Protein intake and renal function in older patients

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Purpose of review
Chronic kidney disease (CKD) is highly prevalent in elderly patients. There is growing recognition of the importance of attention to dietary protein intake (DPI) in this population given their predisposition to age-related changes in kidney function and coexisting comorbidities (i.e., hypertension). We reviewed the impact of DPI on kidney health and survival and the role of dietary protein management in older CKD patients.

Recent findings
While kidney function parameters including glomerular filtration rate (GFR) and renal plasma flow are slightly lower in elderly patients irrespective of CKD status, the kidneys' ability to compensate for increased DPI by augmentation of GFR is preserved until 80 years of age or less. However, long-term consumption of high DPI in individuals of older age and/or with CKD may contribute to kidney function deterioration over time. Prescription of a plant-dominant low-protein diet of 0.6–0.8 g/kg/day with more than 50% from plant sources or very low protein diets less than 0.45 g/kg/day supplemented with essential amino acids or their keto-analogues may be effective in preserving kidney function in older patients and their younger counterparts, while also monitoring for development of protein–energy wasting (PEW).

Summary
Using tailored precision nutrition approaches in prescribing plant-dominant low DPI that also maintains adequate energy and nitrogen balance may ameliorate kidney function decline while also preventing development of PEW in elderly patients with CKD.

Keywords
chronic kidney disease, dietary protein intake, elderly, kidney function, older patient

INTRODUCTION

Dietary protein restriction or avoiding excessive amounts of protein intake are critical strategies in the nutritional management of nondialysis dependent chronic kidney disease (NDD-CKD) patients to prevent the decline of kidney function and incidence of end-stage kidney disease. Current practice guidelines recommend low-protein diets or avoidance of excessive dietary protein intake (DPI) in CKD patients, although stipulations are not made for the impact of advancing age on these recommendations [1]. However, there has been growing recognition of the importance of attention to DPI in elder individuals [2–5]. Older adults with CKD are more predisposed to malnutrition-wasting conditions including sarcopenia, protein–energy wasting (PEW), and frailty, which adversely impact their health and survival [6–8]. Hence, nutritional management considerations in older adults with CKD are more complex, and must harmonize the two overarching goals of dietary protein restriction to slow kidney function decline, while also maintaining adequate energy and nitrogen balance to avoid malnutrition-wasting conditions associated with aging. This review focuses on summarizing existing literature on the effects of DPI on kidney function in older adults, nutritional abnormalities and wasting conditions in older adults with CKD that should be considered when restricting DPI, and the practical implementation of dietary protein restriction with or without supplementation in the elderly with CKD.

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KEY POINTS

- Kidney function including GFR and renal plasma flow are slightly lower in the elderly population irrespective of CKD status.
- The kidneys' ability to compensate for increased protein intake by increasing GFR seems to be preserved until 80 years of age or less.
- The long-term consumption of high-protein intake in individuals of older age and/or with underlying CKD may contribute to the deterioration of kidney health over time.
- A low-protein diet or very low protein diet may be effective in reducing CKD progression in older adults as well as their younger counterparts.
- Older patients with CKD who are prescribed low-protein diets require additional attention to energy and other nutrient needs to prevent the risk of PEW.

KIDNEY FUNCTION IN OLDER CHRONIC KIDNEY DISEASE PATIENTS

The prevalence of CKD markedly increases with age [9▪,10] due to nephron loss and subsequent decline in glomerular filtration rate (GFR) (Table 1). Generally, GFR declines by 0.6–1 ml/min/1.73 m^2/year after age 40 years [11▪], but acute kidney injury, and comorbidities such as diabetes and uncontrolled hypertension can lead to faster GFR decline. In fact, by the 8th decade, over 30% of all nephrons are sclerosed in healthy adults [12–14]. Due to nephron loss with aging and reductions in renal plasma flow (RPF), the kidneys' ability to compensate for increases in DPI by augmenting GFR declines after the 8th decade of life [15]. While, interindividual differences are observed in the elderly, on average GFR and RPF are consequently lower in the older population as compared with their younger counterparts irrespective of the presence of CKD and may lead to inability to augment GFR in the setting of high DPI [16,17]. Many [18,19] but not all studies [15] have demonstrated that adults in their eighth decade may show normal age-associated GFR changes but lack of increase in GFR with amino acid infusions or high dietary protein load [19]. Studies have generally shown lack of GFR augmentation with a GFR stimulus but some studies, such as Fliser *et al.* [15] show no difference in the kidneys' ability to adapt to increases in protein intake by age group. Differences in study findings are likely due to research participant selection. Nephron loss can be present with or without a normal serum creatinine because serum creatinine is an insensitive biomarker and GFR is estimated with serum creatinine values. Older adults with normal GFR may lack kidney function reserve, or ability to augment GFR in the setting of a stimulus. Such persons are at higher risk of acute kidney injury, further GFR decline, and incident CKD. On the contrary, there is no clinical test to detect this lack of kidney function reserve but clinicians should be aware that elderly adults are at highest risk for this deficiency.

In the setting of nephron loss, high-protein diets can be harmful. High-protein diets (e.g., Paleo, Atkins, South Beach, ketogenic diets) have gained popularity as a means to promote weight loss while minimizing loss of lean body mass. In the United States, 41% of adults age 60 years and older are obese (defined by a BMI of $\geq$30 kg/m^2), and one-quarter of Americans age 65 years and older have type 2 diabetes [20]. Multiple age-related factors including body composition changes (i.e., increased body fat and decreased lean body mass) [21–24], insulin resistance [22,23,25,26], and anabolic resistance to

Table 1. Kidney function changes with health aging vs. kidney disease

Kidney function	Aged kidney (healthy aging)	Failing kidney
Glomerular filtration rate	↓In most case	↓
Renal plasma flow	↓	↓
Sodium and water resorption	↓	↓
Fractional excretion of potassium	↓	↑
Fractional excretion of electrolytes	=	↑Ca, Mg, P
Serum electrolytes balance	=	↓Ca, ↑Mg and P
Urinary acidification (adjustment ability of acid–base balance)	Able but difficulty in handling, takes longer time	Altered
Urine concentration capacity	↓	↓
Urine dilution capacity	↓	↓
Production of kidney hormones	=Erythropoietin, parathyroid hormone;↓renin	↓

=, preserved or normal; ↑, elevated; ↓, reduced; Ca, calcium; Mg, magnesium; P, phosphorus.

protein intake [27–30] may result in high demands for protein intake in older adults. However, there are concerns about the risks of prescription of high dietary protein regimens to older patients with elevated BMIs based on growing evidence that higher levels of DPI adversely impact kidney health outcomes (i.e., with subsequent decline in GFR, increases in serum urea nitrogen levels and azotemia, accelerated progression to uremia, and hyperphosphatemia), which may be exacerbated by obesity-related changes in kidney function and structure (i.e., glomerular hyperfiltration, secondary focal segmental glomerular sclerosis) [31,32]. With respect to short-term outcomes, recent randomized controlled trials of DPI have demonstrated mixed findings among older adults, which may have been because of the augmentation in GFR with high DPI [33] as well as lack of an observed adaptive response to high-protein diet or even a tendency toward kidney function decline [18] and such differences are likely due to underlying nephron mass and kidney function reserve. For example, among 99 older men and women with type 2 diabetes among whom the mean age of cohort was 59 years of age and the mean estimated GFR (eGFR) was 71 ml/min/1.73 m^2, high DPI (defined as 30% of total energy intake) administered over a 12-month period resulted in no significant differences in eGFR nor microalbuminuria as compared with low DPI (defined as 15% of total energy intake) [34]. Yet studies of the long-term impact of high DPI upon kidney function have shown inconsistent results [35,36], and more recent data suggest that high DPI may cause harm to kidney health in the long-term particularly among individuals with preexisting CKD and reduced GFR [32,37–39]. In summary, adaptive kidney hemodynamic alterations which occur immediately after a protein and/or amino acid load may be observed in the short-term; however, in individuals of older age and/or with preexisting CKD and substantial nephron loss, long-term consumption of high DPI may contribute to further nephron loss and GFR decline (Table 2).

PROTEIN–ENERGY WASTING IN OLDER CHRONIC KIDNEY DISEASE PATIENTS

There is broad agreement about the ill effects of undernutrition (malnutrition-wasting) particularly among older CKD patients [40–43]. Among the many various complications that may be observed with CKD, PEW is a potent predictor of adverse outcomes including death [6,44,45]. In 2003, Kalantar-Zadeh *et al.* [46] advanced the definition of PEW as 'the state of decreased body pools of protein with or without fat depletion or a state of diminished functional capacity, caused at least partly by inadequate nutrient intake relative to nutrient demand and/or which is improved by nutritional repletion.' In general, malnutrition can result from an inadequate dietary intake (i.e., anorexia nervosa) followed by losses of body fat loss and suppression of gluconeogenesis to minimize muscle protein breakdown [47]; whereas in CKD, there are conditions resulting in loss of lean body mass [48–50]. The prevalence of PEW rises as CKD progresses in part due to activation of proinflammatory cytokines combined with a hypercatabolic state and a gradual decline in appetite [48,49,51]. Perturbations in orexinogenic hormones also lead to decreased consumption of protein and energy [52,53]. Moreover, uremic toxins including catabolic by-products of protein metabolism may exert harmful effects ranging from oxidative stress to endothelial dysfunction, nitric oxide disarrays, renal interstitial fibrosis, sarcopenia, and worsening proteinuria and kidney function [54–56]. In addition to these risk factors, older adults with CKD are at higher risk for PEW due to their age-related changes in body composition over time (i.e., increased body fat and decreased lean body mass [21–23]).

DIETARY PROTEIN RESTRICTION AND KIDNEY FUNCTION IN OLDER ADULTS WITH CHRONIC KIDNEY DISEASE

Reduced DPI has favorable effects on kidney health outcomes, which include amelioration of GFR decline, accompanied by reductions in proteinuria; mitigation of uremic toxin accumulation; and better control of hyperphosphatemia, hyperparathyroidism, and hyperkalemia, which may in turn preserve kidney function and avert or delay the onset of uremic symptoms in CKD patients [57–59]. In advanced stages of NDD-CKD, prescription of low DPI may also be used to defer or delay dialysis initiation [60]. To date, the Modification of Diet in Renal Disease (MDRD) study, which examined 1585 patients ages 18–70 years old over an average period of 2.2 years, has been the largest controlled trial of the effects of dietary protein and phosphorus restriction on CKD outcomes. While the main findings of the MDRD study failed to definitively show the effectiveness of low DPI on CKD progression [61], in a subsequent reanalysis the results suggested that there is a reno-protective effect of low DPI (defined as 0.58 g/kg/day of dietary protein with lower phosphorus intake) vs. higher DPI (defined as 1.3 g/kg/day of dietary protein), such that there was a 10% lower risk of GFR decline over 3 years of follow-up. [62]. A recent meta-analysis of smaller randomized controlled trials has also demonstrated

Table 2. Selected studies of dietary protein intake/amino acid infusions and kidney function

Author (year)	Population, *N*	Study design	Age (year)	BMI (kg/m^2)	eGFR (ml/min/1.73 m^2)	Exposure/Intervention	Outcome	Duration
Acute effect								
Fliser *et al.* (1993)	Healthy young (15) and old (10) men and women	Intervention trial	Median 26/70	Median 22.5/23.3	Median 122/102	AA 0.7 g/kg	GFR, ERPF, RVR, FF	8 h
Short-term effect								
Wagner *et al.* (2007)	Healthy young (12) and old (10) men and women	Crossover trial	Mean 31/60	Mean 25.1/25/8	Mean 92/69 (LPD), 95/77 (HPD)	LPD (0.5 g/kg) and HPD (2.0 g/kg): sources of protein were primarily meat, dairy products, egg white powder	eGFR	1 week/each
Walrand *et al.* (2008)	Healthy young (10) and old (9) men and women	Single-blind randomized crossover trial	Mean 24/70	Mean 23.3/27.2	Mean 106/81 (UPD), 128/74 (HPD)	UPD (1.0, 0.9 g/kg) and HPD (2.0, 1.8 g/kg) for young and old respectively	GFR	10 days/each
Larsen *et al.* (2011)	Type 2 diabetes old men and women (99)	Randomized control trial	Mean 59	27–40	Mean 71	HPD (30% of total energy intake), LPD (15% of total energy intake)	eGFR, mAlb	12 months
Long-term effect								
Lin *et al.* (2010)	Healthy old women in Nurse's Health Study (3348)	Prospective cohort	Median 67	Median 26.4	Median 76	Animal or vegetable DPI estimated by FFQ divided into quartiles	eGFR, mAlb	14 years
Lin *et al.* (2011)	Healthy old women in Nurse's Health Study (3121)	Prospective cohort	Median 67	Median 26.4	Median 76	DPI estimated by FFQ divided into quartiles	eGFR, mAlb	12 years
Beasley *et al.* (2015)	Cardiovascular Health Study (3623)	Prospective cohort	Mean 72	Mean 26.5	Mean 73	Total, animal, and vegetable DPI estimated by FFQ divided into quartiles	eGFR	6.4 years

AA, amino acid; ACR, urinary albumin-to-creatinine ratio; DPI, dietary protein intake; eGFR, estimated glomerular filtration rate; ERPF, effective renal plasma flow; FF, filtration fraction; FFQ, food frequency questionnaire; HPD, high protein diet; LPD, low-protein diet; mAlb, microalbuminuria; RVR, renal vascular resistance; UPD, usual protein diet.

the benefits of a low-protein diet on kidney health outcomes [i.e., reduced risk of kidney failure and end-stage renal disease (ESRD)] [57].

Low-protein diets may have reno-protective effects in both older and younger CKD patients, based on inferences drawn from studies showing similar effect estimates for CKD outcomes among patients across various age ranges [63]. A recent study among 352 patients with stage 3–5 CKD examined the association between amount of DPI (estimated using 24-h urine collection), categorized as very low DPI (<0.6 g/kg/day of dietary protein), low DPI (0.6–0.8 g/kg/day of dietary protein), or moderate DPI (>0.8 g/kg/day of dietary protein), and kidney outcomes stratified by age (i.e., >65 vs. <65 years of age). After a median follow-up 4.2 years, higher DPI was significantly associated with a faster decline in eGFR in the overall cohort and elderly patients, while this association was not statistically significant in younger patients possibly due to small sample size (16, 39, and 38 younger patients in the very low, low, and moderate DPI groups, respectively.) [64].

However, one of the primary concerns of excessive restriction of DPI in older CKD patients has been the risk of developing sarcopenia of old age or PEW, leading ultimately to loss of muscle and fat mass and cachexia, with downstream adverse sequelae including mortality. In general, the requirements for protein intake in older adults is higher than that of younger persons due to age-related anabolism [65,66]. However, epidemiologic data show that older adults with CKD tend to consume less protein, and DPI declines as GFR declines [67]. Moreover, age has a differential effect on CKD-related outcomes, such that older adults with CKD are more likely to die than progress to ESRD than younger adults with CKD [68]. Hence, there are unique considerations with respect to the benefits and risks of low DPI in the older vs. younger population with CKD [31].

SUPPLEMENTED PROTEIN RESTRICTION AND KIDNEY FUNCTION IN OLDER CHRONIC KIDNEY DISEASE PATIENTS

It should be strongly emphasized that when reducing DPI, sufficient energy intake is also needed to avoid impaired nutritional status and subsequent development of PEW [48]. In addition to these considerations regarding energy intake, one strategy that can enhance the salutary effects of a low-protein diet is to supplement it with substitutes such as ketoacid analogues or essential amino acids (EAAs) (Fig. 1) [69▪▪,70]. This may provide a sufficient balance of EAAs, which are usually absent in low-protein diets, as well as an anabolic stimulus without phosphorus or metabolic burden and a lesser impact on proteinuria [71,72].

Different ketoacid analogue and EAA compositions have been shown to have positive impact on CKD outcome, and practice guidelines advise that a very low protein diet that provides 0.28–0.43 g/kg/day of protein intake can be achieved with additional ketoacid analogues or EAAs to meet protein requirements for adults with CKD [1]. Studies that have used supplemented very low protein diets have shown stable or improved serum albumin levels [70,73], reductions in proteinuria [71,72], less severe progression of CKD [73–75], with only subtle changes in lean body mass and fat mass over time [76,77]. Recent meta-analyses have also explored the effectiveness and safety of supplemented low-protein diets [70,78,79]. An Italian randomized control trial of older (≥70 years old) patients with advanced NDD-CKD showed that a very low protein diet (defined as 0.3 g/kg/day of protein) supplemented with ketoacid analogues, EAAs, and vitamins delayed dialysis initiation by approximately 11 months compared with the control group in whom DPI was not restricted, although both groups showed similar mortality rates [80]. In studies examining the long-term safety of supplemented very low protein diet, patients previously exposed to such an intervention continued to have low mortality rates after initiating hemodialysis or after undergoing renal transplantation [81]. While these studies seem reassuring with respect to the potential long-term safety of supplemented low and very low protein diets, it bears mention that most of these were observational studies as opposed to randomized controlled trials.

More recent literature suggests that a patient-centered plant-dominant low-protein diet (PLADO) of 0.6–0.8 g/kg/day composed of more than 50% plant-based sources, administered by dietitians trained in NDD-CKD care, is promising and consistent with precision nutrition directives [82▪]. A recent comprehensive and critical review of the literature concluded that daily red meat consumption over years may heighten risk of CKD, whereas fruit and vegetable proteins may be reno-protective [83–85]. Therefore, PLADO may confer a protective effect on kidney health outcomes and a favorable microbiome balance given its richness in dietary fiber and antioxidants [82▪,86–89].

Given that ESRD patients on hemodialysis tend to be of older age, they are prone to having risk factors leading to PEW, including heightened protein catabolism related to aging, underlying comorbidities, and/or dialysis treatment [90]. Indeed, ESRD patients on hemodialysis are prescribed higher

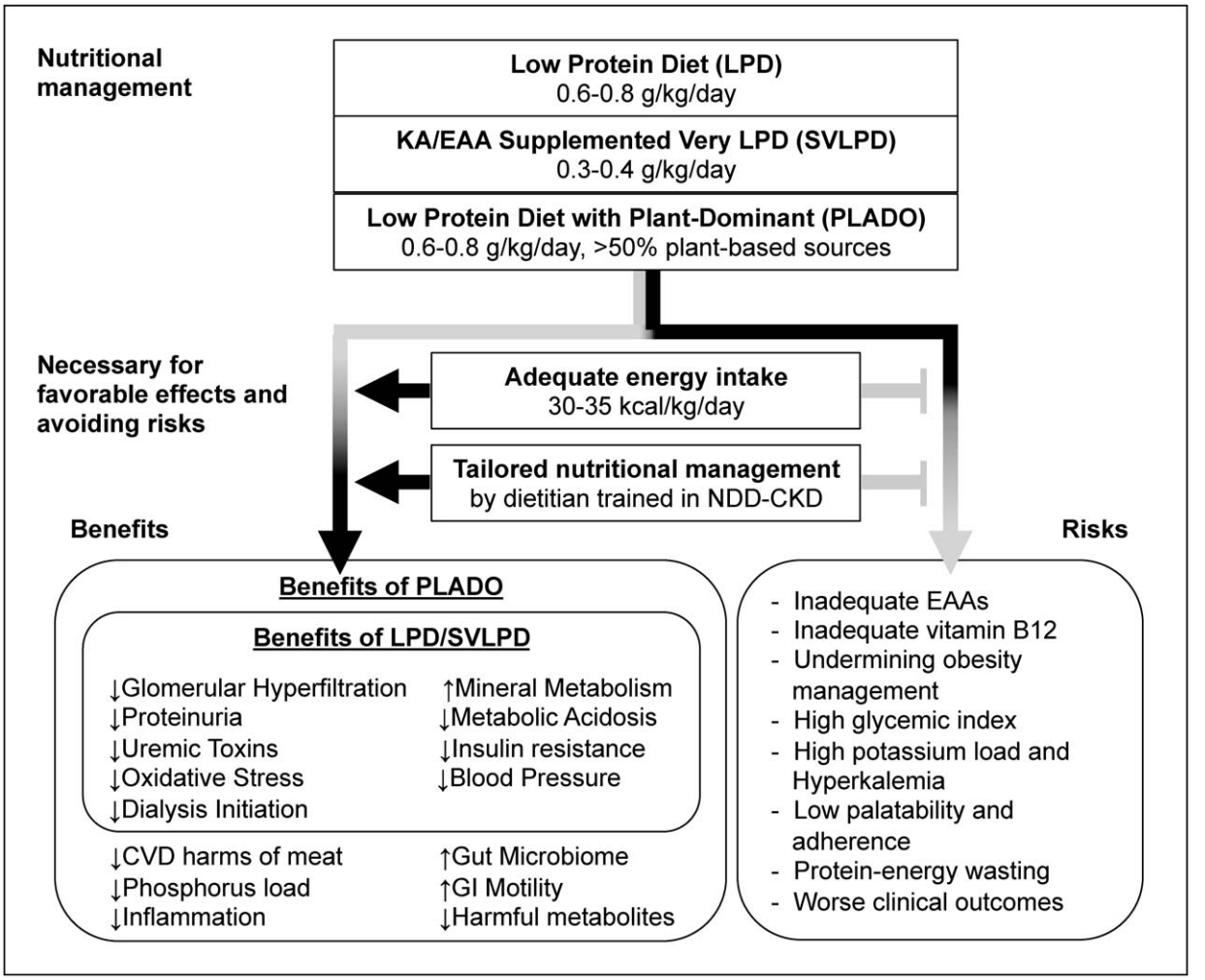

FIGURE 1. Dietary protein intake in the nutritional management of chronic kidney disease patients.

amounts of DPI (i.e., 1.0–1.2 g/kg/day) than that of NDD-CKD patients [1]. However, dialysis patients oftentimes have lower consumption of DPI than these recommended targets. In addition, amongst incident ESRD patients who are initiated on a less frequent hemodialysis strategy, known as incremental hemodialysis, as a means to preserve residual kidney function, adjunctive dietary interventions such as prescribing lower DPI on nondialysis days and higher DPI on dialysis days with sufficient energy intake may be beneficial [91]. Furthermore, recent evidence has suggested the importance of an individualized focus on the nutritional management in ESRD patients transitioning to dialysis [92]. Future studies are needed to define the optimal nutritional management and DPI of advanced CKD patients transitioning to ESRD based on whether they opt to pursue dialysis vs. conservative management.

CONCLUSION

Precision nutritional management that uses a tailored approach in prescribing the amount and sources of dietary protein are particularly needed in older adults with CKD. In addition to using a personalized approach that takes into account a patient's unique characteristics over time when administering a low-protein diet to ameliorate GFR decline and risk of ESRD, close attention is needed to ensure adequate energy and nitrogen balance to prevent the development of PEW in elderly patients with CKD.

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Conflicts of interest

There are no conflicts of interest.

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