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Dietary protein intake and bone across stages of chronic kidney disease

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Abstract

Purpose of Review: This review aims to summarize the current evidence on the effect of very-low-, low-, and high-protein diets on outcomes related to chronic kidney disease-mineral and bone disorder (CKD-MBD) and bone health in patients with CKD.

Recent Findings: Dietary protein restriction in the form of low- and very-low-protein diets have been used to slow down the progression of CKD. These diets can be supplemented with alpha-keto acid (KA) analogs of amino acids. Observational and randomized controlled trials have shown improvements in biochemical markers of CKD-MBD, including reductions in phosphorus, parathyroid hormone, and fibroblast growth factor-23. However, few studies have assessed changes in bone quantity and quality. Furthermore, studies assessing the effects of high-protein diets on CKD-MBD are scarce. Importantly, very-low- and low-protein diets supplemented with KA provide supplemental calcium in amounts that surpass current dietary recommendations, but to date there are no studies on calcium balance with KA.

Summary: Current evidence suggests that dietary protein restriction in CKD may slow disease progression, which may subsequently benefit CKD-MBD and bone health outcomes. However, prospective randomized controlled trials assessing the effects of modulating dietary protein and supplementing with KA on all aspects of CKD-MBD and particularly bone health are needed.

Keywords

nutrition; low protein diets; alpha-keto acid analogue supplementation; chronic kidney disease-mineral bone disorder

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Introduction

Chronic kidney disease (CKD) is a prevalent disease affecting approximately 37 million adults in the US alone [1]. Globally, 13.4% of the population is affected by this progressive disease [2]. However, disease awareness is very low [3] and many more are at risk for disease development due to the prevalence of the most common etiologies of CKD: diabetes mellitus and hypertension [1]. Studies on the burden of CKD show that the residual lifetime incidence of CKD in individuals over 30 years old is estimated as > 50% [4]. CKD is defined by persistent signs of kidney damage (albuminuria) and/or reduced kidney function (filtration capacity) for at least three months [5,6]. Due to the high prevalence of CKD, great financial burden [7,8] and the high mortality rate with kidney failure, the US Department of Health and Human Services released an initiative in July 2019 to increase awareness of kidney failure, increase incentives for kidney donation, and decrease treatment cost [9]. CKD-Mineral Bone Disorder (CKD-MBD) is a highly prevalent consequence of kidney dysfunction. Bone fragility fractures associated with CKD-MBD contribute to the financial burden, hospitalizations, and mortality risk in patients with CKD. This review will focus on the state of knowledge regarding dietary recommendations, particularly for protein intake, and bone health in patients across the stages of CKD.

CKD-MBD is characterized by dysregulation of mineral homeostasis, bone abnormalities, and soft tissue calcification, that increases risk for cardiovascular events, bone fragility fractures, and death [10]. Patients with CKD have a higher incidence of hip fracture at all stages of CKD compared to the general population, and risk increases with CKD severity [11]. A recent study on fracture risk and falls in CKD showed fracture incidence increased in a step-wise manner as eGFR category decreased over a three-year period [12]. Similarly, patients also had an increased incidence of falls over a three-year period as eGFR decreased [12]. Clinical practice guidelines recommend evaluation of patients with decreased eGFR to be treated for nutritional complications and bone disease associated with CKD-MBD[6,13]. Specifically, Kidney Disease Improving Global Outcomes (KDIGO) guidelines recommend monitoring moderate-to-late, pre-dialysis CKD patients with progressively rising parathyroid hormone (PTH) levels for additional bone and mineral complications [6].

High serum PTH increases bone turnover and can increase risk of fracture due to cortical bone loss in patients with CKD [14]. Thus, treatments to mitigate effects of CKD-MBD on bone involve both dietary and pharmacological interventions aimed at management of secondary hyperparathyroidism. Medications include calcimimetics and vitamin D analogs [15]. Dietary phosphorus restriction and phosphate binder medications are prescribed to decrease the phosphate burden accompanied with progressive CKD also in an effort to reduce hyperparathyroidism [16]. Table 1 describes the dietary prescription, or “renal diet,” recommended for patients across stages of CKD. As kidney function declines, dietary protein restriction is prescribed in an attempt to delay kidney disease progression by reducing nitrogenous waste handling demanded from the kidneys. Because of a high positive association of dietary phosphorus and protein content in foods [17,18] restriction of both nutrients go hand in hand. However, strict dietary restrictions, particularly for protein intake, can have unintended negative consequences to overall nutritional status [19], which may also include bone health.

Delaying Disease Progression through Low Protein Intake

Seminal studies in end-stage kidney disease (ESKD) considered decreased dietary protein intake as a strategy to delay kidney decline in animal models [20,21]. Early observations of acute kidney injury progressing to CKD found the progression was instigated by progressively higher glomerular pressure [20]. Lower dietary protein may help prevent kidney function decline by reducing the overall filtration pressure in the nephron [20,22,23] and decreasing net acid excretion [24]. In contrast, one recent study demonstrated that higher daily dietary protein intake in a cohort including all stages of CKD was associated with a higher rate of kidney function decline over 6 years [25].

The Modification of Diet in Renal Disease (MDRD) study is one of the largest studies of moderate CKD patients following protein restriction. While the study's primary results were negative (for further details see Klahr, 1994 [26]), a secondary analysis of this study [27] found that patients who were compliant with a lower protein intake (0.87 g protein/kg/day) had slower eGFR decline when compared to patients consuming a usual protein(1.12 g protein/kg/day) intake [27]. Another recent secondary analysis of the MDRD study found that the lower protein (0.87 g protein/kg/day) cohort experienced a small reduction in serum phosphorus that was sustained over a three-year period compared to those consuming the usual protein intake (1.12 g protein/kg/day) [28]. Thus, there is some evidence that protein restriction may slow CKD progression. However, dietary protein is a nutrient with a large body of evidence supporting a beneficial effect on bone health [29]. The main mechanism of action for benefit is the effect of protein increasing insulin-like growth factor 1 (IGF-1), which stimulates osteoblast activity, decreases osteoclast activity [29], and increases fractional calcium absorption [30]. Kerstetter et al. [30] demonstrated through use of calcium kinetics that increased urine calcium excretion with higher protein intake was the result of higher intestinal absorption, not bone resorption. It follows that several recent meta-analyses in healthy individuals have shown that higher dietary intake of protein is associated with higher total bone mineral density [31]. Similarly, Groenendijk et al. [32] showed that older adults (≥65y) who consumed dietary protein above the RDA of 0.8g/kg/d had higher femoral neck and total hip bone mineral density and that the risk of hip fractures was reduced by 11% (95% CI −16,−6%) compared to those consuming a lower protein diet (<0.8 g/kg/day). As mentioned above, in moderate and advanced pre-dialysis CKD, the guidelines are to lower protein intake. However, the effects of lower protein intake on bone health in CKD are not well described. The following sections will focus on the evidence of effects of protein recommendations on bone health and CKD-MBD outcomes in patients with CKD.

Dietary Protein and CKD-MBD

Low-Protein Diets and Very-Low Protein Diets Supplemented with Alpha-Ketoacid Analogues

Dietary protein modulation is a cornerstone of medical nutrition therapy for patients with CKD [33]. The recommendation often varies between very-low (VLPD) and low-protein diets (LPD) as part of conservative care for patients with advanced CKD. The protein intake for VLPD is 0.3–0.4 g of protein/kg/d and these diets should be supplemented with alpha-

keto acid (KA) analogues of essential amino acids [34]. The protein level for LPD is 0.6-0.8g protein/kg/d and these diets are usually not supplemented with KA [33,35].

LPD is often recommended first to patients as it is less restrictive than VLPD. However, both of these diets can be difficult to implement particularly in Western countries, such as the US, where food manufacturers and food marketing tend to focus on high-protein foods. An analysis of NHANES data [36] showed that dietary protein intake was higher than the RDA of 0.8g/kg/d in most stages of pre-dialysis CKD, males and females, and across all age groups and races/ethnicities, except in individuals with CKD stage 4 that were 55-64 years old. To ease the transition from a high-protein to LPD, and even VLPD + KA, Fois et al. [37] suggest a stepwise system. The first step in this process is to bring dietary protein intake to the RDA (0.8 g/kg/day of protein) and then move into LPD within a 2-6 week time period. Once a LPD has been achieved, a KA could be added if desired. Patients whom are highly compliant may then finally consider a VLPD + KA analogues.

LPD has shown beneficial effects on markers of CKD-MBD, and that added supplementation of KA may be even more beneficial to CKD-MBD patients. In a randomized controlled study, Milovanova et al. [38] showed that a LPD (0.6 g/kg/day of protein) + KA (0.1g/kg/day or 1 pill per 5 kg body weight) reduced serum phosphorus, PTH, and FGF23 and increased serum Klotho in patients with CKD 3b-4 compared to those who only had a LPD without KA supplementation. But, Goto et al. [39] assessed the effects of a LPD alone in patients in both early CKD (eGFR >60ml/min/1.73m^2) and advanced CKD (<30ml/min/1.73m^2). They reported a decrease in intact FGF23 with LPD in both early and advanced CKD, and a decrease in serum phosphorus and PTH only in advanced CKD. Additionally, there was only an increase of 1,25 dihydroxy-vitamin D in the early CKD patients. Bellizzi et al. [40] studied the effects of a LPD supplemented with KA (a mix of amino acids and ketoacid analogs; 1 pill per 5-7 kg body weight/day) and in patients with and without diabetic nephropathy (stage 3-5) to determine safety and efficacy of this treatment. While biomarkers of CKD-MBD were not the primary endpoints of this study, they reported a decrease in serum phosphorus after a period of at least six months. Overall, LPD may provide a benefit in mineral and bone metabolism over normal- or high-protein diets due to associated dietary phosphorus intake. As there is a high priority of preventing the progression of CKD to ESKD and LPD + KA may be an option, future studies should assess the effects of these diets with primary outcomes of CKD-MBD and bone health.

While KA supplementation can be used in combination with a LPD, it is most commonly prescribed in combination with a VPLD. Important to note is that KA are commonly used in countries outside of the US, as KA are not FDA-approved. However, a KA under a Generally Recognized as Safe (GRAS) classification is available as a medical food in the US. Mechanistically, KAs work by binding amino groups found on excess hydrolyzed urea in circulation through transamination. This reaction leads to the formation of an essential amino acid. The net effect of supplementation with KAs is lower circulating urea and higher essential amino acids. However, the reduction of nitrogenous circulating products may also be due to reduced urea generation [34]. Each KA analogue pill contains ketoacids of leucine, isoleucine, valine, and phenylalanine, the hydroxyl acid of methionine, and intact tryptophan, histidine, threonine, and lysine [34,41]. A recommended dose of 4-8 tablets TID

has been proposed, while some researchers have reported a dose of 1pill/5kg to 1pill/10kg of body weight. A typical pill contains 36mg of nitrogen or 0.225g of protein. Importantly for mineral and bone metabolism, the KA analogues are given as salts, often using calcium. Each tablet of the most widely used KA analogue contains 50 mg of calcium, while some preparations used in Europe may contain up to 67 mg/tablet. As an example, with the most widely used preparation, a 70kg person may be taking 600-1,400mg of calcium from KA in addition to dietary sources. The high dose of calcium may have a phosphorus-binding effect, causing a decrease in serum levels of phosphorus, and they have been suggested as phosphate binders [42]. However, the lower serum phosphorus may also be due to decreased intake of organic sources of phosphorus, mostly coming from animal-based foods and higher intake phytate-bound phosphorus subsequent to the VLPD prescription.

There are several RCTs assessing the effect of VLPD + KA on biochemical markers of CKD-MBD. A systematic review and meta-analysis [43] of five clinical trials of VLPD + KA in ESKD patients receiving dialysis found that there was a decrease in serum phosphorus of −1.14 mg/dl (95% CI −1.98, −0.28) and a mean decrease in PTH of −212.35 ng/ml (95% CI −294.28, −130.42) with VLPD +KA. In a randomized controlled trial of 60 moderate staged CKD patients (stage 3b-4; eGFR 15-45 mL/min/1.73 m^2), Di Iorio et al. [44] showed that when patients followed a VLPD + KA for three months, there was a decrease in serum phosphorus and PTH, compared to when consuming a Mediterranean-based diet or usual diet for the same duration. This same group showed that this diet of VLPD +KA led to lower levels of FGF23 [45]. Garneata et al. [46] compared VLPD + KA with LPD and showed that serum phosphorus was lower with VLPD + KA. Overall, these trials show that VLPD + KA may benefit biochemical markers of CKD-MBD. On the other hand, the potentially high calcium burden from KA given as calcium salts should be taken into consideration in regard to risk for calcium retention [47,48] which may increase risk of vascular calcifications.

There are fewer studies reporting on the effect of a LPD or VLPD, with or without KA, on bone turnover markers or bone mineral density in CKD. In 2003, Chauveau et al. [49] published a study on the effects of VLPD + KA on body composition, including bone mineral density. Thirteen, advanced-staged, pre-dialysis CKD patients (eGFR 15 ± 4.7 mL/min/1.73 m^2; mean age 55) were studied on a VLPD + KA (0.3 g protein /kg/day) for 2-years. There was an initial decline in lean body mass after three months with progressive recovery over two years. However, while VLPD + KA supplementation showed no ill effects on biomarkers of nutritional status (weight, BMI, albumin, pre-albumin, and transferrin), total bone mass and lumbar bone mass, hip bone mass, was significantly decreased at one and two years. Mean differences for total bone mass at one and two years were −2.8% and −5.6%, respectively ($P < 0.05$). Conversely, patients experienced a significant decreased in PTH after two years of following a VLPD + KA diet. More studies are needed to assess the direct effect of LPD and VLPD on bone outcomes in CKD patients.

High-protein diets in CKD and ESKD

As opposed to the dietary protein restrictions recommended in pre-dialysis CKD, a high protein intake is recommended for patients with ESKD undergoing dialysis treatment to

offset the increased protein requirements, as well as losses through dialysis [33]. For hemodialysis patients, the recommendation is 1.2g of protein/kg/d, while for those undergoing peritoneal dialysis the recommendation is 1.2-1.3g of protein/kg/d and up to 1.5g/kg/d in case of peritonitis [33,35]. However, higher dietary protein has been shown to increase endogenous acid production and net acid excretion [24]. In the context of kidney dysfunction, already compromised acid-base balance can be further affected by a high-protein diet which may negatively impact bone health.

It is well documented that some degree CKD-MBD is evident in as many as 80% of patients, particularly in those with ESKD undergoing dialysis treatment [13]. We performed a secondary analysis of the IHOPE trial in hemodialysis patients [50] and found that a 12-month supplementation of 30g of whey protein with or without intradialytic bicycling was only beneficial in individuals >60 years of age as it prevented the yearly decrease in total and hip bone mineral density [51]. Similarly, Wesson et al. [52] showed that there was a higher acid retention in an experimental model of kidney disease induced by performing a 2/3 nephrectomy in male and female rats. When paired with a casein diet (termed “acid-producing diet”), these animals also had higher excretion of deoxypyridinoline, possibly due to bone matrix injury from resulting acid retention. Overall, studies on the effect of increased dietary protein intake on biochemical markers of mineral and bone metabolism, bone, and vascular calcification in the dialysis population are generally lacking and warrant further study.

Plant-Based Diets as an Approach to Mitigate Bone Catabolism in CKD

Plant-based diets, or diets using plants as the main form of protein, have been shown to be beneficial in decreasing risk factors for many chronic diseases, including CKD. CKD patients have a unique opportunity to leverage these benefits by using plant-based foods to substitute animal sources of protein in a VLPD and LPD. By choosing plant-based diets, CKD patients are consuming less of the proteins that provide titratable acid, such as phosphorus and sulfur-containing amino acids [53]. This decreased acid load is beneficial to the kidney and also aids in correction of potential metabolic acidosis [54–56], both of which may ultimately translate to benefits to bone. A new study of the Atherosclerosis Risk in Communities (ARIC) cohort found that CKD patients who adhered to an overall plant-based diet had a lower risk of eGFR decline [57]. Additionally, in 2014, Moorthi et al. [58] found a decrease in FGF23 and other markers of CKD-MBD in CKD patients consuming a diet of 70% plant-based protein and 30% protein from animal sources. Finally, Goraya et al. [59] found that increasing fruit and vegetable intake over the course of one year was able to improve markers of metabolic acidosis in moderate CKD patients. These studies suggest that patients could modify their diet while still including some animal protein sources and may gain benefits of delaying their disease progression. Further studies of plant-based diets in CKD with bone health and fracture outcomes are needed to determine whether these potential benefits extend to bone.

Summary and Conclusion

CKD is a prevalent disease across the globe, which is associated with a high risk for bone fragility fractures. There are few studies assessing the effects of dietary protein recommendations in CKD on bone health and CKD-MBD outcomes. There is evidence that low-protein dietary interventions may delay CKD disease progression, and some studies show additional benefits to biomarkers of CKD-MBD, but there is a general lack of data on the effects of these diets on bone turnover markers, bone mineral density, and fracture. Indeed, assessing biomarkers of bone turnover in CKD is challenging due to renal excretion of the most common biomarkers (e.g. procollagen type I N-propeptide (P1NP), and C-terminal telopeptide of type I collagen (CTX)) [60]. Further, while BMD from DEXA is informative and is now recommended by KDIGO or assessment of fracture risk in patients with CKD, it does not fully capture the cortical porosity and the variable bone disease within CKD-MBD [6]. But, despite an overall lack of low protein diet studies in CKD with bone outcomes, it is reasonable to postulate that decreasing risk for disease progression may ultimately aid in the risk reduction for fractures associated with CKD-MBD.

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Table 1.

Dietary Recommendations across Stages of CKD

CKD stage	Energy (kcal/kg)	Protein (g/kg body weight/day)	Phosphorus (mg/day)	Potassium (g/day)	Sodium (g/day)
CKD Stage 1-4	35 kcal/kg for patients <60 y.o. 30 kcal/kg for patients > 60 y.o. [33]	0.6-0.8 g/kg/day [33,35]	No restriction until hyperphosphatemia [35]	No restriction until hyperkalemia is present [35]	<2.4 g/day [5]
ESKD; Dialysis	35kcal/kg for patients <60y.o. 30-35 kcal/kg for ≥ 60 y.o. [33]	HD: 1.2g/kg/d PD: 1.2-1.3 g/kg/day and up to 1.5 g/kg/d in case of peritonitis [33]	800-1000 mg/d for patients with serum P greater than 4.5 mg/dL [35]	≤2-4 g/day [35]	HD: 2-3 g/day PD: 2-4 g/day [35]