

Review

The Role of Diet in Bone and Mineral Metabolism and Secondary Hyperparathyroidism

Matteo Bargagli ^{1,2,*}, Maria Arena ¹, Alessandro Naticchia ¹, Giovanni Gambaro ³, Sandro Mazzaferro ^{4,5}, Daniel Fuster ^{6,†} and Pietro Manuel Ferraro ^{1,2,*}

¹ U.O.C. Nefrologia, Dipartimento di Scienze Mediche e Chirurgiche, Fondazione Policlinico Universitario A. Gemelli IRCCS, 00168 Roma, Italy; maria.arena90@virgilio.it (M.A.); alessandro.naticchia@policlinicogemelli.it (A.N.)

² Dipartimento Universitario di Medicina e Chirurgia Traslazionale, Università Cattolica del Sacro Cuore, 00168 Roma, Italy

³ U.O.C. Nefrologia, Azienda Ospedaliera Universitaria Integrata di Verona, 37126 Verona, Italy; giovanni.gambaro@univr.it

⁴ Department of Translational and Precision Medicine, Sapienza University of Rome, 00161 Rome, Italy; sandro.mazzaferro@uniroma1.it

⁵ Nephrology Unit, Policlinico Umberto I, 00161 Rome, Italy

⁶ Department of Nephrology and Hypertension, Inselspital, Bern University Hospital, University of Bern, 3010 Bern, Switzerland; daniel.fuster@dbmr.unibe.ch

* Correspondence: matteo.bargagli@unicatt.it (M.B.); pietromanuel.ferraro@unicatt.it (P.M.F.); Tel.: +39-06-3015-7825 (M.B.); +39-06-3015-7819 (P.M.F.); Fax: +39-06-3015-9423 (M.B. & P.M.F.)

† Contributed equally to the article.



Citation: Bargagli, M.; Arena, M.; Naticchia, A.; Gambaro, G.; Mazzaferro, S.; Fuster, D.; Ferraro, P.M. The Role of Diet in Bone and Mineral Metabolism and Secondary Hyperparathyroidism. *Nutrients* **2021**, *13*, 2328. <https://doi.org/10.3390/nu13072328>

Academic Editors:

Evangelia Charmandari,
George Mastorakos and Odysseas
Androustos

Received: 8 June 2021

Accepted: 5 July 2021

Published: 7 July 2021

Publisher's Note: MDPI stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.



Copyright: © 2021 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

Abstract: Bone disorders are a common complication of chronic kidney disease (CKD), obesity and gut malabsorption. Secondary hyperparathyroidism (SHPT) is defined as an appropriate increase in parathyroid hormone (PTH) secretion, driven by either reduced serum calcium or increased phosphate concentrations, due to an underlying condition. The available evidence on the effects of dietary advice on secondary hyperparathyroidism confirms the benefit of a diet characterized by decreased phosphate intake, avoiding low calcium and vitamin D consumption (recommended intakes 1000–1200 mg/day and 400–800 UI/day, respectively). In addition, low protein intake in CKD patients is associated with a better control of SHPT risk factors, although its strength in avoiding hyperphosphatemia and the resulting outcomes are debated, mostly for dialyzed patients. Ultimately, a consensus on the effect of dietary acid loads in the prevention of SHPT is still lacking. In conclusion, a reasonable approach for reducing the risk for secondary hyperparathyroidism is to individualize dietary manipulation based on existing risk factors and concomitant medical conditions. More studies are needed to evaluate long-term outcomes of a balanced diet on the management and prevention of secondary hyperparathyroidism in at-risk patients at.

Keywords: bone and mineral metabolism; secondary hyperparathyroidism; chronic kidney disease; dietary advice

1. Introduction

Bone and mineral metabolism is characterized by a complex interaction between minerals and hormones such as calcium, phosphate and magnesium, parathyroid hormone (PTH), fibroblast growth factor-23 (FGF23) and active vitamin D (1,25(OH)₂D₃). Bone disorders are a common complication of chronic kidney disease (CKD) and dietary advice plays a fundamental role in its management [1,2]. Here, we review the physiology and pathophysiology of bone and mineral metabolism and the effect of diet in its regulation.

2. Methods

In this article, we reviewed the available literature regarding the association between diet and all causes of secondary hyperparathyroidism. We searched articles from accessible

online databases (PubMed, the Cochrane library, and Web of Science). The articles of interest were obtained using the following search terms: (“diet” OR “dietary advice” OR “foods” OR “nutrition”) AND (“secondary hyperparathyroidism” OR “mineral and bone disorder” OR “CKD-MBD”). In this review, only articles written in English language and with available full text were included. A total of 198 references were included in this review.

3. Physiology of Bone and Mineral Metabolism

Bone is a specialized connective tissue hardened by apatite, a form of calcium phosphate. The homeostasis of bone is regulated by three different kind of cells: osteoclasts, osteoblasts and osteocytes [3,4]. Osteoblasts are responsible for bone formation and secretion of non-mineralized bone matrix [5]. The activation of PTH, $1,25(\text{OH})_2\text{D}_3$, growth hormone (GH) and estrogen receptors on osteoblasts surface leads to the production of insulin-like growth factor 1 (IGF1), a crucial autocrine hormone that drives postnatal skeletal growth [3]. Osteoclasts are indirectly stimulated by PTH via osteoblasts to release calcium phosphate from bone [5] and are regulated by the osteoprotegerin/receptor activator nuclear receptor ligand (OPG/RANK-L) system [6]: osteoblasts express RANKL, which binds RANK on the surface of osteoclast precursors, inducing their maturation. When the decoy receptor OPG is secreted by osteoblasts, it binds RANK-L with higher affinity than RANK [7], preventing excessive bone resorption [8]. By contrast, decreased OPG secretion increases stimulation of osteoclasts [6]. Besides, osteocytes, the differentiated form of osteoblasts [9], secrete several hormones (e.g., FGF23 and sclerostin) and express matrix proteins that regulate bone–mineral remodeling [9].

Almost 99% of total body calcium is stored in bones, with a calcium/phosphate ratio of 2:1 [3]. The total calcium balance is regulated by PTH, $1,25(\text{OH})_2\text{D}_3$, and calcitonin through their interaction with the kidneys, bones and gastrointestinal tract [10]: a reduction in serum calcium induces PTH and $1,25(\text{OH})_2\text{D}_3$ secretion, increasing both its renal retention and intestinal absorption, whereas hypercalcemia is counterbalanced by calcitonin secretion and PTH inhibition. Besides, recent research points to discoveries about the links between bone cells and bone marrow cells, whose interactions might help explain the occurrence of bone disease in inflammatory states [11].

Intestinal calcium uptake is either paracellular or transcellular, and the latter is positively regulated by calcitriol activation [12].

The kidneys fine tune the serum calcium concentration by increasing or decreasing its urinary excretion. Calcium reabsorption mainly occurs by the paracellular route in the proximal tubule and thick ascending limb (TAL) driven by active sodium reabsorption, whereas in the distal convoluted tubule (DCT) calcium reabsorption is transcellular and regulated by PTH, calcitonin and $1,25(\text{OH})_2\text{D}_3$ [13]. Furthermore, activation of the calcium-sensing receptor (CaSR) inhibits calcium transport along the TAL through upregulation of claudin-14, which likely blocks divalent cation permeable pores formed by claudin-16 and claudin-19 in this segment [14,15].

PTH, $1,25(\text{OH})_2\text{D}_3$, FGF23 and Klotho are also involved in maintaining a constant serum phosphate concentration. Phosphate is mainly stored in bone [16] and is transported transcellularly by Na-Pi cotransporters, in either the small intestine (NpT2b, SLC34A2) or the proximal tubule (NpT2a and NpT2c, SLC34A1 and SLC34A3, respectively). PTH exerts its phosphaturic function by reducing NpT2a and NpT2c activity [16], but it decreases the expression of NpT2b [17], as well. Moreover, low serum phosphate levels increase $1,25(\text{OH})_2\text{D}_3$ synthesis [18], whereas hyperphosphatemia inhibits 1α -hydroxylase exacerbating $1,25(\text{OH})_2\text{D}_3$ deficiency [19].

Both increased dietary phosphate intake and calcitriol stimulate FGF23 secretion [20,21]. However, the activation of the Fibroblast Growth Factor Receptor 1 by FGF23 requires a cofactor named Klotho, a kidney-derived hormone. FGF23 reduces the expression of tubular sodium/phosphate cotransporters [22] and inhibits the synthesis of $1,25(\text{OH})_2\text{D}_3$ by downregulation of 1α -hydroxylase [23] and increases the degradation of $1,25(\text{OH})_2\text{D}_3$

by stimulating its degrading enzyme 24-hydroxylase [24,25]. In addition, FGF23 acts on parathyroid tissue to decrease PTH secretion [26].

4. Pathophysiology of Secondary Hyperparathyroidism

Secondary hyperparathyroidism (SHPT) is defined as (appropriately) increased PTH secretion due to an underlying stimulus. The pathophysiological *primus movens* of the increased PTH secretion is either reduced serum calcium or increased serum phosphate concentrations [27]. The most frequent conditions associated with SHPT include gut malabsorption, renal failure, or other causes of vitamin D deficiency (Figure 1) [27,28]. Reduced vitamin D concentration is commonly found in obese patients, although the underlying mechanism is not completely understood: reduced outdoor physical activity and vitamin D sequestration in adipose tissue have been hypothesized [29,30]. Apart from the origin of vitamin D deficiency, an inverse association between BMI and serum 25(OH)D₃ concentrations was found [31–33]. Bariatric surgery [34] may also lead to vitamin D deficiency of multifactorial origin: obese patients are at higher risk for vitamin D insufficiency and the surgical procedure may predispose these patients to malabsorption syndrome [35,36]. Gut malabsorption is also a known complication of celiac disease and inflammatory bowel diseases such as Crohn's disease [37–39]. Conversely, reduced intestinal uptake of calcium alone is not enough to cause SHPT, unless accompanied by severe vitamin D deficiency or additional risk factors such as renal failure [40].

Of note, hypomagnesemia, a described complication of gut malabsorption [41], may worsen SHPT by inducing hypocalcemia, low serum 1,25(OH)₂D₃ and impaired PTH secretion and increased skeletal PTH resistance [42].

Secondary hyperparathyroidism and mineral and bone disorders are some of the most common complications of chronic kidney disease (CKD-MBD), even in early stages [43,44].

During CKD progression, phosphate is progressively retained with a subsequent reduction in serum calcium, due to the formation and deposition of calcium-phosphate salts [45]. This stimulates PTH secretion to restore serum calcium concentration and reduce serum phosphate through its phosphaturic effect on renal tubules. An additional effect of hyperphosphatemia is the inhibition of 1,25(OH)₂D₃ synthesis, either directly, or indirectly by increasing plasma FGF23 concentration [46,47]. Furthermore, decreased glomerular filtration rate (GFR) and low serum 25(OH)D₃ limit the synthesis of active vitamin D in these patients [48]. Besides, both reduced active vitamin D concentration and inhibited CaSR activity driven by raised serum phosphate insufficiently suppress PTH secretion [49–52]. Hyperphosphatemia also stimulates progressive parathyroid hyperplasia with a subsequent reduction in the expression of vitamin D and calcium receptors, predisposing patients to a dysregulation of the parathyroid cells' response to circulating calcium and calcitriol [21]. Moreover, either hypocalcemia, hyperphosphatemia or decreased serum calcitriol could lead to a reduction in VDR expression, worsening 1,25(OH)₂D₃ resistance on parathyroid cells [53].

Increased circulating plasma FGF23 concentrations are already present in early CKD stages, long before the occurrence of hyperphosphatemia [54,55]. Another player in the field is represented by Klotho, the coreceptor of FGF23, responsible for its selective target organ effects. Circulating soluble alpha-Klotho levels are reduced very early in CKD and it is thus possible that increments of FGF23 represent a compensatory response of osteocytes to reduced peripheral response [56]. Increased plasma FGF23 is associated with increased mortality [57–59] and poor cardiovascular outcomes [60–63].

Similarly, PTH levels start to increase at normal or near normal GFR levels, long before the onset of hypocalcemia or hyperphosphatemia [44]. Whatever the cause, once secondary hyperparathyroidism develops, it increases the risk for several conditions. Elevated PTH levels are associated with endothelial stress, vascular calcification, increased risk for cardiovascular events and heart failure and increased mortality [64]. SHPT is also associated with poor anemia control and resistance to erythropoietin therapy in CKD

patients [65], peripheral and central nervous system and immunological dysfunction, glucose and lipid metabolic alterations [66].

Ultimately, osteocytes and osteoclasts seem to be involved in the function of a new anatomical microenvironment of hematopoietic stem cells (HSCs), known as the bone marrow niche [67]. These provide support to HSCs maturation, proliferation, and mobilization. Recently, chronic inflammatory diseases such as diabetes and CKD have been hypothesized to induce bone niche dysfunctions [11]. In fact, PTH, vitamin D, FGF23 and CaSR all have a role in niche regulation and a model of CKD-MBD found a significant reduction in HSCs in bone marrow, coupled with higher immature colony-forming units in the spleen and peripheral blood [68].

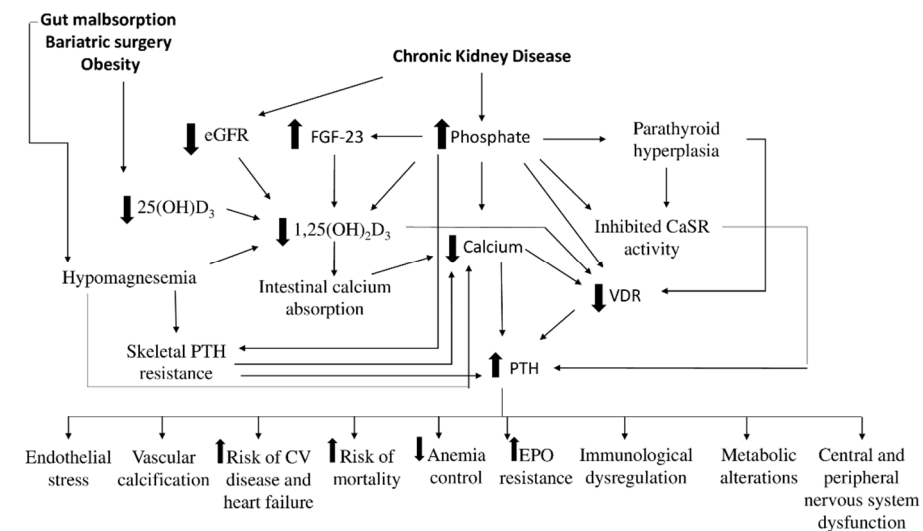


Figure 1. Mechanisms of secondary hyperparathyroidism.

5. Effect of Diet on Bone and Mineral Metabolism Homeostasis and Secondary Hyperparathyroidism

5.1. Dietary Protein Intake

Bone health is influenced by several nutrients and food components that are normally ingested daily, through different mechanisms, including: endocrine and/or paracrine effects, actions on bone turnover and the homeostasis of calcium, phosphate and magnesium [69].

Several studies investigated the role of dietary protein intake on bone mineral density (BMD), bone mineral content (BMC) and the risk of fracture. The data from randomized controlled trials (RCTs) are contradictory: some authors demonstrated a positive relationship between protein intake and BMD in different bone segments [70–73], while others found no association between protein intake and bone mass [74–80]. Cohort studies revealed similar conflicting results [81–85]. A possible explanation for the association may be related to IGF-I secretion: Schürch et al. [73] demonstrated that increased protein intake causes a rise in circulating IGF-I, which exerts an anabolic effect on bone (Table 4). At the same time, low serum IGF-I was associated with reduced BMD and cortical bone thickness in a rat model of low protein diet [86,87]. The source of dietary protein seems to be equally relevant for bone health: a low-protein, soy-based diet significantly decreases femoral cortical thickness, compared to a low-protein, casein-oriented diet, in mice [88].

With respect to bone and mineral biomarkers, a number of clinical trials analyzed the effect of dietary protein consumption on osteocalcin concentration, with conflicting results: Uenishi et al. [89] and Bharadwaj et al. [90] found higher levels in patients with increased protein intake, whereas others observed no differences in osteocalcin concentrations [71–73,76,91,92]. Furthermore, Kerstetter et al. [76] reported that in case of low protein consumption, the intestinal absorption of calcium is reduced with a consequent increase in circulating PTH and calcitriol. The intake of dietary protein also seems to be

inversely associated with PTH secretion [93], possibly indicating a beneficial effect of a protein-oriented diet.

5.2. Dietary Acid and Alkali Intake

Since the 1920s it has been known that there is a positive association of protein intake with urinary calcium excretion [94] and both renal and extrarenal mechanisms seem to be involved [95]. A possible explanation for this phenomenon relates to the acid load induced by dietary protein. Meat and fish are rich in sulfur-containing amino acids, generating a fixed metabolic acid load. On the contrary, fruits and vegetables provide more alkali than acids [96]. Acid retention stimulates bone resorption by activating osteoclasts and inhibiting osteoblasts [97]. In addition, acid loading increases urinary calcium excretion due to altered tubular calcium handling. These changes are independent of PTH, 1,25(OH)₂D₃ and tubular sodium handling [98,99]. As a consequence, dietary acid loads were found to be associated with a negative calcium balance and low BMD [93,97,98,100,101]. Recent data, however, suggest that acid-load-independent mechanisms may also be involved in the increase in urinary calcium by dietary protein [102], including higher filtered load and reduced fractional tubular reabsorption of calcium due to increased GFR or augmented intestinal calcium uptake, especially in cases of high protein and low calcium intake [103,104].

Renal net acid excretion from diet can be estimated, using a validated formula, through determination of the potential renal acid load of foods (PRAL) (Table 1) [105]. Cao et al. [93] found that a diet characterized by higher PRAL increased both urinary calcium excretion and its intestinal absorption (Table 4).

The alkaline diet theory affirms that a diet rich in fruit and vegetables would be essential for maintaining bone integrity, although the data regarding this hypothesis are controversial [106]. Frassetto et al. [107] and MacDonald et al. [108] provided no evidence for such a theory, whereas RCT data [109] supported it: 60 mEq of potassium citrate supplementation significantly increased BMD after 24 months, in 201 elderly patients without CKD.

A Mediterranean diet, which is rich in legumes and vegetables, was indeed associated with higher bone mineral density [110], an effect possibly mediated by the high alkali and low acid content of the diet [111–113]. However, an alkali-oriented diet is also associated with increased magnesium intake. In fact, magnesium deficiency has been linked to impaired bone growth, osteoblastic and osteoclastic activity, osteopenia, bone fragility and altered calcium metabolism [42]. Few studies also suggested that magnesium supplementation is associated with increased BMD and reduced bone turnover [114–116].

Table 1. Foods with high PRAL (PRAL in mEq per 100 g serving).

Cereal and Grain	Fish and Shellfish	Meat and Poultry	Others
Wheat (12.26)	Tuna (9.19–12.71)	Chicken (8.73–13.84)	Leavening agents (270.16)
Rye (11.95)	Salmon (11.11)	Veal (4.96–12.64)	Sweets (0.38–85.40)
Couscous (7.60)	Mackerel (5.13–8.42)	Beef (4.83–12.53)	Cheese (6.18–21.29)
Rice (6.98)	Crab (8.37)	Pork (3.99–12.44)	Eggs (9.42)
Macaroni (6.93)	Lobster (7.44)	Turkey (7.37–10.49)	Nuts (−16.04; 8.71)
Breakfast cereals (0.23)	Cod (6.53)	Lamb (4.41)	

Data from the US Department for Agriculture (USDA).

5.3. Calcium Intake

Peak bone mass in early adulthood strongly depends on dietary calcium intake and skeletal calcium retention [117,118]. Several studies demonstrated that calcium consumption significantly predicts total body bone mass, and subjects with reduced calcium intake may not achieve their target peak bone mass [119–121]. Moreover, a Japanese study reported a positive association between calcium intake and bone density in young adults [122] and higher dietary calcium improved BMC and BMD [123]. Thus, the amount of dietary calcium (Table 2), along with its interaction with vitamin D, seems to play an important role in bone and mineral homeostasis. In fact, Spiegel et al. [124] found an inverse relationship between dietary calcium content, 1,25(OH)₂D₃ and PTH levels (Table 4). Despite a reduc-

tion in circulating $1,25(\text{OH})_2\text{D}_3$, net intestinal calcium absorption was found to be increased with a high calcium diet, probably through augmented paracellular absorption [125]. Conversely, in case of a low calcium diet, the $1,25(\text{OH})_2\text{D}_3$ -dependent transcellular intestinal uptake of calcium prevails [69]. Although both vitamin D and animal-derived calcium intake have been inversely correlated with PTH [126], some other authors observed a null effect of total dietary calcium on the risk for SHPT [40]. This led to the hypothesis that calcium bioavailability (and hence the impact on PTH) varies by dietary source. Accordingly, Gannagé-Yared et al. [126] confirmed the abovementioned inverse association between PTH and dairy and animal sources of calcium, whereas vegetable-derived calcium caused no changes in plasma PTH concentrations [127]. The latter may be at least partially explained by the high oxalate content of plant-derived foods, which is known to decrease intestinal calcium absorption [126].

In view of these results, one may expect a deleterious effect on bone health of a diet in which vegetables and fruits are the only source of calcium. However, it is well known that such a diet is associated with higher BMD [128]. The underlying mechanisms are currently not clear and may be multifactorial [129]. Certainly, the reduced acid and increased magnesium content of a diet rich in vegetables and fruits has also to be taken into account. By contrast, a strict vegetarian diet is associated with lower $25(\text{OH})\text{D}_3$ levels and characterized by low dietary calcium intake and an increased PTH concentration [130].

Table 2. Foods with high calcium content (calcium content in mg per 100 g serving).

Dairy	Animal-Derived	Vegetables	Others
Milk (276 mg)	Sardines (286 mg)	Lamb's quarters (362 mg)	Tahini (902 mg)
Kefir (247 mg)	Salmon (179–212 mg)	Nettles (334 mg)	Almond milk (345 mg)
Buttermilk (222 mg)		Amaranth (216 mg)	Rice milk (221 mg)
Yogurt (216 mg)		Spinach (191 mg)	
Cheese (138–333 mg)		Soybeans (175 mg)	
Greek yogurt (116 mg)		Kale (94 mg)	

Data from the US Department for Agriculture (USDA 2002) and Ferraro et al. [100].

5.4. Phosphate Intake

Phosphate is an essential nutrient in the human diet (Table 3) and plays an important role in intracellular signaling and energy metabolism and is a key constituent of cell membranes and bone. The available literature clearly demonstrates that a high dietary phosphate intake increases plasma PTH (Table 4) [131–137]. Accordingly, Hayakawa et al. [138] found parathyroid cell proliferation and increased PTH secretion in an animal model with high dietary phosphate intake. In fact, the initial phosphaturic response after either an intestinal or intravenous phosphate load occurred after the increase in circulating PTH, whereas the rise in circulating FGF23 and the fall in $1,25(\text{OH})_2\text{D}_3$ were noted later [139].

A diet rich in phosphate and low in calcium increased plasma PTH in younger adults [131], although there was no difference compared with an isolated low calcium diet [140]. In addition, Katsumata et al. [141] found that if an elevated dietary phosphate intake is accompanied by high calcium intake, it blunts the effect of the increased phosphate load on PTH secretion. Two large surveys showed no relationship between dietary phosphate intake and BMD or BMC, confirming the beneficial effects of a diet rich in calcium or with a high calcium/phosphate ratio on bone [142,143]. In contrast, however, the abovementioned studies observed a direct association between low phosphate intake and decreased BMD [142,143].

Table 3. Foods with high phosphate content (phosphate content per 100 g serving).

Dairy Products	Meat and Fish	Legumes and Vegetables	Others
Cheese (464–602 mg)	Canned sardines (489 mg)	Soybeans (180 mg)	Sesame seeds (616 mg)
Cottage cheese (116–143 mg)	Canned salmon (326 mg)	Mushrooms (140 mg)	Walnuts (510 mg)
Yogurt, all types (89–141 mg)	Pork (173–294 mg)	Chickpeas (130 mg)	Pistachio nuts (500 mg)
Milk (87–110 mg)	Veal (237–258 mg)	Beans (103 mg)	Almonds (440 mg)
	Beef (178–231 mg)	Cabbage (70 mg)	Curry powder (260 mg)
	Tuna (138 mg)	Broccoli (60 mg)	Peanuts (250 mg)

Data from the Harvard T.H. Chan School of Public Health Nutrition Department.

Table 4. Dietary factors associated with an increased risk of SHPT.

Dietary Factors	Potential Effect on Bone and Mineral Metabolism
High protein intake	Increased IGF-I and osteocalcin
High dietary acid load	Increased urinary calcium excretion
Low calcium intake	Increased 1,25(OH) ₂ D ₃ and PTH
Insufficient vitamin D supplementation	Reduced renal reabsorption and intestinal uptake of calcium
Low fruits and vegetables intake	Potential decrease in BMD
Low magnesium intake	Potential osteopenia and negative calcium balance
Higher phosphate intake	Increased FGF23 and PTH

5.5. Lipid Consumption

Obesity is known to alter vitamin D metabolism by reducing circulating 25(OH)D₃ through an incompletely understood mechanism [144]. Mice fed with a diet rich in saturated fatty acids showed reduced 25(OH)D₃ and increased 1,25(OH)₂D₃ concentrations, compared to a low-fat diet. This was caused by induction of renal 1 α -hydroxylase, inhibition of 24-hydroxylase and decreased expression of 25-hydroxylase mRNA in the liver and elevated plasma PTH. Thus, the authors hypothesized that a high fat diet might induce a state of increased PTH secretion, leading to altered 1,25(OH)₂D₃ regulation, partially explaining the reduced activity of hepatic 25-hydroxylase in obese patients [145].

On the contrary, a greater consumption of monounsaturated fatty acids, such as olive oil, has been found to improve bone health [146,147]. They contain phenolic compounds that can positively modulate the proliferation and maturation of osteoblastic cells by increasing alkaline phosphatase activity and calcium ions deposition in the extracellular matrix [148]. Tyrosol and hydroxytyrosol, two of the main phenolic compounds of olive oil, have been found to improve the loss of bone mass induced by inflammation [149].

Finally, recent evidence suggests a positive effect of weight loss on 25(OH)D₃ concentrations, demonstrating a direct association between serum vitamin D and weight reduction [150–152], especially when the weight loss was between 5% and 10% [150,151].

6. Diet and Secondary Hyperparathyroidism in Non-Dialysis-Dependent CKD

The mainstay of CKD-related secondary hyperparathyroidism treatment is the correction of the pathogenic triggers known to induce or worsen this condition. Hyperphosphatemia is indeed the most common risk factor associated with SHPT in case of reduced renal function [153]. First-line therapy therefore aims at avoiding hyperphosphatemia. Historically, the most common dietary advice was to reduce protein intake, especially consumption of animal-derived foods [154]. In the last decade, dietary advice for protein restriction changed, focusing not on the absolute intake of phosphates but rather on the sources of the phosphates ingested [155,156].

The KDOQI nutritional guidelines 2020 [1] suggested that metabolically stable patients affected by CKD stage G3–G5 should start a very low protein diet (0.55–0.6 or 0.28–0.43 g/kg/day with keto-acid/amino acid analogues) to reduce CKD progression and death. However, only a few RCTs have investigated the effect of such a diet on nutritional parameters including serum albumin, total protein or muscle strength [157,158] and a risk of sarcopenia and malnutrition might exist, especially for older patients.

In addition the updated KDIGO guideline on CKD-MBD 2017 suggests maintaining serum phosphate in the reference range in patients affected by CKD stage G3a–G5 by reducing dietary phosphate intake or starting a phosphate binder [159].

RCTs with clinical outcomes on phosphate binders showed that the obtained reduction in circulating phosphate was indeed accompanied by lower mortality for both dialyzed and non-dialyzed CKD patients [160,161], whereas calcium-free phosphate binders seem to also reduce the progression of vascular calcifications [162]. On the contrary, the efficacy of dietary measures on plasma phosphate is controversial: some authors find only a modest or null effect of dietary phosphate restriction in lowering serum phosphate [160,163–165], which does not necessarily reflect total phosphate balance and reduced phosphate intake may be counterbalanced by a compensatory decrease in FGF23 and PTH concentration. To confirm these mechanisms, Ritter and colleagues found a direct association between phosphate restriction and calcium-sensing receptor (CaSR) expression and function in a uremic rat model. Switching from a 1.2% to a 0.2% phosphate diet led to normalization of CaSR expression, arrested parathyroid hyperplasia and reduced PTH [166]. At the same time, it was reported that phosphate restriction elicits a fall in circulating FGF23 concentrations in CKD patients [167].

An analysis of patients with estimated GFR < 60 mL/min/1.73 m² and available 24 h dietary data in the Third National Health and Nutrition Examination Survey [168], revealed that participants in either the highest or the lowest quartile for dietary phosphate intake had no differences in serum phosphate concentrations. In addition, in patients not receiving maintenance hemodialysis, phosphate intake was not associated with all-cause mortality.

More recently, Selamet et al. [169] observed that dietary phosphate intake, estimated through 24 h urinary phosphate excretion in 795 patients with CKD stage G3a-G5, was not associated with higher risk of end-stage kidney disease and all-cause mortality. The authors raised a concern regarding excessive dietary protein restriction and the inherent risk for malnutrition, which is already known to increase the risk of death in CKD patients [170].

These results may lead to the conclusion that dietary advice yields only a modest effect on the management of SHPT. However, the use of urinary phosphate excretion alone may be not a strong predictor of phosphate balance in patients affected by CKD [171]: in patients with normal renal function, a dietary phosphate load does not lead to hyperphosphatemia because of a compensatory increase in urinary phosphate excretion induced by phosphaturic hormones such as PTH and FGF-23 [167,172]. In contrast, in patients with advanced CKD, this response is impaired, possibly increasing the risk of a positive phosphate balance, even if salivary and gastrointestinal phosphate clearances are increased [173–175].

At the same time, significant differences between direct determination of phosphate contents in foods compared with nutritional databases were recently reported [155]. This inaccuracy, together with hidden dietary phosphate sources, raises further concern in predicting the average intake of phosphate in CKD patients by dietary recalls and it may at least partially explain the heterogeneous results in the literature on the effects of phosphate restriction. The utility of the urinary phosphate/urea nitrogen ratio in the identification of patients with higher inorganic phosphate intake was recently demonstrated [176]. This may be used as a useful tool for monitoring hidden dietary phosphate sources in CKD patients.

The relationship between the phosphate content of foods and its gastrointestinal absorption is even more complex. In fact, the source of dietary phosphate has been demonstrated to modify the risk of hyperphosphatemia as well. This was shown in a crossover trial including nine patients with CKD stages G3-G4, who switched from a meat-based diet to a purely vegetarian diet [155]. Although the total dietary intakes of phosphate (795 vs. 810 mg/day, respectively) and calcium (1176 vs. 1310 mg/day, respectively) were similar, the patients consuming only vegetarian foods showed reduced plasma phosphate and FGF23 concentrations and a slight increase in PTH, compared to the meat-based diet.

An analysis of 2918 participants in the Chronic Renal Insufficiency Cohort (CRIC) [177] with available dietary data confirmed the former results: higher intake of plant vs. meat proteins was associated with reduced plasma FGF23 and increased serum bicarbonate concentrations, without affecting serum phosphate or plasma PTH levels.

The source of dietary phosphate likely explains these results: the bioavailability of inorganic phosphate, which is commonly used as a food preservative and in processed meat, is high [156,178,179]. Despite the total amount of phosphate being similar between meat and vegetables, the organic phosphate found in vegetables such as legumes, nuts and cereals is mainly present in form of phytate [180]. Since humans lack the phytate degrading enzyme phytase, the bioavailability of phosphate in plants is reduced compared with animal proteins.

The linkage between altered acid-base homeostasis and SHPT in CKD patients is well characterized and a state of metabolic acidosis was found to be associated with worsening mineral bone disease by directly increasing bone buffering, PTH and FGF23 secretion [181–183], leading to negative calcium balance and loss of bone mineral density [97,184].

Recently, dietary acid load was also taken into account in the regulation of phosphate homeostasis. Higher dietary acid load has been associated with reduced plasma bicarbonate in patients affected by CKD [185]. This was shown to be counterbalanced by higher serum phosphate and urinary phosphate excretion, in both cases probably due to a compensatory increase in titratable acid excretion and bone buffering [185,186].

In CKD patients, serum calcium concentration is normal until the most advanced stages of the disease, when it may decrease. Whereas the development of hypocalcemia is a further stimulation for PTH secretion, excessive positive calcium balance may increase the risk for ectopic calcifications and cardiovascular risk. The available evidence on dietary calcium [124,187] show that a balanced calcium intake of approximately 800–1000 mg/day decreases plasma PTH without affecting serum calcium or phosphate concentrations in non-dialyzed CKD patients who are not taking active vitamin D. These considerations are in line with the average recommended calcium consumption for healthy subjects [188].

7. Diet and Secondary Hyperparathyroidism in Dialysis-Dependent CKD

The nutritional requirements of CKD patients change substantially when they start renal replacement therapy [1,189]. As previously described for CKD patients, increased plasma PTH and hyperphosphatemia have been found to be a frequent and deleterious condition associated with the progression of mineral bone disease and an increased risk for all-cause mortality [190–192]. Furthermore, it was estimated that CKD-MBD accounts for up to 20% of overall mortality in hemodialysis patients [193]. Besides, in those patients there is also a high risk of malnutrition, which itself is linked to higher mortality rates. Hence, the latest nutritional guidelines on CKD [1] recommend avoidance of a low protein diet in both hemodialysis and peritoneal dialysis patients and advocate a daily dietary protein intake between 1.0 and 1.2 g/kg body weight. Instead of pursuing a low protein diet, it was demonstrated that a useful method for reducing phosphate intake is to counsel hemodialysis patients on identifying foods containing phosphate additives, leading to a significant serum phosphate decrease after 3 months [194].

Compared to non-dialysis dependent CKD, the maintenance of a neutral calcium balance is much more complex in hemodialysis patients: it is influenced by calcium consumption, active vitamin D supplementation, calcium content in the dialysate and dialysis modality [195]. It was proposed that if total calcium intake exceeds 1500 mg/day, especially in patients receiving active vitamin D analogues [196], it would increase the risk for extraosseous calcifications [197].

8. Conclusions

The available evidence on dietary manipulation in the management of secondary hyperparathyroidism confirms the beneficial effect of a diet characterized by lower phosphate and balanced calcium (800–1000 and 1000–1200 mg/day for CKD patients and the general population, respectively) [119,123] and vitamin D (400–800 IU/day) [198] content, especially in a subset of medical conditions such as CKD, obesity and gut malabsorption. Besides, reduced protein intake in CKD patients is associated with better control of SHPT risk factors, although its strength in maintaining serum phosphate in the reference range

and the resulting outcomes are debated, mostly for dialyzed patients. In addition, consensus on the effect of dietary acid loads on bone health has not been reached. In conclusion, a reasonable approach for reducing the risk for secondary hyperparathyroidism is to individualize dietary manipulation based on existing risk factors and concomitant medical conditions. More studies are needed to evaluate long-term outcomes of a balanced diet on the management and prevention of secondary hyperparathyroidism in at-risk patients.

Funding: This research received no external funding.

Conflicts of Interest: The authors declare no conflict of interest.

Disclosures: P.M.F. received consultant fees and grant support from Allena Pharmaceuticals, Alnylam, AstraZeneca, BioHealth Italia, Vifor Fresenius. P.M.F., M.B., M.A. and A.N. are members of the European Reference Network for Rare Kidney Diseases (ERKNet)—Project ID No 739532. All the other authors report no disclosures.

References

- Ikizler, T.A.; Burrowes, J.D.; Byham-Gray, L.D.; Campbell, K.L.; Carrero, J.-J.; Chan, W.; Fouque, D.; Friedman, A.N.; Ghaddar, S.; Goldstein-Fuchs, D.J.; et al. KDOQI Clinical Practice Guideline for Nutrition in CKD: 2020 Update. *Am. J. Kidney Dis.* **2020**, *76*, S1–S107. [\[CrossRef\]](#)
- Bargagli, M.; Tio, M.C.; Waikar, S.S.; Ferraro, P.M. Dietary Oxalate Intake and Kidney Outcomes. *Nutrients* **2020**, *12*, 2673. [\[CrossRef\]](#) [\[PubMed\]](#)
- Itani, O.; Tsang, R. Normal bone and mineral physiology and metabolism. In *Neonatal Nutrition and Metabolism*; Thureen, P.J., Hay, W.W., Eds.; Cambridge University Press: Cambridge, UK, 2006; pp. 185–228. ISBN 978-1-107-41179-1.
- Datta, H.K.; Ng, W.F.; Walker, J.A.; Tuck, S.P.; Varanasi, S.S. The Cell Biology of Bone Metabolism. *J. Clin. Pathol.* **2008**, *61*, 577–587. [\[CrossRef\]](#) [\[PubMed\]](#)
- Sarko, J. Bone and Mineral Metabolism. *Emerg. Med. Clin. N. Am.* **2005**, *23*, 703–721. [\[CrossRef\]](#) [\[PubMed\]](#)
- Moe, S.M. Disorders of Calcium, Phosphorus, and Magnesium. *Am. J. Kidney Dis.* **2005**, *45*, 213–218. [\[CrossRef\]](#)
- Infante, M.; Fabi, A.; Cognetti, F.; Gorini, S.; Caprio, M.; Fabbri, A. RANKL/RANK/OPG System beyond Bone Remodeling: Involvement in Breast Cancer and Clinical Perspectives. *J. Exp. Clin. Cancer Res.* **2019**, *38*, 12. [\[CrossRef\]](#)
- Boyce, B.F.; Xing, L. The RANKL/RANK/OPG Pathway. *Curr. Osteoporos. Rep.* **2007**, *5*, 98–104. [\[CrossRef\]](#)
- Clarke, B. Normal Bone Anatomy and Physiology. *Clin. J. Am. Soc. Nephrol.* **2008**, *3*, S131–S139. [\[CrossRef\]](#) [\[PubMed\]](#)
- Cashman, K.D. Calcium Intake, Calcium Bioavailability and Bone Health. *Br. J. Nutr.* **2002**, *87*, S169–S177. [\[CrossRef\]](#)
- Mazzaferro, S.; Bagordo, D.; De Martini, N.; Pasquali, M.; Rotondi, S.; Tartaglione, L.; Stenvinkel, P. Inflammation, Oxidative Stress, and Bone in Chronic Kidney Disease in the Osteoimmunology Era. *Calcif. Tissue Int.* **2021**, 1–9. [\[CrossRef\]](#)
- Christakos, S. Recent Advances in Our Understanding of 1,25-Dihydroxyvitamin D(3) Regulation of Intestinal Calcium Absorption. *Arch. Biochem. Biophys.* **2012**, *523*, 73–76. [\[CrossRef\]](#) [\[PubMed\]](#)
- Seldin, D.W. Renal Handling of Calcium. *Nephron* **1999**, *81* (Suppl. 1), 2–7. [\[CrossRef\]](#) [\[PubMed\]](#)
- Loupy, A.; Ramakrishnan, S.K.; Wootla, B.; Chambrey, R.; de la Faille, R.; Bourgeois, S.; Bruneval, P.; Mandet, C.; Christensen, E.I.; Faure, H.; et al. PTH-Independent Regulation of Blood Calcium Concentration by the Calcium-Sensing Receptor. *J. Clin. Investig.* **2012**, *122*, 3355–3367. [\[CrossRef\]](#) [\[PubMed\]](#)
- Frische, S.; Alexander, R.T.; Ferreira, P.; Tan, R.S.G.; Wang, W.; Svenningsen, P.; Skjødt, K.; Dimke, H. Localization and Regulation of Claudin-14 in Experimental Models of Hypercalcemia. *Am. J. Physiol. Ren. Physiol.* **2021**, *320*, F74–F86. [\[CrossRef\]](#) [\[PubMed\]](#)
- Razzaque, M.S. FGF23-Mediated Regulation of Systemic Phosphate Homeostasis: Is Klotho an Essential Player? *Am. J. Physiol. Ren. Physiol.* **2009**, *296*, F470–F476. [\[CrossRef\]](#)
- Khundmiri, S.J.; Murray, R.D.; Lederer, E. PTH and Vitamin D. *Compr. Physiol.* **2016**, *6*, 561–601. [\[CrossRef\]](#)
- Tanaka, Y.; Deluca, H.F. The Control of 25-Hydroxyvitamin D Metabolism by Inorganic Phosphorus. *Arch. Biochem. Biophys.* **1973**, *154*, 566–574. [\[CrossRef\]](#)
- Llach, F.; Massry, S.G. On the Mechanism of Secondary Hyperparathyroidism in Moderate Renal Insufficiency. *J. Clin. Endocrinol. Metab.* **1985**, *61*, 601–606. [\[CrossRef\]](#) [\[PubMed\]](#)
- Antoniucci, D.M.; Yamashita, T.; Portale, A.A. Dietary Phosphorus Regulates Serum Fibroblast Growth Factor-23 Concentrations in Healthy Men. *J. Clin. Endocrinol. Metab.* **2006**, *91*, 3144–3149. [\[CrossRef\]](#)
- Cunningham, J.; Locatelli, F.; Rodriguez, M. Secondary Hyperparathyroidism: Pathogenesis, Disease Progression, and Therapeutic Options. *Clin. J. Am. Soc. Nephrol.* **2011**, *6*, 913–921. [\[CrossRef\]](#)
- Werner, A.; Kinne, R.K. Evolution of the Na-P(i) Cotransport Systems. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* **2001**, *280*, R301–R312. [\[CrossRef\]](#)
- Nguyen-Yamamoto, L.; Karaplis, A.C.; St-Arnaud, R.; Goltzman, D. Fibroblast Growth Factor 23 Regulation by Systemic and Local Osteoblast-Synthesized 1,25-Dihydroxyvitamin D. *J. Am. Soc. Nephrol.* **2017**, *28*, 586–597. [\[CrossRef\]](#) [\[PubMed\]](#)

24. Liu, S.; Tang, W.; Zhou, J.; Stubbs, J.R.; Luo, Q.; Pi, M.; Quarles, L.D. Fibroblast Growth Factor 23 Is a Counter-Regulatory Phosphaturic Hormone for Vitamin D. *J. Am. Soc. Nephrol.* **2006**, *17*, 1305–1315. [[CrossRef](#)]
25. Shimada, T.; Hasegawa, H.; Yamazaki, Y.; Muto, T.; Hino, R.; Takeuchi, Y.; Fujita, T.; Nakahara, K.; Fukumoto, S.; Yamashita, T. FGF-23 Is a Potent Regulator of Vitamin D Metabolism and Phosphate Homeostasis. *J. Bone Min. Res.* **2004**, *19*, 429–435. [[CrossRef](#)]
26. Ben-Dov, I.Z.; Galitzer, H.; Lavi-Moshayoff, V.; Goetz, R.; Kuro-o, M.; Mohammadi, M.; Sirkis, R.; Naveh-Many, T.; Silver, J. The Parathyroid Is a Target Organ for FGF23 in Rats. *J. Clin. Invest.* **2007**, *117*, 4003–4008. [[CrossRef](#)] [[PubMed](#)]
27. Jamal, S.A.; Miller, P.D. Secondary and Tertiary Hyperparathyroidism. *J. Clin. Densitom.* **2013**, *16*, 64–68. [[CrossRef](#)]
28. Chandran, M.; Wong, J. Secondary and Tertiary Hyperparathyroidism in Chronic Kidney Disease: An Endocrine and Renal Perspective. *Indian J. Endocrinol. Metab.* **2019**, *23*, 391–399. [[CrossRef](#)]
29. Pourshahidi, L.K. Vitamin D and Obesity: Current Perspectives and Future Directions. *Proc. Nutr. Soc.* **2015**, *74*, 115–124. [[CrossRef](#)] [[PubMed](#)]
30. Wortsman, J.; Matsuoka, L.Y.; Chen, T.C.; Lu, Z.; Holick, M.F. Decreased Bioavailability of Vitamin D in Obesity. *Am. J. Clin. Nutr.* **2000**, *72*, 690–693. [[CrossRef](#)]
31. Vimalaewaran, K.S.; Berry, D.J.; Lu, C.; Tikkanen, E.; Pilz, S.; Hiraki, L.T.; Cooper, J.D.; Dastani, Z.; Li, R.; Houston, D.K.; et al. Causal Relationship between Obesity and Vitamin D Status: Bi-Directional Mendelian Randomization Analysis of Multiple Cohorts. *PLoS Med.* **2013**, *10*, e1001383. [[CrossRef](#)] [[PubMed](#)]
32. Yetley, E.A. Assessing the Vitamin D Status of the US Population. *Am. J. Clin. Nutr.* **2008**, *88*, 558S–564S. [[CrossRef](#)]
33. Cheng, S.; Massaro, J.M.; Fox, C.S.; Larson, M.G.; Keyes, M.J.; McCabe, E.L.; Robins, S.J.; O'Donnell, C.J.; Hoffmann, U.; Jacques, P.F.; et al. Adiposity, Cardiometabolic Risk, and Vitamin D Status: The Framingham Heart Study. *Diabetes* **2010**, *59*, 242–248. [[CrossRef](#)] [[PubMed](#)]
34. Borges, J.L.C.; de Miranda, I.S.M.; Sarquis, M.M.S.; Borba, V.; Maeda, S.S.; Lazaretti-Castro, M.; Blinkey, N. Obesity, Bariatric Surgery, and Vitamin D. *J. Clin. Densitom.* **2018**, *21*, 157–162. [[CrossRef](#)]
35. Chakhtoura, M.T.; Nakhoul, N.N.; Shawwa, K.; Mantzoros, C.; El Hajj Fuleihan, G.A. Hypovitaminosis D in Bariatric Surgery: A Systematic Review of Observational Studies. *Metabolism* **2016**, *65*, 574–585. [[CrossRef](#)] [[PubMed](#)]
36. Wei, J.-H.; Lee, W.-J.; Chong, K.; Lee, Y.-C.; Chen, S.-C.; Huang, P.-H.; Lin, S.-J. High Incidence of Secondary Hyperparathyroidism in Bariatric Patients: Comparing Different Procedures. *Obes. Surg.* **2018**, *28*, 798–804. [[CrossRef](#)] [[PubMed](#)]
37. Krupa-Kozak, U. Pathologic Bone Alterations in Celiac Disease: Etiology, Epidemiology, and Treatment. *Nutrition* **2014**, *30*, 16–24. [[CrossRef](#)] [[PubMed](#)]
38. Selby, P.L.; Davies, M.; Adams, J.E.; Mawer, E.B. Bone Loss in Celiac Disease Is Related to Secondary Hyperparathyroidism. *J. Bone Min. Res.* **1999**, *14*, 652–657. [[CrossRef](#)]
39. Jahnsen, J.; Falch, J.A.; Mowinckel, P.; Aadland, E. Vitamin D Status, Parathyroid Hormone and Bone Mineral Density in Patients with Inflammatory Bowel Disease. *Scand. J. Gastroenterol.* **2002**, *37*, 192–199. [[CrossRef](#)]
40. Nordin, B.E.C.; Morris, H.A.; Horowitz, M.; Coates, P.S.; O'Loughlin, P.D.; Need, A.G. Calcium Malabsorption Does Not Cause Secondary Hyperparathyroidism. *Calcif. Tissue Int.* **2009**, *85*, 31–36. [[CrossRef](#)] [[PubMed](#)]
41. Arasaradnam, R.P.; Bolton, R.P. Hypomagnesaemia Due to Malabsorption Is Not Always Responsive to Oral Magnesium Oxide Supplementation Alone. *Gut* **2002**, *50*, 897. [[CrossRef](#)]
42. Fatemi, S.; Ryzen, E.; Flores, J.; Endres, D.B.; Rude, R.K. Effect of Experimental Human Magnesium Depletion on Parathyroid Hormone Secretion and 1,25-Dihydroxyvitamin D Metabolism. *J. Clin. Endocrinol. Metab.* **1991**, *73*, 1067–1072. [[CrossRef](#)] [[PubMed](#)]
43. Uchiyama, T.; Ohkido, I.; Nakashima, A.; Saito, Y.; Okabe, M.; Yokoo, T. Severe Chronic Kidney Disease Environment Reduced Calcium-Sensing Receptor Expression in Parathyroid Glands of Adenine-Induced Rats Even without High Phosphorus Diet. *BMC Nephrol.* **2020**, *21*, 219. [[CrossRef](#)]
44. Dhayat, N.A.; Ackermann, D.; Pruijm, M.; Ponte, B.; Ehret, G.; Guessous, I.; Leichter, A.B.; Paccaud, F.; Mohaupt, M.; Fiedler, G.-M.; et al. Fibroblast Growth Factor 23 and Markers of Mineral Metabolism in Individuals with Preserved Renal Function. *Kidney Int.* **2016**, *90*, 648–657. [[CrossRef](#)]
45. Brown, E.M. Extracellular Ca²⁺ Sensing, Regulation of Parathyroid Cell Function, and Role of Ca²⁺ and Other Ions as Extracellular (First) Messengers. *Physiol. Rev.* **1991**, *71*, 371–411. [[CrossRef](#)] [[PubMed](#)]
46. Slatopolsky, E.; Brown, A.; Dusso, A. Calcium, Phosphorus and Vitamin D Disorders in Uremia. *Cardiovasc. Disord. Hemodial.* **2005**, *149*, 261–271. [[CrossRef](#)]
47. Komaba, H.; Fukagawa, M. FGF23-Parathyroid Interaction: Implications in Chronic Kidney Disease. *Kidney Int.* **2010**, *77*, 292–298. [[CrossRef](#)]
48. González, E.A.; Sachdeva, A.; Oliver, D.A.; Martin, K.J. Vitamin D Insufficiency and Deficiency in Chronic Kidney Disease. A Single Center Observational Study. *Am. J. Nephrol.* **2004**, *24*, 503–510. [[CrossRef](#)]
49. Silver, J.; Yalcindag, C.; Sela-Brown, A.; Kilav, R.; Naveh-Many, T. Regulation of the Parathyroid Hormone Gene by Vitamin D, Calcium and Phosphate. *Kidney Int. Suppl.* **1999**, *73*, S2–S7. [[CrossRef](#)]
50. Gogusev, J.; Duchambon, P.; Hory, B.; Giovannini, M.; Goureau, Y.; Sarfati, E.; Drüeke, T.B. Depressed Expression of Calcium Receptor in Parathyroid Gland Tissue of Patients with Hyperparathyroidism. *Kidney Int.* **1997**, *51*, 328–336. [[CrossRef](#)]

51. Yano, S.; Sugimoto, T.; Tsukamoto, T.; Chihara, K.; Kobayashi, A.; Kitazawa, S.; Maeda, S.; Kitazawa, R. Association of Decreased Calcium-Sensing Receptor Expression with Proliferation of Parathyroid Cells in Secondary Hyperparathyroidism. *Kidney Int.* **2000**, *58*, 1980–1986. [[CrossRef](#)]
52. Centeno, P.P.; Herberger, A.; Mun, H.-C.; Tu, C.; Nemeth, E.F.; Chang, W.; Conigrave, A.D.; Ward, D.T. Phosphate Acts Directly on the Calcium-Sensing Receptor to Stimulate Parathyroid Hormone Secretion. *Nat. Commun.* **2019**, *10*, 4693. [[CrossRef](#)]
53. Garfia, B.; Cañadillas, S.; Canalejo, A.; Luque, F.; Siendones, E.; Quesada, M.; Almadén, Y.; Aguilera-Tejero, E.; Rodríguez, M. Regulation of Parathyroid Vitamin D Receptor Expression by Extracellular Calcium. *J. Am. Soc. Nephrol.* **2002**, *13*, 2945–2952. [[CrossRef](#)]
54. Gutierrez, O.; Isakova, T.; Rhee, E.; Shah, A.; Holmes, J.; Colterone, G.; Jüppner, H.; Wolf, M. Fibroblast Growth Factor-23 Mitigates Hyperphosphatemia but Accentuates Calcitriol Deficiency in Chronic Kidney Disease. *J. Am. Soc. Nephrol.* **2005**, *16*, 2205–2215. [[CrossRef](#)] [[PubMed](#)]
55. Wahl, P.; Wolf, M. FGF23 in Chronic Kidney Disease. *Adv. Exp. Med. Biol.* **2012**, *728*, 107–125. [[CrossRef](#)]
56. Rotondi, S.; Pasquali, M.; Tartaglione, L.; Muci, M.L.; Mandanici, G.; Leonangeli, C.; Sales, S.; Farcomeni, A.; Mazzaferro, S. Soluble α -Klotho Serum Levels in Chronic Kidney Disease. *Int. J. Endocrinol.* **2015**, *2015*, 872193. [[CrossRef](#)]
57. Gutiérrez, O.M.; Mannstadt, M.; Isakova, T.; Rauh-Hain, J.A.; Tamez, H.; Shah, A.; Smith, K.; Lee, H.; Thadhani, R.; Jüppner, H.; et al. Fibroblast Growth Factor 23 and Mortality among Patients Undergoing Hemodialysis. *N. Engl. J. Med.* **2008**, *359*, 584–592. [[CrossRef](#)]
58. Isakova, T.; Gutiérrez, O.M.; Chang, Y.; Shah, A.; Tamez, H.; Smith, K.; Thadhani, R.; Wolf, M. Phosphorus Binders and Survival on Hemodialysis. *J. Am. Soc. Nephrol.* **2009**, *20*, 388–396. [[CrossRef](#)]
59. Ix, J.H.; Shlipak, M.G.; Wassel, C.L.; Whooley, M.A. Fibroblast Growth Factor-23 and Early Decrements in Kidney Function: The Heart and Soul Study. *Nephrol. Dial. Transpl.* **2010**, *25*, 993–997. [[CrossRef](#)] [[PubMed](#)]
60. Vogt, I.; Haffner, D.; Leifheit-Nestler, M. FGF23 and Phosphate-Cardiovascular Toxins in CKD. *Toxins* **2019**, *11*, 647. [[CrossRef](#)]
61. Isakova, T.; Wahl, P.; Vargas, G.S.; Gutiérrez, O.M.; Scialla, J.; Xie, H.; Appleby, D.; Nessel, L.; Bellovich, K.; Chen, J.; et al. Fibroblast Growth Factor 23 Is Elevated before Parathyroid Hormone and Phosphate in Chronic Kidney Disease. *Kidney Int.* **2011**, *79*, 1370–1378. [[CrossRef](#)] [[PubMed](#)]
62. Jimbo, R.; Shimosawa, T. Cardiovascular Risk Factors and Chronic Kidney Disease-FGF23: A Key Molecule in the Cardiovascular Disease. *Int. J. Hypertens.* **2014**, *2014*, 381082. [[CrossRef](#)]
63. Palmer, S.C.; Hayen, A.; Macaskill, P.; Pellegrini, F.; Craig, J.C.; Elder, G.J.; Strippoli, G.F.M. Serum Levels of Phosphorus, Parathyroid Hormone, and Calcium and Risks of Death and Cardiovascular Disease in Individuals with Chronic Kidney Disease: A Systematic Review and Meta-Analysis. *JAMA* **2011**, *305*, 1119–1127. [[CrossRef](#)]
64. Kestenbaum, B.; Katz, R.; de Boer, I.; Hoofnagle, A.; Sarnak, M.J.; Shlipak, M.G.; Jenny, N.S.; Siscovick, D.S. Vitamin D, Parathyroid Hormone, and Cardiovascular Events among Older Adults. *J. Am. Coll. Cardiol.* **2011**, *58*, 1433–1441. [[CrossRef](#)] [[PubMed](#)]
65. Tanaka, M.; Komaba, H.; Fukagawa, M. Emerging Association Between Parathyroid Hormone and Anemia in Hemodialysis Patients. *Apher. Dial.* **2018**, *22*, 242–245. [[CrossRef](#)] [[PubMed](#)]
66. Messa, P.; Alfieri, C.M. Secondary and Tertiary Hyperparathyroidism. *Front. Horm. Res.* **2019**, *51*, 91–108. [[CrossRef](#)]
67. Mazzaferro, S.; Cianciolo, G.; De Pascalis, A.; Guglielmo, C.; Urena Torres, P.A.; Bover, J.; Tartaglione, L.; Pasquali, M.; La Manna, G. Bone, Inflammation and the Bone Marrow Niche in Chronic Kidney Disease: What Do We Know? *Nephrol. Dial. Transpl.* **2018**, *33*, 2092–2100. [[CrossRef](#)]
68. Aleksinskaya, M.A.; Monge, M.; Siebelt, M.; Slot, E.M.; Koekkoek, K.M.; de Bruin, R.G.; Massy, Z.A.; Weinans, H.; Rabelink, T.J.; Fibbe, W.E.; et al. Chronic Kidney Failure Mineral Bone Disorder Leads to a Permanent Loss of Hematopoietic Stem Cells through Dysfunction of the Stem Cell Niche. *Sci. Rep.* **2018**, *8*, 15385. [[CrossRef](#)] [[PubMed](#)]
69. Cashman, K.D. Diet, Nutrition, and Bone Health. *J. Nutr.* **2007**, *137*, 2507S–2512S. [[CrossRef](#)]
70. Thorpe, M.P.; Jacobson, E.H.; Layman, D.K.; He, X.; Kris-Etherton, P.M.; Evans, E.M. A Diet High in Protein, Dairy, and Calcium Attenuates Bone Loss over Twelve Months of Weight Loss and Maintenance Relative to a Conventional High-Carbohydrate Diet in Adults. *J. Nutr.* **2008**, *138*, 1096–1100. [[CrossRef](#)]
71. Sukumar, D.; Ambia-Sobhan, H.; Zurfluh, R.; Schluskel, Y.; Stahl, T.J.; Gordon, C.L.; Shapses, S.A. Areal and Volumetric Bone Mineral Density and Geometry at Two Levels of Protein Intake during Caloric Restriction: A Randomized, Controlled Trial. *J. Bone Min. Res.* **2011**, *26*, 1339–1348. [[CrossRef](#)] [[PubMed](#)]
72. Tengstrand, B.; Cederholm, T.; Söderqvist, A.; Tidermark, J. Effects of Protein-Rich Supplementation and Nandrolone on Bone Tissue after a Hip Fracture. *Clin. Nutr.* **2007**, *26*, 460–465. [[CrossRef](#)] [[PubMed](#)]
73. Schürch, M.A.; Rizzoli, R.; Slosman, D.; Vadas, L.; Vergnaud, P.; Bonjour, J.P. Protein Supplements Increase Serum Insulin-like Growth Factor-I Levels and Attenuate Proximal Femur Bone Loss in Patients with Recent Hip Fracture. A Randomized, Double-Blind, Placebo-Controlled Trial. *Ann. Intern. Med.* **1998**, *128*, 801–809. [[CrossRef](#)]
74. Tirosh, A.; de Souza, R.J.; Sacks, F.; Bray, G.A.; Smith, S.R.; LeBoff, M.S. Sex Differences in the Effects of Weight Loss Diets on Bone Mineral Density and Body Composition: POUNDS LOST Trial. *J. Clin. Endocrinol. Metab.* **2015**, *100*, 2463–2471. [[CrossRef](#)]
75. Jesudason, D.; Nordin, B.C.; Keogh, J.; Clifton, P. Comparison of 2 Weight-Loss Diets of Different Protein Content on Bone Health: A Randomized Trial. *Am. J. Clin. Nutr.* **2013**, *98*, 1343–1352. [[CrossRef](#)]

76. Kerstetter, J.E.; Bihuniak, J.D.; Brindisi, J.; Sullivan, R.R.; Mangano, K.M.; Larocque, S.; Kotler, B.M.; Simpson, C.A.; Cusano, A.M.; Gaffney-Stomberg, E.; et al. The Effect of a Whey Protein Supplement on Bone Mass in Older Caucasian Adults. *J. Clin. Endocrinol. Metab.* **2015**, *100*, 2214–2222. [[CrossRef](#)]
77. Zhu, K.; Meng, X.; Kerr, D.A.; Devine, A.; Solah, V.; Binns, C.W.; Prince, R.L. The Effects of a Two-Year Randomized, Controlled Trial of Whey Protein Supplementation on Bone Structure, IGF-1, and Urinary Calcium Excretion in Older Postmenopausal Women. *J. Bone Min. Res.* **2011**, *26*, 2298–2306. [[CrossRef](#)]
78. Flodin, L.; Sääf, M.; Cederholm, T.; Al-Ani, A.N.; Ackermann, P.W.; Samnegård, E.; Dalen, N.; Hedström, M. Additive Effects of Nutritional Supplementation, Together with Bisphosphonates, on Bone Mineral Density after Hip Fracture: A 12-Month Randomized Controlled Study. *Clin. Interv. Aging* **2014**, *9*, 1043–1050. [[CrossRef](#)] [[PubMed](#)]
79. Li, Z.; Treyzon, L.; Chen, S.; Yan, E.; Thames, G.; Carpenter, C.L. Protein-Enriched Meal Replacements Do Not Adversely Affect Liver, Kidney or Bone Density: An Outpatient Randomized Controlled Trial. *Nutr. J.* **2010**, *9*, 72. [[CrossRef](#)] [[PubMed](#)]
80. Kukuljan, S.; Nowson, C.A.; Bass, S.L.; Sanders, K.; Nicholson, G.C.; Seibel, M.J.; Salmon, J.; Daly, R.M. Effects of a Multi-Component Exercise Program and Calcium-Vitamin-D3-Fortified Milk on Bone Mineral Density in Older Men: A Randomised Controlled Trial. *Osteoporos. Int.* **2009**, *20*, 1241–1251. [[CrossRef](#)]
81. Hannan, M.T.; Tucker, K.L.; Dawson-Hughes, B.; Cupples, L.A.; Felson, D.T.; Kiel, D.P. Effect of Dietary Protein on Bone Loss in Elderly Men and Women: The Framingham Osteoporosis Study. *J. Bone Min. Res.* **2000**, *15*, 2504–2512. [[CrossRef](#)] [[PubMed](#)]
82. Recker, R.R.; Davies, K.M.; Hinders, S.M.; Heaney, R.P.; Stegman, M.R.; Kimmel, D.B. Bone Gain in Young Adult Women. *JAMA* **1992**, *268*, 2403–2408. [[CrossRef](#)]
83. Dawson-Hughes, B.; Harris, S.S. Calcium Intake Influences the Association of Protein Intake with Rates of Bone Loss in Elderly Men and Women. *Am. J. Clin. Nutr.* **2002**, *75*, 773–779. [[CrossRef](#)]
84. Ho, S.C.; Chan, S.G.; Yip, Y.B.; Chan, C.S.Y.; Woo, J.L.F.; Sham, A. Change in Bone Mineral Density and Its Determinants in Pre- and Perimenopausal Chinese Women: The Hong Kong Perimenopausal Women Osteoporosis Study. *Osteoporos. Int.* **2008**, *19*, 1785–1796. [[CrossRef](#)] [[PubMed](#)]
85. Sahni, S.; Broe, K.E.; Tucker, K.L.; McLean, R.R.; Kiel, D.P.; Cupples, L.A.; Hannan, M.T. Association of Total Protein Intake with Bone Mineral Density and Bone Loss in Men and Women from the Framingham Offspring Study. *Public Health Nutr.* **2014**, *17*, 2570–2576. [[CrossRef](#)] [[PubMed](#)]
86. Bourrin, S.; Ammann, P.; Bonjour, J.P.; Rizzoli, R. Dietary Protein Restriction Lowers Plasma Insulin-like Growth Factor I (IGF-I), Impairs Cortical Bone Formation, and Induces Osteoblastic Resistance to IGF-I in Adult Female Rats. *Endocrinology* **2000**, *141*, 3149–3155. [[CrossRef](#)] [[PubMed](#)]
87. Bourrin, S.; Toromanoff, A.; Ammann, P.; Bonjour, J.P.; Rizzoli, R. Dietary Protein Deficiency Induces Osteoporosis in Aged Male Rats. *J. Bone Min. Res.* **2000**, *15*, 1555–1563. [[CrossRef](#)]
88. Rouy, E.; Vico, L.; Laroche, N.; Benoit, V.; Rousseau, B.; Blachier, F.; Tomé, D.; Blais, A. Protein Quality Affects Bone Status during Moderate Protein Restriction in Growing Mice. *Bone* **2014**, *59*, 7–13. [[CrossRef](#)]
89. Uenishi, K.; Ishida, H.; Toba, Y.; Aoe, S.; Itabashi, A.; Takada, Y. Milk Basic Protein Increases Bone Mineral Density and Improves Bone Metabolism in Healthy Young Women. *Osteoporos. Int.* **2007**, *18*, 385–390. [[CrossRef](#)]
90. Bharadwaj, S.; Naidu, A.G.T.; Betageri, G.V.; Prasadarao, N.V.; Naidu, A.S. Milk Ribonuclease-Enriched Lactoferrin Induces Positive Effects on Bone Turnover Markers in Postmenopausal Women. *Osteoporos. Int.* **2009**, *20*, 1603–1611. [[CrossRef](#)]
91. Aoe, S.; Toba, Y.; Yamamura, J.; Kawakami, H.; Yahiro, M.; Kumegawa, M.; Itabashi, A.; Takada, Y. Controlled Trial of the Effects of Milk Basic Protein (MBP) Supplementation on Bone Metabolism in Healthy Adult Women. *Biosci. Biotechnol. Biochem.* **2001**, *65*, 913–918. [[CrossRef](#)]
92. Aoe, S.; Koyama, T.; Toba, Y.; Itabashi, A.; Takada, Y. A Controlled Trial of the Effect of Milk Basic Protein (MBP) Supplementation on Bone Metabolism in Healthy Menopausal Women. *Osteoporos. Int.* **2005**, *16*, 2123–2128. [[CrossRef](#)]
93. Cao, J.J.; Johnson, L.K.; Hunt, J.R. A Diet High in Meat Protein and Potential Renal Acid Load Increases Fractional Calcium Absorption and Urinary Calcium Excretion without Affecting Markers of Bone Resorption or Formation in Postmenopausal Women. *J. Nutr.* **2011**, *141*, 391–397. [[CrossRef](#)]
94. Sherman, H.; Rose, M. Calcium requirement of maintenance in man. *J. Biol. Chem.* **1920**, *44*, 21–27. [[CrossRef](#)]
95. Lemann, J.; Bushinsky, D.A.; Hamm, L.L. Bone Buffering of Acid and Base in Humans. *Am. J. Physiol. Ren. Physiol.* **2003**, *285*, F811–F832. [[CrossRef](#)]
96. Kerstetter, J.E.; O'Brien, K.O.; Insogna, K.L. Dietary Protein, Calcium Metabolism, and Skeletal Homeostasis Revisited. *Am. J. Clin. Nutr.* **2003**, *78*, 584S–592S. [[CrossRef](#)]
97. Krieger, N.S.; Frick, K.K.; Bushinsky, D.A. Mechanism of Acid-Induced Bone Resorption. *Curr. Opin. Nephrol. Hypertens.* **2004**, *13*, 423–436. [[CrossRef](#)] [[PubMed](#)]
98. Mangano, K.M.; Walsh, S.J.; Kenny, A.M.; Insogna, K.L.; Kerstetter, J.E. Dietary Acid Load Is Associated with Lower Bone Mineral Density in Men with Low Intake of Dietary Calcium. *J. Bone Min. Res.* **2014**, *29*, 500–506. [[CrossRef](#)] [[PubMed](#)]
99. Trinchieri, A.; Zanetti, G.; Currò, A.; Lizzano, R. Effect of Potential Renal Acid Load of Foods on Calcium Metabolism of Renal Calcium Stone Formers. *Eur. Urol.* **2001**, *39* (Suppl. 2), 33–36. [[CrossRef](#)]
100. Ferraro, P.M.; Bargagli, M.; Trinchieri, A.; Gambaro, G. Risk of Kidney Stones: Influence of Dietary Factors, Dietary Patterns, and Vegetarian–Vegan Diets. *Nutrients* **2020**, *12*, 779. [[CrossRef](#)] [[PubMed](#)]
101. Ferraro, P.M.; Bargagli, M. Dietetic and Lifestyle Recommendations for Stone Formers. *Arch. Esp. Urol.* **2021**, *74*, 112–122.

102. Maalouf, N.M.; Moe, O.W.; Adams-Huet, B.; Sakhaee, K. Hypercalciuria Associated with High Dietary Protein Intake Is Not Due to Acid Load. *J. Clin. Endocrinol. Metab.* **2011**, *96*, 3733–3740. [[CrossRef](#)] [[PubMed](#)]
103. Calvez, J.; Poupin, N.; Chesneau, C.; Lassale, C.; Tomé, D. Protein Intake, Calcium Balance and Health Consequences. *Eur. J. Clin. Nutr.* **2012**, *66*, 281–295. [[CrossRef](#)]
104. Hunt, J.R.; Johnson, L.K.; Fariba Roughead, Z.K. Dietary Protein and Calcium Interact to Influence Calcium Retention: A Controlled Feeding Study. *Am. J. Clin. Nutr.* **2009**, *89*, 1357–1365. [[CrossRef](#)] [[PubMed](#)]
105. Remer, T.; Manz, F. Potential Renal Acid Load of Foods and Its Influence on Urine PH. *J. Am. Diet. Assoc.* **1995**, *95*, 791–797. [[CrossRef](#)]
106. Hanley, D.A.; Whiting, S.J. Does a High Dietary Acid Content Cause Bone Loss, and Can Bone Loss Be Prevented with an Alkaline Diet? *J. Clin. Densitom.* **2013**, *16*, 420–425. [[CrossRef](#)]
107. Frassetto, L.A.; Hardcastle, A.C.; Sebastian, A.; Aucott, L.; Fraser, W.D.; Reid, D.M.; Macdonald, H.M. No Evidence That the Skeletal Non-Response to Potassium Alkali Supplements in Healthy Postmenopausal Women Depends on Blood Pressure or Sodium Chloride Intake. *Eur. J. Clin. Nutr.* **2012**, *66*, 1315–1322. [[CrossRef](#)] [[PubMed](#)]
108. Macdonald, H.M.; Black, A.J.; Aucott, L.; Duthie, G.; Duthie, S.; Sandison, R.; Hardcastle, A.C.; Lanham New, S.A.; Fraser, W.D.; Reid, D.M. Effect of Potassium Citrate Supplementation or Increased Fruit and Vegetable Intake on Bone Metabolism in Healthy Postmenopausal Women: A Randomized Controlled Trial. *Am. J. Clin. Nutr.* **2008**, *88*, 465–474. [[CrossRef](#)]
109. Jehle, S.; Hulter, H.N.; Krapf, R. Effect of Potassium Citrate on Bone Density, Microarchitecture, and Fracture Risk in Healthy Older Adults without Osteoporosis: A Randomized Controlled Trial. *J. Clin. Endocrinol. Metab.* **2013**, *98*, 207–217. [[CrossRef](#)] [[PubMed](#)]
110. Park, Y.; Moon, H.-J.; Paik, D.-J.; Kim, D.-Y. Effect of Dietary Legumes on Bone-Specific Gene Expression in Ovariectomized Rats. *Nutr. Res. Pr.* **2013**, *7*, 185–191. [[CrossRef](#)]
111. Kajarabille, N.; Díaz-Castro, J.; Hijano, S.; López-Frías, M.; López-Aliaga, I.; Ochoa, J.J. A New Insight to Bone Turnover: Role of ω -3 Polyunsaturated Fatty Acids. *Sci. World J.* **2013**, *2013*, 589641. [[CrossRef](#)]
112. Anandacoomarasamy, A.; Fransen, M.; March, L. Obesity and the Musculoskeletal System. *Curr. Opin. Rheumatol.* **2009**, *21*, 71–77. [[CrossRef](#)]
113. Elefteriou, F.; Takeda, S.; Ebihara, K.; Magre, J.; Patano, N.; Kim, C.A.; Ogawa, Y.; Liu, X.; Ware, S.M.; Craigen, W.J.; et al. Serum Leptin Level Is a Regulator of Bone Mass. *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 3258–3263. [[CrossRef](#)] [[PubMed](#)]
114. Stendig-Lindberg, G.; Tepper, R.; Leichter, I. Trabecular Bone Density in a Two Year Controlled Trial of Peroral Magnesium in Osteoporosis. *Magnes. Res.* **1993**, *6*, 155–163.
115. Abraham, G.E.; Grewal, H. A Total Dietary Program Emphasizing Magnesium Instead of Calcium. Effect on the Mineral Density of Calcaneous Bone in Postmenopausal Women on Hormonal Therapy. *J. Reprod. Med.* **1990**, *35*, 503–507.
116. Dimai, H.P.; Porta, S.; Wirnsberger, G.; Lindschinger, M.; Pamperl, I.; Dobnig, H.; Wilders-Truschning, M.; Lau, K.H. Daily Oral Magnesium Supplementation Suppresses Bone Turnover in Young Adult Males. *J. Clin. Endocrinol. Metab.* **1998**, *83*, 2742–2748. [[CrossRef](#)] [[PubMed](#)]
117. Zhu, K.; Prince, R.L. Calcium and Bone. *Clin. Biochem.* **2012**, *45*, 936–942. [[CrossRef](#)]
118. Gemeinschaften, E.; Kommission, E. (Eds.) *Report on Osteoporosis in the European Community: Action for Prevention; Employment & Social Affairs Health; Publications Office of the European Union Communities: Luxembourg, 1998; ISBN 978-92-828-5333-7.*
119. Matkovic, V.; Goel, P.K.; Badenhop-Stevens, N.E.; Landoll, J.D.; Li, B.; Ilich, J.Z.; Skugor, M.; Nagode, L.A.; Mobley, S.L.; Ha, E.-J.; et al. Calcium Supplementation and Bone Mineral Density in Females from Childhood to Young Adulthood: A Randomized Controlled Trial. *Am. J. Clin. Nutr.* **2005**, *81*, 175–188. [[CrossRef](#)]
120. Vatanparast, H.; Baxter-Jones, A.; Faulkner, R.A.; Bailey, D.A.; Whiting, S.J. Positive Effects of Vegetable and Fruit Consumption and Calcium Intake on Bone Mineral Accrual in Boys during Growth from Childhood to Adolescence: The University of Saskatchewan Pediatric Bone Mineral Accrual Study. *Am. J. Clin. Nutr.* **2005**, *82*, 700–706. [[CrossRef](#)] [[PubMed](#)]
121. Zhu, K.; Greenfield, H.; Zhang, Q.; Du, X.; Ma, G.; Foo, L.H.; Cowell, C.T.; Fraser, D.R. Growth and Bone Mineral Accretion during Puberty in Chinese Girls: A Five-Year Longitudinal Study. *J. Bone Min. Res.* **2008**, *23*, 167–172. [[CrossRef](#)] [[PubMed](#)]
122. Ito, S.; Ishida, H.; Uenishi, K.; Murakami, K.; Sasaki, S. The Relationship between Habitual Dietary Phosphorus and Calcium Intake, and Bone Mineral Density in Young Japanese Women: A Cross-Sectional Study. *Asia Pac. J. Clin. Nutr.* **2011**, *20*, 411–417.
123. Tang, B.M.P.; Eslick, G.D.; Nowson, C.; Smith, C.; Bensoussan, A. Use of Calcium or Calcium in Combination with Vitamin D Supplementation to Prevent Fractures and Bone Loss in People Aged 50 Years and Older: A Meta-Analysis. *Lancet* **2007**, *370*, 657–666. [[CrossRef](#)]
124. Spiegel, D.M.; Brady, K. Calcium Balance in Normal Individuals and in Patients with Chronic Kidney Disease on Low- and High-Calcium Diets. *Kidney Int.* **2012**, *81*, 1116–1122. [[CrossRef](#)] [[PubMed](#)]
125. Pérez, A.V.; Picotto, G.; Carpentieri, A.R.; Rivoira, M.A.; Peralta López, M.E.; Tolosa de Talamoni, N.G. Minireview on Regulation of Intestinal Calcium Absorption. Emphasis on Molecular Mechanisms of Transcellular Pathway. *Digestion* **2008**, *77*, 22–34. [[CrossRef](#)] [[PubMed](#)]
126. Gannagé-Yared, M.-H.; Chemali, R.; Sfeir, C.; Maalouf, G.; Halaby, G. Dietary Calcium and Vitamin D Intake in an Adult Middle Eastern Population: Food Sources and Relation to Lifestyle and PTH. *Int. J. Vitam. Nutr. Res.* **2005**, *75*, 281–289. [[CrossRef](#)]
127. Kinyamu, H.K.; Gallagher, J.C.; Rafferty, K.A.; Balhorn, K.E. Dietary Calcium and Vitamin D Intake in Elderly Women: Effect on Serum Parathyroid Hormone and Vitamin D Metabolites. *Am. J. Clin. Nutr.* **1998**, *67*, 342–348. [[CrossRef](#)] [[PubMed](#)]

128. Xie, H.-L.; Wu, B.-H.; Xue, W.-Q.; He, M.-G.; Fan, F.; Ouyang, W.-F.; Tu, S.-L.; Zhu, H.-L.; Chen, Y.-M. Greater Intake of Fruit and Vegetables Is Associated with a Lower Risk of Osteoporotic Hip Fractures in Elderly Chinese: A 1:1 Matched Case-Control Study. *Osteoporos. Int.* **2013**, *24*, 2827–2836. [[CrossRef](#)]
129. Prynne, C.J.; Mishra, G.D.; O’Connell, M.A.; Muniz, G.; Laskey, M.A.; Yan, L.; Prentice, A.; Ginty, F. Fruit and Vegetable Intakes and Bone Mineral Status: A Cross Sectional Study in 5 Age and Sex Cohorts. *Am. J. Clin. Nutr.* **2006**, *83*, 1420–1428. [[CrossRef](#)]
130. Lamberg-Allardt, C.; Kärkkäinen, M.; Seppänen, R.; Biström, H. Low Serum 25-Hydroxyvitamin D Concentrations and Secondary Hyperparathyroidism in Middle-Aged White Strict Vegetarians. *Am. J. Clin. Nutr.* **1993**, *58*, 684–689. [[CrossRef](#)]
131. Calvo, M.S.; Kumar, R.; Heath, H. Persistently Elevated Parathyroid Hormone Secretion and Action in Young Women after Four Weeks of Ingesting High Phosphorus, Low Calcium Diets. *J. Clin. Endocrinol. Metab.* **1990**, *70*, 1334–1340. [[CrossRef](#)]
132. Calvo, M.S.; Heath, H. Acute Effects of Oral Phosphate-Salt Ingestion on Serum Phosphorus, Serum Ionized Calcium, and Parathyroid Hormone in Young Adults. *Am. J. Clin. Nutr.* **1988**, *47*, 1025–1029. [[CrossRef](#)]
133. Brixen, K.; Nielsen, H.K.; Charles, P.; Mosekilde, L. Effects of a Short Course of Oral Phosphate Treatment on Serum Parathyroid Hormone(1-84) and Biochemical Markers of Bone Turnover: A Dose-Response Study. *Calcif. Tissue Int.* **1992**, *51*, 276–281. [[CrossRef](#)]
134. Kärkkäinen, M.; Lamberg-Allardt, C. An Acute Intake of Phosphate Increases Parathyroid Hormone Secretion and Inhibits Bone Formation in Young Women. *J. Bone Min. Res.* **1996**, *11*, 1905–1912. [[CrossRef](#)] [[PubMed](#)]
135. Whybro, A.; Jagger, H.; Barker, M.; Eastell, R. Phosphate Supplementation in Young Men: Lack of Effect on Calcium Homeostasis and Bone Turnover. *Eur. J. Clin. Nutr.* **1998**, *52*, 29–33. [[CrossRef](#)] [[PubMed](#)]
136. Grimm, M.; Müller, A.; Hein, G.; Fünfstück, R.; Jahreis, G. High Phosphorus Intake Only Slightly Affects Serum Minerals, Urinary Pyridinium Crosslinks and Renal Function in Young Women. *Eur. J. Clin. Nutr.* **2001**, *55*, 153–161. [[CrossRef](#)]
137. Kemi, V.E.; Kärkkäinen, M.U.M.; Lamberg-Allardt, C.J.E. High Phosphorus Intakes Acutely and Negatively Affect Ca and Bone Metabolism in a Dose-Dependent Manner in Healthy Young Females. *Br. J. Nutr.* **2006**, *96*, 545–552.
138. Hayakawa, Y.; Tanaka, Y.; Funahashi, H.; Imai, T.; Matsuura, N.; Oiwa, M.; Kikumori, T.; Mase, T.; Tominaga, Y.; Nakao, A. Hyperphosphatemia Accelerates Parathyroid Cell Proliferation and Parathyroid Hormone Secretion in Severe Secondary Parathyroid Hyperplasia. *Endocr. J.* **1999**, *46*, 681–686. [[CrossRef](#)] [[PubMed](#)]
139. Scanni, R.; vonRotz, M.; Jehle, S.; Hulter, H.N.; Krapf, R. The Human Response to Acute Enteral and Parenteral Phosphate Loads. *J. Am. Soc. Nephrol.* **2014**, *25*, 2730–2739. [[CrossRef](#)] [[PubMed](#)]
140. Barger-Lux, M.J.; Heaney, R.P.; Lanspa, S.J.; Healy, J.C.; DeLuca, H.F. An Investigation of Sources of Variation in Calcium Absorption Efficiency. *J. Clin. Endocrinol. Metab.* **1995**, *80*, 406–411. [[CrossRef](#)] [[PubMed](#)]
141. Katsumata, S.; Matsuzaki, H.; Uehara, M.; Suzuki, K. Effects of Dietary Calcium Supplementation on Bone Metabolism, Kidney Mineral Concentrations, and Kidney Function in Rats Fed a High-Phosphorus Diet. *J. Nutr. Sci. Vitam.* **2015**, *61*, 195–200. [[CrossRef](#)]
142. Lee, A.W.; Cho, S.S. Association between Phosphorus Intake and Bone Health in the NHANES Population. *Nutr. J.* **2015**, *14*, 28. [[CrossRef](#)]
143. Lee, K.-J.; Kim, K.-S.; Kim, H.-N.; Seo, J.-A.; Song, S.-W. Association between Dietary Calcium and Phosphorus Intakes, Dietary Calcium/Phosphorus Ratio and Bone Mass in the Korean Population. *Nutr. J.* **2014**, *13*, 114. [[CrossRef](#)]
144. Zakharova, I.; Klimov, L.; Kuryaninova, V.; Nikitina, I.; Malyavskaya, S.; Dolbnya, S.; Kasyanova, A.; Atanesyan, R.; Stoyan, M.; Todieva, A.; et al. Vitamin D Insufficiency in Overweight and Obese Children and Adolescents. *Front. Endocrinol.* **2019**, *10*, 103. [[CrossRef](#)] [[PubMed](#)]
145. Park, J.M.; Park, C.Y.; Han, S.N. High Fat Diet-Induced Obesity Alters Vitamin D Metabolizing Enzyme Expression in Mice. *Biofactors* **2015**, *41*, 175–182. [[CrossRef](#)]
146. Martínez-Ramírez, M.J.; Palma, S.; Martínez-González, M.A.; Delgado-Martínez, A.D.; de la Fuente, C.; Delgado-Rodríguez, M. Dietary Fat Intake and the Risk of Osteoporotic Fractures in the Elderly. *Eur. J. Clin. Nutr.* **2007**, *61*, 1114–1120. [[CrossRef](#)] [[PubMed](#)]
147. Trichopoulou, A.; Georgiou, E.; Bassiakos, Y.; Lipworth, L.; Lagiou, P.; Proukakis, C.; Trichopoulos, D. Energy Intake and Monounsaturated Fat in Relation to Bone Mineral Density among Women and Men in Greece. *Prev. Med.* **1997**, *26*, 395–400. [[CrossRef](#)]
148. Hagiwara, K.; Goto, T.; Araki, M.; Miyazaki, H.; Hagiwara, H. Olive Polyphenol Hydroxytyrosol Prevents Bone Loss. *Eur. J. Pharm.* **2011**, *662*, 78–84. [[CrossRef](#)] [[PubMed](#)]
149. Puel, C.; Mathey, J.; Agalias, A.; Kati-Coulibaly, S.; Mardon, J.; Obled, C.; Davicco, M.-J.; Lebecque, P.; Horcajada, M.-N.; Skaltsounis, A.L.; et al. Dose-Response Study of Effect of Oleuropein, an Olive Oil Polyphenol, in an Ovariectomy/Inflammation Experimental Model of Bone Loss in the Rat. *Clin. Nutr.* **2006**, *25*, 859–868. [[CrossRef](#)] [[PubMed](#)]
150. Rock, C.L.; Emond, J.A.; Flatt, S.W.; Heath, D.D.; Karanja, N.; Pakiz, B.; Sherwood, N.E.; Thomson, C.A. Weight Loss Is Associated with Increased Serum 25-Hydroxyvitamin D in Overweight or Obese Women. *Obes. Silver Spring* **2012**, *20*, 2296–2301. [[CrossRef](#)]
151. Mason, C.; Xiao, L.; Imayama, I.; Duggan, C.R.; Bain, C.; Foster-Schubert, K.E.; Kong, A.; Campbell, K.L.; Wang, C.-Y.; Neuhaus, M.L.; et al. Effects of Weight Loss on Serum Vitamin D in Postmenopausal Women. *Am. J. Clin. Nutr.* **2011**, *94*, 95–103. [[CrossRef](#)]
152. Tzotzas, T.; Papadopoulou, F.G.; Tziomalos, K.; Karras, S.; Gastaris, K.; Perros, P.; Krassas, G.E. Rising Serum 25-Hydroxy-Vitamin D Levels after Weight Loss in Obese Women Correlate with Improvement in Insulin Resistance. *J. Clin. Endocrinol. Metab.* **2010**, *95*, 4251–4257. [[CrossRef](#)] [[PubMed](#)]

153. Slatopolsky, E.; Caglar, S.; Pennell, J.P.; Taggart, D.D.; Canterbury, J.M.; Reiss, E.; Bricker, N.S. On the Pathogenesis of Hyperparathyroidism in Chronic Experimental Renal Insufficiency in the Dog. *J. Clin. Investig.* **1971**, *50*, 492–499. [[CrossRef](#)]
154. Liu, Z.; Su, G.; Guo, X.; Wu, Y.; Liu, X.; Zou, C.; Zhang, L.; Yang, Q.; Xu, Y.; Ma, W. Dietary Interventions for Mineral and Bone Disorder in People with Chronic Kidney Disease. *Cochrane Database Syst. Rev.* **2015**, *2015*. [[CrossRef](#)]
155. Moe, S.M.; Zidehsarai, M.P.; Chambers, M.A.; Jackman, L.A.; Radcliffe, J.S.; Trevino, L.L.; Donahue, S.E.; Asplin, J.R. Vegetarian Compared with Meat Dietary Protein Source and Phosphorus Homeostasis in Chronic Kidney Disease. *Clin. J. Am. Soc. Nephrol.* **2011**, *6*, 257–264. [[CrossRef](#)]
156. Sherman, R.A.; Mehta, O. Phosphorus and Potassium Content of Enhanced Meat and Poultry Products: Implications for Patients Who Receive Dialysis. *Clin. J. Am. Soc. Nephrol.* **2009**, *4*, 1370–1373. [[CrossRef](#)] [[PubMed](#)]
157. Kloppenburg, W.D.; Stegeman, C.A.; Hovinga, T.K.K.; Vastenburg, G.; Vos, P.; de Jong, P.E.; Huisman, R.M. Effect of Prescribing a High Protein Diet and Increasing the Dose of Dialysis on Nutrition in Stable Chronic Haemodialysis Patients: A Randomized, Controlled Trial. *Nephrol. Dial. Transpl.* **2004**, *19*, 1212–1223. [[CrossRef](#)]
158. Cianciaruso, B.; Pota, A.; Bellizzi, V.; Giuseppe, D.D.; Di Micco, L.; Minutolo, R.; Pisani, A.; Sabbatini, M.; Ravani, P. Effect of a Low—Versus Moderate-Protein Diet on Progression of CKD: Follow-up of a Randomized Controlled Trial. *Am. J. Kidney Dis.* **2009**, *54*, 1052–1061. [[CrossRef](#)] [[PubMed](#)]
159. Ketteler, M.; Block, G.A.; Evenepoel, P.; Fukagawa, M.; Herzog, C.A.; McCann, L.; Moe, S.M.; Shroff, R.; Tonelli, M.A.; Toussaint, N.D.; et al. Executive Summary of the 2017 KDIGO Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD) Guideline Update: What’s Changed and Why It Matters. *Kidney Int.* **2017**, *92*, 26–36. [[CrossRef](#)] [[PubMed](#)]
160. Block, G.A.; Wheeler, D.C.; Persky, M.S.; Kestenbaum, B.; Ketteler, M.; Spiegel, D.M.; Allison, M.A.; Asplin, J.; Smits, G.; Hoofnagle, A.N.; et al. Effects of Phosphate Binders in Moderate CKD. *J. Am. Soc. Nephrol.* **2012**, *23*, 1407–1415. [[CrossRef](#)] [[PubMed](#)]
161. Di Iorio, B.; Molony, D.; Bell, C.; Cucciniello, E.; Bellizzi, V.; Russo, D.; Bellasi, A. INDEPENDENT Study Investigators Sevelamer versus Calcium Carbonate in Incident Hemodialysis Patients: Results of an Open-Label 24-Month Randomized Clinical Trial. *Am. J. Kidney Dis.* **2013**, *62*, 771–778. [[CrossRef](#)]
162. Iorio, B.D.; Bellasi, A.; Russo, D. Mortality in Kidney Disease Patients Treated with Phosphate Binders: A Randomized Study. *Clin. J. Am. Soc. Nephrol.* **2012**, *7*, 487–493. [[CrossRef](#)]
163. Isakova, T.; Gutiérrez, O.M.; Smith, K.; Epstein, M.; Keating, L.K.; Jüppner, H.; Wolf, M. Pilot Study of Dietary Phosphorus Restriction and Phosphorus Binders to Target Fibroblast Growth Factor 23 in Patients with Chronic Kidney Disease. *Nephrol. Dial. Transpl.* **2011**, *26*, 584–591. [[CrossRef](#)]
164. Seifert, M.E.; de las Fuentes, L.; Rothstein, M.; Dietzen, D.J.; Bierhals, A.J.; Cheng, S.C.; Ross, W.; Windus, D.; Dávila-Román, V.G.; Hruska, K.A. Effects of Phosphate Binder Therapy on Vascular Stiffness in Early-Stage Chronic Kidney Disease. *Am. J. Nephrol.* **2013**, *38*, 158–167. [[CrossRef](#)]
165. Oliveira, R.B.; Cancela, A.L.E.; Gracioli, F.G.; Dos Reis, L.M.; Draibe, S.A.; Cuppari, L.; Carvalho, A.B.; Jorgetti, V.; Canziani, M.E.; Moysés, R.M.A. Early Control of PTH and FGF23 in Normophosphatemic CKD Patients: A New Target in CKD-MBD Therapy? *Clin. J. Am. Soc. Nephrol.* **2010**, *5*, 286–291. [[CrossRef](#)]
166. Ritter, C.S.; Martin, D.R.; Lu, Y.; Slatopolsky, E.; Brown, A.J. Reversal of Secondary Hyperparathyroidism by Phosphate Restriction Restores Parathyroid Calcium-Sensing Receptor Expression and Function. *J. Bone Miner. Res.* **2002**, *17*, 2206–2213. [[CrossRef](#)]
167. Sigrist, M.; Tang, M.; Beaulieu, M.; Espino-Hernandez, G.; Er, L.; Djurdjev, O.; Levin, A. Responsiveness of FGF-23 and Mineral Metabolism to Altered Dietary Phosphate Intake in Chronic Kidney Disease (CKD): Results of a Randomized Trial. *Nephrol. Dial. Transpl.* **2013**, *28*, 161–169. [[CrossRef](#)] [[PubMed](#)]
168. Murtaugh, M.A.; Filipowicz, R.; Baird, B.C.; Wei, G.; Greene, T.; Beddhu, S. Dietary Phosphorus Intake and Mortality in Moderate Chronic Kidney Disease: NHANES III. *Nephrol. Dial. Transpl.* **2012**, *27*, 990–996. [[CrossRef](#)]
169. Selamet, U.; Tighiouart, H.; Sarnak, M.J.; Beck, G.; Levey, A.S.; Block, G.; Ix, J.H. Relationship of Dietary Phosphate Intake with Risk of End-Stage Renal Disease and Mortality in Chronic Kidney Disease Stages 3–5: The Modification of Diet in Renal Disease Study. *Kidney Int.* **2016**, *89*, 176–184. [[CrossRef](#)] [[PubMed](#)]
170. Menon, V.; Kopple, J.D.; Wang, X.; Beck, G.J.; Collins, A.J.; Kusek, J.W.; Greene, T.; Levey, A.S.; Sarnak, M.J. Effect of a Very Low-Protein Diet on Outcomes: Long-Term Follow-up of the Modification of Diet in Renal Disease (MDRD) Study. *Am. J. Kidney Dis.* **2009**, *53*, 208–217. [[CrossRef](#)]
171. Mazzaferro, S.; de Martini, N.; Cannata-Andía, J.; Cozzolino, M.; Messa, P.; Rotondi, S.; Tartaglione, L.; Pasquali, M.; On Behalf of The Era-Edta Ckd-Mbd Working Group. Null Focus on the Possible Role of Dietary Sodium, Potassium, Phosphate, Magnesium, and Calcium on CKD Progression. *J. Clin. Med.* **2021**, *10*, 958. [[CrossRef](#)]
172. Vervloet, M.G.; van Ittersum, F.J.; Büttler, R.M.; Heijboer, A.C.; Blankenstein, M.A.; ter Wee, P.M. Effects of Dietary Phosphate and Calcium Intake on Fibroblast Growth Factor-23. *Clin. J. Am. Soc. Nephrol.* **2011**, *6*, 383–389. [[CrossRef](#)] [[PubMed](#)]
173. Savica, V.; Calò, L.A.; Caldarera, R.; Cavaleri, A.; Granata, A.; Santoro, D.; Savica, R.; Muraca, U.; Mallamace, A.; Bellinghieri, G. Phosphate Salivary Secretion in Hemodialysis Patients: Implications for the Treatment of Hyperphosphatemia. *Nephron. Physiol.* **2007**, *105*, 52–55. [[CrossRef](#)] [[PubMed](#)]
174. Savica, V.; Calò, L.; Santoro, D.; Monardo, P.; Granata, A.; Bellinghieri, G. Salivary Phosphate Secretion in Chronic Kidney Disease. *J. Ren. Nutr.* **2008**, *18*, 87–90. [[CrossRef](#)]

175. Tonelli, M.; Pannu, N.; Manns, B. Oral Phosphate Binders in Patients with Kidney Failure. *N. Engl. J. Med.* **2010**, *362*, 1312. [[CrossRef](#)] [[PubMed](#)]
176. Pendón-Ruiz de Mier, M.V.; Vergara, N.; Rodelo-Haad, C.; López-Zamorano, M.D.; Membrives-González, C.; López-Baltanás, R.; Muñoz-Castañeda, J.R.; Caravaca, F.; Martín-Malo, A.; Felsenfeld, A.J.; et al. Assessment of Inorganic Phosphate Intake by the Measurement of the Phosphate/Urea Nitrogen Ratio in Urine. *Nutrients* **2021**, *13*, 292. [[CrossRef](#)] [[PubMed](#)]
177. Scialla, J.J.; Appel, L.J.; Wolf, M.; Yang, W.; Zhang, X.; Sozio, S.M.; Miller, E.R.; Bazzano, L.A.; Cuevas, M.; Glenn, M.J.; et al. Plant Protein Intake Is Associated with Fibroblast Growth Factor 23 and Serum Bicarbonate Levels in Patients with Chronic Kidney Disease: The Chronic Renal Insufficiency Cohort Study. *J. Ren. Nutr.* **2012**, *22*, 379–388. [[CrossRef](#)] [[PubMed](#)]
178. Kalantar-Zadeh, K.; Gutekunst, L.; Mehrotra, R.; Kovesdy, C.P.; Bross, R.; Shinaberger, C.S.; Noori, N.; Hirschberg, R.; Benner, D.; Nissenson, A.R.; et al. Understanding Sources of Dietary Phosphorus in the Treatment of Patients with Chronic Kidney Disease. *Clin. J. Am. Soc. Nephrol.* **2010**, *5*, 519–530. [[CrossRef](#)] [[PubMed](#)]
179. Benini, O.; D'Alessandro, C.; Gianfaldoni, D.; Cupisti, A. Extra-Phosphate Load From Food Additives in Commonly Eaten Foods: A Real and Insidious Danger for Renal Patients. *J. Ren. Nutr.* **2011**, *21*, 303–308. [[CrossRef](#)]
180. Schlemmer, U.; Frølich, W.; Prieto, R.M.; Grases, F. Phytate in Foods and Significance for Humans: Food Sources, Intake, Processing, Bioavailability, Protective Role and Analysis. *Mol. Nutr. Food Res.* **2009**, *53* (Suppl. 2), S330–S375. [[CrossRef](#)]
181. Campion, K.L.; McCormick, W.D.; Warwicker, J.; Khayat, M.E.B.; Atkinson-Dell, R.; Steward, M.C.; Delbridge, L.W.; Mun, H.-C.; Conigrave, A.D.; Ward, D.T. Pathophysiologic Changes in Extracellular PH Modulate Parathyroid Calcium-Sensing Receptor Activity and Secretion via a Histidine-Independent Mechanism. *J. Am. Soc. Nephrol.* **2015**, *26*, 2163–2171. [[CrossRef](#)]
182. Disthabanchong, S.; Martin, K.J.; McConkey, C.L.; Gonzalez, E.A. Metabolic Acidosis Up-Regulates PTH/PTHrP Receptors in UMR 106-01 Osteoblast-like Cells. *Kidney Int.* **2002**, *62*, 1171–1177. [[CrossRef](#)]
183. Krieger, N.S.; Culbertson, C.D.; Kyker-Snowman, K.; Bushinsky, D.A. Metabolic Acidosis Increases Fibroblast Growth Factor 23 in Neonatal Mouse Bone. *Am. J. Physiol. Ren. Physiol.* **2012**, *303*, F431–F436. [[CrossRef](#)] [[PubMed](#)]
184. Raphael, K.L. Metabolic Acidosis in CKD: Core Curriculum 2019. *Am. J. Kidney Dis.* **2019**, *74*, 263–275. [[CrossRef](#)]
185. Izkizler, H.O.; Zelnick, L.; Ruzinski, J.; Curtin, L.; Utzschneider, K.M.; Kestenbaum, B.; Himmelfarb, J.; de Boer, I.H. Dietary Acid Load Is Associated with Serum Bicarbonate but Not Insulin Sensitivity in Chronic Kidney Disease. *J. Ren. Nutr.* **2016**, *26*, 93–102. [[CrossRef](#)]
186. Khairallah, P.; Isakova, T.; Asplin, J.; Hamm, L.; Dobre, M.; Rahman, M.; Sharma, K.; Leonard, M.; Miller, E.; Jaar, B.; et al. Acid Load and Phosphorus Homeostasis in CKD. *Am. J. Kidney Dis.* **2017**, *70*, 541–550. [[CrossRef](#)] [[PubMed](#)]
187. Hill, K.M.; Martin, B.R.; Wastney, M.E.; McCabe, G.P.; Moe, S.M.; Weaver, C.M.; Peacock, M. Oral Calcium Carbonate Affects Calcium but Not Phosphorus Balance in Stage 3–4 Chronic Kidney Disease. *Kidney Int.* **2013**, *83*, 959–966. [[CrossRef](#)]
188. Institute of Medicine (US). Committee to Review Dietary Reference Intakes for Vitamin D and Calcium. In *Dietary Reference Intakes for Calcium and Vitamin D*; Ross, A.C., Taylor, C.L., Yaktine, A.L., Del Valle, H.B., Eds.; The National Academies Collection: Reports funded by National Institutes of Health; National Academies Press: Washington, DC, USA, 2011.
189. Lai, S.; Amabile, M.I.; Bargagli, M.B.; Musto, T.G.; Martinez, A.; Testorio, M.; Mastroluca, D.; Lai, C.; Aceto, P.; Molfino, A.; et al. Peritoneal Dialysis in Older Adults: Evaluation of Clinical, Nutritional, Metabolic Outcomes, and Quality of Life. *Medicine* **2018**, *97*, e11953. [[CrossRef](#)] [[PubMed](#)]
190. Block, G.A.; Klassen, P.S.; Lazarus, J.M.; Ofsthun, N.; Lowrie, E.G.; Chertow, G.M. Mineral Metabolism, Mortality, and Morbidity in Maintenance Hemodialysis. *J. Am. Soc. Nephrol.* **2004**, *15*, 2208–2218. [[CrossRef](#)] [[PubMed](#)]
191. Kestenbaum, B.; Sampson, J.N.; Rudser, K.D.; Patterson, D.J.; Seliger, S.L.; Young, B.; Sherrard, D.J.; Andress, D.L. Serum Phosphate Levels and Mortality Risk among People with Chronic Kidney Disease. *J. Am. Soc. Nephrol.* **2005**, *16*, 520–528. [[CrossRef](#)] [[PubMed](#)]
192. Block, G.A.; Kilpatrick, R.D.; Lowe, K.A.; Wang, W.; Danese, M.D. CKD–Mineral and Bone Disorder and Risk of Death and Cardiovascular Hospitalization in Patients on Hemodialysis. *Clin. J. Am. Soc. Nephrol.* **2013**, *8*, 2132–2140. [[CrossRef](#)]
193. Danese, M.D.; Belozeroff, V.; Smirnakis, K.; Rothman, K.J. Consistent Control of Mineral and Bone Disorder in Incident Hemodialysis Patients. *Clin. J. Am. Soc. Nephrol.* **2008**, *3*, 1423–1429. [[CrossRef](#)]
194. Sullivan, C.; Sayre, S.S.; Leon, J.B.; Machehano, R.; Love, T.E.; Porter, D.; Marbury, M.; Sehgal, A.R. Effect of Food Additives on Hyperphosphatemia among Patients with End-Stage Renal Disease: A Randomized Controlled Trial. *JAMA* **2009**, *301*, 629–635. [[CrossRef](#)]
195. Gotch, F.; Levin, N.W.; Kotanko, P. Calcium Balance in Dialysis Is Best Managed by Adjusting Dialysate Calcium Guided by Kinetic Modeling of the Interrelationship between Calcium Intake, Dose of Vitamin D Analogues and the Dialysate Calcium Concentration. *Blood Purif.* **2010**, *29*, 163–176. [[CrossRef](#)] [[PubMed](#)]
196. Bushinsky, D.A. Contribution of Intestine, Bone, Kidney, and Dialysis to Extracellular Fluid Calcium Content. *Clin. J. Am. Soc. Nephrol.* **2010**, *5* (Suppl. 1), S12–S22. [[CrossRef](#)] [[PubMed](#)]
197. London, G.M.; Guérin, A.P.; Marchais, S.J.; Métivier, F.; Pannier, B.; Adda, H. Arterial Media Calcification in End-Stage Renal Disease: Impact on All-Cause and Cardiovascular Mortality. *Nephrol. Dial. Transpl.* **2003**, *18*, 1731–1740. [[CrossRef](#)] [[PubMed](#)]
198. Bouillon, R. Comparative Analysis of Nutritional Guidelines for Vitamin D. *Nat. Rev. Endocrinol.* **2017**, *13*, 466–479. [[CrossRef](#)]