progression to renal failure, even though the results were not statistically significant [86]. Slowing of CKD progression in T1DM but not T2DM patients was reported in a recent meta-analysis of 15 studies including 1965 patients achieving a mean protein intake of 0.83 g/kg/day [87]. Another meta-analysis similarly found no significant association between changes in GFR and LPD in patients with T1DM or T2DM and CKD, although a significant decrease in proteinuria or albuminuria was observed in the LPD group [61]. The most recent observational study with the largest cohort of diabetic CKD patients (n = 149) concluded that moderate (0.6 g/kg/day) LPD is safe in diabetic patients and may play a role in delaying the initiation of dialysis, with no difference between T1DM and T2DM [88].

As kidney function declines, food choices and portions must be adjusted to meet the required restrictions in phosphorus, potassium and protein. Diets high in fiber and low in glycemic index are also commonly high in potassium and phosphorus. Nevertheless, a higher fiber intake and the use of low-glycemic index foods should be encouraged within the constraints of the CKD stage. A fiber intake between 15 and 25 g/1000 Kcal/day should be encouraged [20]. Low potassium fruits and vegetables, such as pears, apples, berries and green beans can be recommended, and those unable to achieve the targeted fiber intake through the diet could add natural tasteless fiber supplements to their food or drink. While not on a LPD using protein-free foods, choosing cereals with lower glycemic index should be encouraged, such as parboiled rice, “al dente” pasta, cracked wheat and sourdough breads. Generally, the carbohydrate content of a LPD is at least 60% of total energy [89]. Protein-free foods are the main contributors to the carbohydrate content of diets because they represent a source of energy free from nitrogen and very low in potassium and phosphorus. Possible negative effects on the glycemic control of diabetic patients have been counteracted by improving the nutritional content of these products. The fiber content is significantly higher, which reduces the glycemic index of the products and allows the implementation of LPDs for diabetic patients with minimal effect on serum glucose levels.

Enteral supplementation

Since the risk of malnutrition increases in parallel to renal function worsening and the need for more restrictive diets, frequent monitoring of patients is essential. Unsupervised LPDs have been shown to be deleterious since patients tend to reduce also total energy intake [90]. On these grounds, an early and regular dietary counseling still represents the first step for the prevention and treatment of PEW in CKD. When dietary counseling is not sufficient to achieve planned nutritional requirements oral nutritional supplements (ONS) or supplementary enteral nutrition (EN) can be prescribed. Specialized ONS for CKD patients taken twice a day can add up to 10 Kcal/kg/day with minimum protein content over spontaneous intake, favoring the achievement of nutritional targets. In patients with severe PEW, spontaneous intakes less than 20 Kcal/kg/day, stress conditions and/or with major swallowing difficulties, the use of EN as nocturnal supplementation or complete daily nutritional support should be preferred [3].

According to ESPEN guidelines, the goals of enteral nutrition in adult renal failure are prevention and treatment of undernutrition, correction of uremic metabolic disturbances, prevention of electrolyte disturbances, attenuation of CKD progression through restriction of protein and phosphate, and preservation of intestinal mucosal integrity and function [45]. PEW prevalence in this population is estimated between 20 and 45% [3], and 1 in 5 patients with CKD stages 4 to 5 will develop PEW before the initiation of dialysis [90]. Furthermore, the presence of PEW at the initiation of dialysis is predictive of future mortality risk [46].

A neutral or positive nitrogen balance requires adequate protein and energy intake, since low-energy intakes may lead to PEW. Dietary protein and energy intakes of 0.6–0.8 g/kg/day and 30–35 Kcal/kg/day, respectively, should preserve protein stores [2, 3]. Loss of appetite, however, is associated with the uremic syndrome and deterioration of renal function is directly correlated with a decrease in food intake. In addition to a reduction in oral intake, PEW also may be caused by restrictive dietary regimens, gastrointestinal factors, metabolic acidosis, inflammation and endocrine factors [45].

Exploration of the association between frailty and CKD has recently gained research interest. Unintentional weight loss is one of the signs of frailty. Frailty was approximately twice as likely in persons with mild or early-stage CKD versus those without CKD and the odds of frailty were inversely related to eGFR; one-fifth of persons with an eGFR <40 ml/min/1.73 m^2 were frail [91]. The prevalence of frailty was

14% higher in middle-aged [92] and 15% higher in elderly [93] non-dialyzed CKD patients versus matched populations with normal renal function. All three aforementioned studies found higher mortality in frail persons with CKD versus their healthy counterparts. Oral nutrition supplementation, or tube feedings, might represent possible interventions to optimize nutrient intake in frail patients whose lack of energy may affect procuring and preparing food.

ESPEN recommends initiating enteral nutrition to optimize nutrient intake in undernourished CKD patients or if adequate oral intake cannot be achieved. Disease-specific and hypercaloric oral supplements are low in protein, sodium, potassium and phosphorus content; thus they can help the management of CKD in order to prevent malnutrition [1, 3, 45].

Adherence

Adherence is a multifaceted process influenced by human experience since it is impacted by societal, economic and personal factors, including education level, interaction with healthcare providers and the clinical care setting. The scope and complexity of adhering to dietary prescriptions in CKD presents many challenges to patients. The overwhelming volume of dietary information coming from various sources can make it difficult for patients to comply with a dietary plan meeting individual needs. The Internet has a plethora of both factual and factious dietary recommendations. Confusion arising from discrepancies between information provided at nutrition counseling and via informal communication pathways may lead the patient to make independent decisions on what and how much to eat.

Adherence to a special diet, which can be considered therapy in CKD, affects not only the types of foods eaten but also meal preparation practices. Few studies have evaluated positive or negative factors affecting adherence in predialysis CKD patients. The availability of specially manufactured low-protein foods was positively related to adherence [94] and male gender was associated with higher adherence to either a LPD or a modified protein diet [64]. A lack of proper nutrition counselling is usually associated with non-adherence in terms of over-consumption of protein in non-dialyzed CKD patients prescribed a LPD.

Recommendations for improving adherence

Providing different choices and strict control over what is eaten, rather than restrictions, might provide greater freedom to eat more normally. Although not a pre-defined outcome, adherence was high with a simplified vegetarian LPD supplemented with alpha-keto analogues allowing 1–3 free-choice meals per week [95, 96]. Dietary restrictions, especially those for LPD, should be accompanied by counseling on alternative food choices [46]. Individualized nutrition counseling has a positive effect on overall nutritional status [97], improves measures of quality of life [97] and enhances the reduction in protein intake [98]. In contrast to patients provided only with general information before being started on a moderate LPD, adherence was higher in patients provided with a list of specific tips for modifying their diet [99]. It may be possible to maintain adequate caloric intake during an LPD by providing non-protein supplements. Significant reduction in urine urea excretion without reduction of caloric intake has been demonstrated in non-dialyzed patients taking a daily non-protein calorie supplement [100].

Conclusions

The evidence for improving patient outcomes through nutritional interventions is primarily based on small randomized clinical trials providing low level of evidence. This means there is inconclusive evidence regarding when to begin, the range of protein restriction, and the effects of LPD on slowing renal failure. Soundly designed randomized controlled studies with definitive renal endpoints need to be conducted to identify and confirm any possible relationship between level and duration of protein intake and renal outcomes.

A meaningful reduction of cardiac risk may be difficult to achieve with diet in this population. While evidence exits to support the benefits of switching from unsaturated to mono- and polyunsaturated fat, studies to date in the non-dialyzed CKD population are inconclusive and contradictory. Studies evaluating benefits achieved from n-3 PUFA in the general population, such as decreasing triglycerides, documenting vascular and cardiac hemodynamics, and lowering serum total and LDL cholesterol, should be replicated in the non-dialyzed CKD population.

Fiber seems to be the forgotten macronutrient in dietary management of non-dialyzed CKD patients. While the literature is vast regarding the health benefits of fiber for the general population, few professional guidelines have established an adequate daily fiber intake. Little is known about actual fiber intake, but indications are that lower intakes in non-dialyzed CKD patients are likely related to restrictions to prevent or correct hyperkalemia. Low-level evidence exists on fiber lowering serum urea and creatinine and on a protective effect against inflammation in CKD. A strict vegetarian diet rich in fiber may not appeal to all patients, but a diet based on vegetables and fruits is safe and possibly beneficial for patients with CKD, increasing food choices and palatability.

A thorough assessment of the CKD patient should include data on eating habits and patterns with family members in attendance. Efforts to correct nutritional deficits should begin early in the disease process and be tailored to individual tastes, cultural traditions, food procurement and

preparation capabilities, and possibly economic standing. Re-assessment of nutritional status should be conducted as CKD progresses to identify changes in comorbidities, appetite and psychosocial well-being. Strict dietary restrictions may cause unintended outcomes and should be avoided. ONS or enteral nutrition, with the goal of achieving optimal nutritional status, might be a viable option in some cases.

Patients of all ages are increasingly becoming 'tech savvy'. New technologies, such as wearable sensors and their accompanying apps, as well as interactive nutrient calculators for mobile devices, provide anywhere/anytime information to guide food choices. Nephrology and nutrition expertise is required to aid development of these digital-based information sources.

Patients with CKD on conservative treatment comprise an increasingly larger proportion of the CKD population. Yet, research on the dietary needs of this group has been neglected. A summary of the recommendations is available in Appendix Box 1. Future research should be aimed at investigating the relationship between diet and outcomes specific to this group.

Acknowledgements We thanks Mrs Carol Krcmar, RN MN for collaboration.

Compliance with ethical standards

Financial disclosure None declared.

Conflict of interest The author declares that there is no competing interest.

Ethical approval This article does not contain any studies with human participants performed by any of the authors.

Appendix

Box 1 Summary of recommendations

	Recommendation	Why?
Lipids intake	Fat intake based on the Mediterranean diet Avoid saturated fatty acids, preference for food containing PUFA Encourage the use of omega 3 PUFA rich foods Encourage the use of olive oil, rich in monounsaturated fatty acids	To improve cardiovascular health Manage dyslipidemia
Fiber intake	Intake of 20–30 g/day Encourage the use of whole grain foods, legumes, fruits and vegetables	Management of dyslipidemia Control of uremia and metabolic acidosis Improve GI function Glycemic control for diabetic patients
Protein intake	LPD (0.6 g/kg/day) for moderate to advanced stages of CKD Do not give >1 g/kg/day in early stages of CKD Use of protein-free foods to improve energy intake and avoid PEW	Manage uremic symptoms and delay the initiation of dialysis Avoid hyperfiltration
Carbohydrate	Limit use of fructose-containing foods and drinks	Limited evidence shows an increase in uric acid production and renal damage
Oral/enteral supplementation	Use specialized formulae for patients with CKD Target to achieve a total intake >25 Kcal/kg/day and 0.6 g/kg/day of proteins Prefer total/nocturnal enteral nutrition when spontaneous intake <20 Kcal/kg/day and in the presence of swallowing difficulties	Prevention of PEW when nutritional counseling is not successful Treatment of PEW

CKD chronic kidney disease, *GI* gastrointestinal, *LPD* low protein diet, *PEW* protein energy wasting, *PUFA* polyunsaturated fatty-acids

References

1. Kalantar-Zadeh K, Cano NJ, Budde K et al (2011) Diets and enteral supplements for improving outcomes in chronic kidney disease. Nat Rev Nephrol 7:369–384
2. Ikizler TA, Cano NJ, Franch H et al (2013) Prevention and treatment of protein energy wasting in chronic kidney disease patients: a consensus statement by the International Society of Renal Nutrition and Metabolism. Kidney Int 84:1096–1107
3. Sabatino A, Regolist G, Karupaiah T et al (2017) Protein energy wasting and nutritional supplementation in patients with end-stage renal disease on hemodialysis. Clin Nutr 36:663–671
4. Mozaffarian D, Wu JHY (2011) Omega-3 fatty acids and cardiovascular disease: effects on risk factors, molecular pathways and clinical events. J Am Coll Cardiol 58:2047–2067
5. Chiavaroli L, Mirrahimi A, Sievenpiper JL, Jenkins DJA, Darling PB (2014) Dietary fiber effects in chronic kidney disease: a systematic review and meta-analysis of controlled feeding trials. Eur J Clin Nutr 69:761–768

6. Vaziri ND, Moradi J (2006) Mechanisms of dyslipidemia of chronic renal failure. Hemodial Int 10:1–7
7. De Goeij MCM, Rotmans JI, Matthijssen X, de Jager DJ, Dekker FW, Halbesma N (2015) Lipid levels and renal function decline in pre-dialysis patients. Nephron Extra 5:19–29
8. Rahman M, Yang W, Akkina S et al (2014) Relation of serum lipids and lipoproteins with progression of CKD: the CRIC study. Clin J Am Soc Nephrol 9:1190–1198
9. Sofi F, Cesari F, Abbate R, Gensini GF, Casini A (2008) Adherence to Mediterranean diet and health status: meta-analysis. BMJ 337:a1344
10. Mekki K, Bouzidi-Bekada N, Kaddous A, Bouchenak M (2010) Mediterranean diet improves dyslipidemia and biomarkers in chronic renal failure patients. Food Funct 1:110–115
11. Huang X, Jiménez-Moleón JJ, Lindholm B et al (2013) Mediterranean diet, kidney function, and mortality in men with CKD. Clin J Am Soc Nephrol 8:1548–1555
12. Lauretani F, Semba RD, Bandinelli S et al (2008) Plasma polyunsaturated fatty acids and the decline of renal function. Clin Chem 54:475–481
13. Gopinath B, Harris DC, Flood VM, Burlutsky G, Mitchell P (2011) Consumption of long-chain n-3 PUFA, α-linolenic acid and fish is associated with the prevalence of chronic kidney disease. Br J Nutr 105:1361–1368
14. Yuzbashian E, Asghari G, Mirmiran P, Hosseini FS, Azizi F (2015) Associations of dietary macronutrients with glomerular filtration rate and kidney dysfunction: Tehran lipid and glucose study. J Nephrol 28:173–180
15. Kidney Disease: Improving Global Outcomes (KDIGO) Lipid Work Group (2013) KDIGO clinical practice guidelines for lipid management in chronic kidney disease. Kidney Int Suppl 3:259–305
16. Toigo G, Aparicio M, Attman P-O et al (2000) (ESPEN) Expert Working Group report on nutrition in adult patients with renal insufficiency (part 1 of 2). Clin Nutr 19:197–207
17. Ash S, Campbell K, MacLaughlin H et al (2006) Evidence based guidelines for the nutritional management of chronic kidney disease. Nutr Diet 63:S35–S45
18. Johnson DW, Atai E, Chan M et al (2013) KHA-CARI guideline: early chronic kidney disease: detection, prevention and management. Nephrology 18:340–350
19. National Kidney Foundation (2007) KDOQI Clinical practice guidelines and clinical practice recommendations for diabetes and chronic kidney disease. Am J Kidney Dis 49:S1–S180
20. Whitham D (2014) Nutrition for the prevention and treatment of chronic kidney disease in diabetes. Can J Diabetes 38:344–348
21. Huang X, Lindholm B, Stenvinkel P, Carrero JJ (2013) Dietary fat modification in patients with chronic kidney disease: n-3 fatty acids and beyond. J Nephrol 26:960–974
22. Ferraro PM, Ferraccioli GF, Gambaro G, Fulignati P, Costanzi S (2009) Combined treatment with renin-angiotensin system blockers and polyunsaturated fatty acids in proteinuric IgA nephropathy: a randomized controlled trial. Nephrol Dial Transpl 24:156–160
23. Miller ER, Juraschek P, Appel LJ et al (2009) The effect of n-3 long-chain polyunsaturated fatty acid supplementation on urine protein excretion and kidney function: meta-analysis of clinical trials. Am J Clin Nutr 89:1937–1945
24. Donadio JV, Larson TS, Bergstralh EJ, Grande JP (2001) A randomized trial of high-dose compared with low-dose omega-3 fatty acids in severe IgA nephropathy. J Am Soc Nephrol 12:791–799
25. Alexopoulos E, Stangou M, Pantzaki A, Kirmizis D, Memmos D (2004) Treatment of severe IgA nephropathy with omega-3 fatty acids: the effect of a "very low dose" regimen. Renal Fail 26:453–459
26. Friedman AN, Yu Z, Densi C et al (2013) Fatty acids and other risk factors for sudden cardiac death in patients starting hemodialysis. Am J Nephrol 38:12–18
27. Svensson M, Christensen JH, Solling J, Schmidt EB (2004) The effect of n-3 fatty acids on plasma lipids and lipoproteins and blood pressure in patients with CRF. Am J Kidney Dis 44:77–83
28. Mori TA, Burke V, Puddey IB et al (2009) The effects of [omega]3 fatty acids and coenzyme Q_{10} on blood pressure and heart rate in chronic kidney disease: a randomized controlled trial. J Hyperten 27:1863–1872
29. Madsen T, Schmidt EB, Christensen JH (2007) The effect of n-3 fatty acids on C-reactive protein levels in patients with chronic renal failure. J Ren Nutr 17:258–263
30. Calder PC (2006) N-3 polyunsaturated fatty acids, inflammation and inflammatory diseases. Am J Clin Nutr 83:1505S–1509S
31. Noori N, Dukkipati R, Kovesdy CP et al (2011) Dietary omega-3 fatty acid, ratio of omega-6 to omega-3 intake, inflammation, and survival in long-term hemodialysis patients. Am J Kidney Dis 58:248–256
32. Guebre-Egziabher F, Debard C, Drai J et al (2013) Differential dose effect of fish oil on inflammation and adipose tissue gene expression in chronic kidney disease patients. Nutrition 29:730–736
33. Deike E, Bowden RG, Moreillon JJ et al (2012) The effects of fish oil supplementation on markers of inflammation in chronic kidney disease patients. J Ren Nutr 22:572–577
34. Slavin JL (2008) Position of the American Dietetic Association: health implications of dietary fiber. J Am Dietetic Assoc 108:1716–1731
35. Threapleton DE, Greenwood DC, Evans CEL (2013) Dietary fibre intake and risk of cardiovascular disease: systematic review and meta-analysis. BMJ 347:f6879
36. Sabatino A, Regolisti G, Brusasco I, Cabassi A, Morabito S, Fiaccadori E (2015) Alterations of intestinal barrier and microbiota in chronic kidney disease. Nephrol Dial Transpl 30:924–933
37. Younes H, Egret N, Hadj-Abdelkader M et al (2006) Fermentable carbohydrate supplementation alters nitrogen excretion in chronic renal failure. J Renal Nutr 16:67–74
38. Goraya N, Simoni J, Jo C, Wesson DE (2012) Dietary acid reduction with fruits and vegetables or bicarbonate attenuates kidney injury in patients with a moderately reduced glomerular filtration rate due to hypertensive nephropathy. Kidney Int 81:86–93
39. Goraya N, Simoni J, Jo C-H, Wesson DE (2013) A comparison of treating metabolic acidosis in CKD stage 4 hypertensive kidney disease with fruits and vegetables or sodium bicarbonate. Clin J Am Soc Nephrol 8:371–381
40. Salmean YA, Zello GA, Dahl WJ (2013) Foods with added fiber improve stool frequency in individuals with chronic kidney disease with no impact on appetite or overall quality of life. BMC Res Notes 6:510
41. Krishnamurthy VMR, Wei G, Baird BC et al (2012) High dietary fiber intake is associated with decreased inflammation and all-cause mortality in patients with chronic kidney disease. Kidney Int 81:300–306
42. Fassett RG, Robertson IK, Geraghty DP, Ball MJ, Coombes JS (2007) Dietary intake of patients with chronic kidney disease entering the LORD trial: adjusting for underreporting. J Renal Nutr 17:235–242
43. National Kidney Foundation (2007) KDOQI™ clinical practice guidelines and clinical practice recommendations for diabetes and chronic kidney disease. Am J Kidney Dis 49(suppl 2):S1–S180
44. Kidney Disease: Improving Global Outcomes (KDIGO) Lipid Work Group (2013) KDIGO clinical practice guideline for lipid management in chronic kidney disease. Kidney Int Suppl 3:259–305

45. Cano N, Fiaccadori E, Tesinsky P et al (2006) ESPEN Guidelines on Enteral Nutrition: adult renal failure. Clin Nutr 25:295–310
46. National Kidney Foundation (2000) KDOQI™ clinical practice guidelines nutrition in chronic renal failure. Am J Kidney Dis 35(suppl 2):S1–S104
47. National Clinical Guideline Centre (2014) Chronic kidney disease. Early identification and management of chronic kidney disease in adults in primary and secondary care. National Institute for Health and Care Excellence (NICE), London, p 59 (Clinical guideline; n° 182)
48. National Kidney Foundation (2004) K/DOQI clinical practice guidelines on hypertension and antihypertensive agents in chronic kidney disease. Am J Kidney Dis 43(suppl 2):S1–S290
49. Duenhas MR, Draibe SA, Avesani CM, Sesso R, Cuppari L (2003) Influence of renal function on spontaneous dietary intake and on nutritional status of chronic renal insufficiency patoeints. Eur J Clin Nutr 57:1473–1478
50. Lawson JA, Lazarus R, Kelly JJ (2001) Prevalence and prognostic significance of malnutrition in chronic renal insufficiency. J Renal Nutr 11:16–22
51. Bernard S, Fouque D, Laville M, Zech P (1996) Effects of low-protein diet supplemented with ketoacids on plasma lipids in adult chronic renal failure. Miner Electrolyte Metab 22:143–146
52. Malvy D, Maingourd C, Pengloan J, Bagros P, Nivet H (1999) Effects of severe protein restriction with ketoanalogues in advanced renal failure. J Am Coll Nutr 18:481–486
53. Cianciaruso B, Pota A, Pisani A et al (2008) Metabolic effects of two low protein diets in chronic kidney disease stage 4–5–a randomized controlled trial. Nephrol Dial Transpl 23:636–644
54. Di Iorio BR, Minutolo R, De Nicola L et al (2003) Supplemented very low protein diet ameliorates responsiveness to erythropoietin in chronic renal failure. Kidney Int 64:1822–1828
55. Bellizzi V, Di Iorio BR, De Nicola L et al (2007) Very low protein diet supplemented with ketoanalogs improves blood pressure control in chronic kidney disease. Kidney Int 71:245–251
56. Chauveau P, Combe C, Rigalleau V, Vendrely B, Aparicio M (2007) Restricted protein diet is associated with decrease in proteinuria: consequences on the progression of renal failure. J Ren Nutr 17:250–257
57. Di Iorio BR, Bellizzi V, Bellasi A et al (2013) Phosphate attenuates the anti-proteinuric effect of very low-protein diet in CKD patients. Nephrol Dial Transpl 28:632–640
58. Chauveau P, Vendrely B, El Haggan W et al (2003) Body composition of patients on a very low-protein diet: a two-year survey with DEXA. J Ren Nutr 13:282–287
59. Vendrely B, Chauveau P, Barthe N et al (2003) Nutrition in hemodialysis patients previously on a supplemented very low protein diet. Kidney Int 63:1491–1498
60. Fouque D, Laville M (2009) Low protein diets for chronic kidney disease in non diabetic adults. Cochrane Database Syst Rev 3:CD001892
61. Pedrini MT, Levey AS, Lau J, Chalmers TC, Wang PH (1996) The effect of dietary protein restriction on the progression of diabetic and nondiabetic renal diseases: a meta-analysis. Ann Intern Med 124:627–632
62. Brunori G, Viola BF, Parrinello G et al (2007) Efficacy and safety of a very-low-protein diet when postponing dialysis in the elderly: a prospective randomized multicenter controlled study. Am J Kidney Dis 49:569–580
63. Mitch WE, Remuzzi G (2004) Diets for patients with chronic kidney disease, still worth prescribing. J Am Soc Nephrol 15:234–237
64. Cianciaruso B, Pota A, Pisani A, Torraca S, Annecchini R, Lombardi P et al (2008) Metabolic effects of two low protein diets in chronic kidney disease stage IV–V: a randomized controlled trial. Nephrol Dial Transpl 23:636–644
65. Appel LJ, Moore TJ, Obarzanek E et al (1997) A clinical trial of the effects of dietary patterns on blood pressure DASH Collaborative Research Group. N Engl J Med 336:1117–1124
66. Sacks FM, Svetkey LP, Vollmer WM et al (2001) Effects on blood pressure of reduced dietary sodium and the Dietary Approaches to Stop Hypertension (DASH) diet DASH-Sodium Collaborative Research Group. N Engl J Med 344:3–10
67. Conlin PR, Chow D, Miller ER 3rd et al (2000) The effect of dietary patterns on blood pressure control in hypertensive patients: results from the Dietary Approaches to Stop Hypertension (DASH) trial. Am J Hypertens 13:949–955
68. Brenner BM, Meyer TW, Hostetter TH (1982) Dietary protein intake and the progressive nature of kidney disease: the role of hemodynamically mediated glomerular injury in the pathogenesis of progressive glomerular sclerosis in aging, renal ablation, and intrinsic renal disease. N Engl J Med 307:652–659
69. Fouque D, Laville M (2009) Low protein diets for chronic kidney disease in non-diabetic adults. Cochrane Database Syst Rev 3:CD001892
70. Knight EL, Stampfer MJ, Hankinson SE, Spiegelman D, Curhan GC (2003) The impact of protein intake on renal function decline in women with normal renal function or mild renal insufficiency. Ann Intern Med 138:460–467
71. Huang MC, Chen ME, Hung HC et al (2008) Inadequate energy and excess protein intakes may be associated with worsening renal function in chronic kidney disease. J Renal Nutr 18:187–194
72. Kovesdy CP, Kopple JK, Kalantar-Zadeh K (2013) Management of protein-energy wasting in non-dialysis-dependent chronic kidney disease: reconciling low protein intake with nutritional therapy. Am J Clin Nutr 97:1163–1177
73. Carrero JJ, Cozzolino M (2014) Nutritional therapy, phosphate control and renal protection. Nephron Clin Pract 126:1–7
74. Bellizzi V, Bianchi S, Bolasco P et al (2016) A Delphi consensus panel on nutritional therapy in chronic kidney disease. J Nephrol 29:593–602
75. Johnson RJ, Sanchez-Lozada LG, Nakagawa T (2010) The effect of fructose on renal biology and disease. J Am Soc Nephrol 21:2036–2039
76. Singh AK, Kari JA (2013) Metabolic syndrome and chronic kidney disease. Curr Opin Nephrol Hypertens 22:198–203
77. Mende C (2015) Management of chronic kidney disease: the relationship between serum uric acid and development of nephropathy. Adv Ther 32:1177–1191
78. Bomback AS, Derebail VK, Shoham DA et al (2010) Sugar-sweetened soda consumption, hyperuricemia, and kidney disease. Kidney Int 77:609–616
79. Nakayama T, Kosugi T, Gersch M et al (2010) Dietary fructose causes tubulointerstitial injury in the normal rat kidney. Am J Physiol Renal Physiol 298:F712-720
80. Cirillo P, Gersch MS, Mu W et al (2009) Ketohexokinase-dependent metabolism of fructose induces proinflammatory mediators in proximal tubular cells. J Am Soc Nephrol 20:545–553
81. Wang DD, Sievenpiper JL, de Souza RJ, Chiavaroli L, Ha V et al (2012) The effects of fructose intake on serum uric acid vary among controlled dietary trials. J Nutr 142:916–923
82. Brymora A, Flisiński M, Johnson RJ et al (2012) Low-fructose diet lowers blood pressure and inflammation in patients with chronic kidney disease. Nephrol Dial Transpl 27:608–612
83. Nezu U, Kamiyama H, Kondo Y et al (2013) Effect of low-protein diet on kidney function in diabetic nephropathy: meta-analysis of randomised controlled trials. BMJ Open 3:e002934
84. Giordano M, Ciarambino T, Castellino P et al (2014) Long-term effects of moderate protein diet on renal function and low-grade

inflammation in older adults with type 2 diabetes and chronic kidney disease. Nutrition 30:1045–1049
85. Pan Y, Guo LL, Jin HM (2008) Low-protein diet for diabetic nephropathy: a meta-analysis of randomized controlled trials. Am J Clin Nutr 88:660–666
86. Robertson LM, Waugh N (2007) Robertson A. Protein restriction for diabetic renal disease. Cochrane Database Syst Rev 4:CD002181
87. Rughooputh MS, Zeng R, Yao Y (2015) Protein diet restriction slows chronic kidney disease progression in non-diabetic and in type 1 diabetic patients, but not in type 2 diabetic patients: a meta-analysis of randomized controlled trials using glomerular filtration rate as a surrogate. PLoS One 10:e0145505
88. Piccoli GB, Ventrella F, Capizzi I et al (2016) Low-protein diets in diabetic chronic kidney disease (CKD) patients: are they feasible and worth the effort? Nutrients 8:E649
89. D'Alessandro C, Piccoli GB, Calella P et al (2016) "Dietaly": practical issues for the nutritional management of CKD patients in Italy. BMC Nephrol 17:102
90. Bellizzi V, Cupisti A, Locatelli F et al (2016) Low-protein diets for chronic kidney diseases patiens: the Italian experience. BMC Nephrol 17:77
91. Wilhelm-Leen ER, Hall YN, Tamura MK, Chertow GM (2009) Frailty and chronic kidney disease: the Third National Health and Nutrition Evaluation Survey. Am J Med 122:664–671
92. Roshanravan B, Khatri M, Robinson-Cohen C et al (2012) A prospective study of frailty in nephrology-referred patients with CKD. Am J Kidney Dis 60:912–921
93. Shlipak MG, Stehman-Breen C, Fried LF et al (2004) The presence of frailty in elderly persons with chronic renal insufficiency. Am J Kidney Dis 43:861–867
94. Kanazawa Y, Nakao T, Ohya Y, Shimomitsu (2006) Association of socio-psychological factors with the effects of low protein diet for the prevention of the progression of chronic renal failure. Intern Med 45:199–206
95. Cupisti A, D'Alessandro C, Morelli E et al (2004) Nutritional status and dietary manipulation in predialysis chronic renal failure patients. J Ren Nutr 14:127–133
96. Piccoli GB, Ferraresi M, Deagostini MC et al (2013) Vegetarian low-protein diets supplemented with keto analogues: a niche for the few or an option for many? Nephrol Dial Transpl 28:2295–2305
97. Campbell KL, Ash S, Davies PS, Bauer JD (2008) Randomized controlled trial of nutritional counseling on body composition and dietary intake in severe CKD. Am J Kidney Dis 51:748–758
98. Paes-Barreto JG, Barreto Silva MI, Qureshi AR et al (2013) Can renal nutrition education improve adherence to a low-protein diet in patients with stages 3 to 5 chronic kidney disease? J Ren Nutr 23:164–171
99. Pisani A, Riccio E, Bellizzi V et al (2016) 6-tips diet: a simplified dietary approach in patients with chronic renal disease. A clinical randomized trial. Clin Exp Nephrol 20:433–442
100. Wu HL, Sung JM, Kao MD, Wang MC, Tseng CC, Chen ST (2013) Nonprotein calorie supplement improves adherence to low-protein diet and exerts beneficial responses on renal function in chronic kidney disease. J Ren Nutr 23:271–276