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CKJ REVIEW

Hypomagnesemia: a potential underlooked cause of persistent vitamin D deficiency in chronic kidney disease

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ABSTRACT

Magnesium and vitamin D play important roles in most cells of the body. These nutrients act in a coordinated fashion to maintain physiologic functions of various organs, and their abnormal balance could adversely affect these functions. Therefore, deficient states of both nutrients may lead to several chronic medical conditions and increased cardiovascular and all-cause mortality. Chronic kidney disease (CKD) patients have altered metabolism of both magnesium and vitamin D. Some studies indicate that magnesium could have a role in the synthesis and metabolism of vitamin D, and that magnesium supplementation substantially reversed the resistance to vitamin D treatment in some clinical situations. Recent observational studies also found that magnesium intake significantly interacted with vitamin D status and, particularly with the risk of cardiovascular mortality. It is therefore essential to ensure adequate levels of magnesium to obtain the optimal benefits of vitamin D supplementation in CKD patients. In this review, we discuss magnesium physiology, magnesium and vitamin D metabolism in CKD, potential metabolic interactions between magnesium and vitamin D and its clinical relevance, as well as the possible role of magnesium supplementation to assure adequate vitamin D levels.

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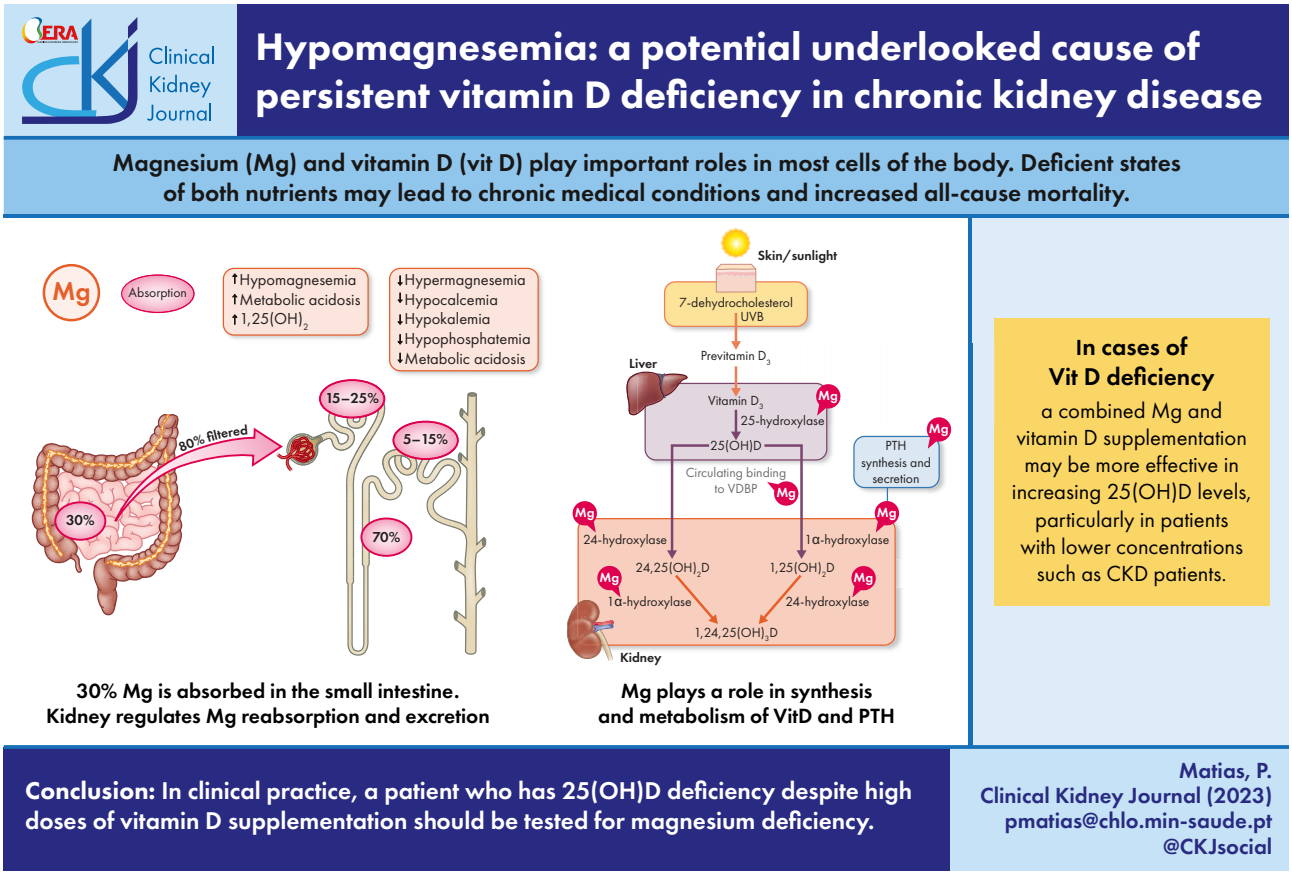
GRAPHICAL ABSTRACT



Keywords: magnesium, mortality, secondary hyperparathyroidism, vascular calcifications, vitamin D

INTRODUCTION

Vitamin D deficiency causes rickets among children and osteomalacia in adults [1]. Many epidemiologic studies suggest that low vitamin D status may also be associated to all-cause mortality [2, 3], and with several non-skeletal chronic diseases such as type 2 diabetes [4], cardiovascular diseases [5, 6], and some cancer types [7]. Despite food fortification and supplementation in several countries, studies have observed that low vitamin D status is still relatively common whereas a large portion of the interpersonal variation in serum 25-hydroxyvitamin D [25(OH)D] levels is unexplained [8]. Chronic kidney disease (CKD) patients, obese, older adults, diabetics, gastrectomized, and with malabsorption syndromes [8] are at a higher risk for vitamin D deficiency.

Magnesium (Mg) is the second most abundant intracellular cation and seems to play a role in the synthesis and metabolism of parathyroid hormone (PTH) and vitamin D [9, 10]. Previous studies in animal models have shown that the activities of the three major enzymes (25-hydroxylase; 1α-hydroxylase; 24-hydroxylase) that determine 1,25-dihydroxyvitamin D levels [1,25$(OH)_2$ D] [9–11] could be Mg dependent, meaning that Mg deficiency may lead to reduced 1,25$(OH)_2$ D. It was also demonstrated, in humans, the potential relationship between Mg and vitamin D binding protein (VDBP) [12] (Fig. 1). Furthermore, Mg deficiency has been implicated since a long time ago in 'magnesium-dependent vitamin D-resistant rickets' [9].

In this article, we review Mg homeostasis, causes of hypomagnesemia, altered Mg and vitamin D metabolism in CKD, the possible role of Mg in vitamin D metabolism, how Mg deficiency can affect the response to vitamin D supplementation, and the potential role of Mg supplementation in restoring vitamin D levels.

PHYSIOLOGY OF MAGNESIUM HOMEOSTASIS

Only ~30% of the total dietary Mg is absorbed in the small intestine, but in deficient states higher absorption can exist, either by a saturable transport system or by passive diffusion [13]. There are two processes responsible for intestinal Mg absorption. The first is active transport, which depends on a transient receptor potential melastatin (TRPM) 6- and 7-members of the long transient receptor potential channel family—which also play a central role in intestinal calcium (Ca) transport. The second and most important is a passive process that occurs by a paracellular pathway [13].

The kidney mainly regulates Mg excretion, where 80% of total plasma Mg is filtered by the glomerulus. The filtered Mg is reabsorbed by the renal tubules: 10–25% in the proximal tubule, 60–70% in the thick ascending limb (TAL), and 5% in the

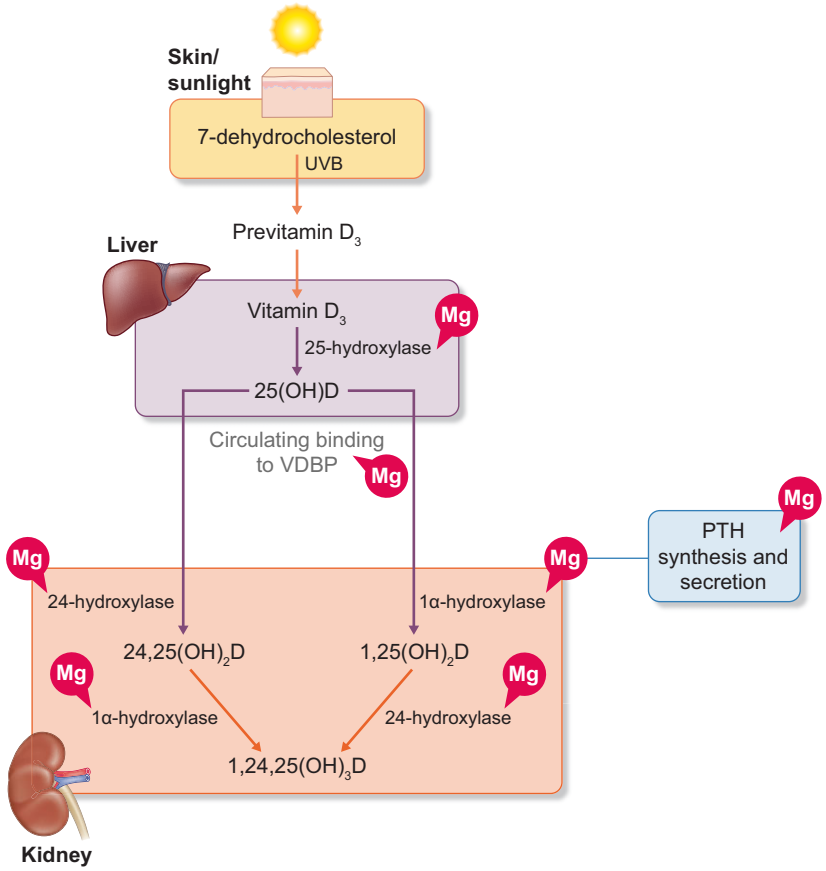


Figure 1: Potential interactions of magnesium in vitamin D metabolism - magnesium is involved in both activation and inactivation of vitamin D.
Abbreviations: Mg, magnesium; 1,25(OH)2D, 1,25-dihydroxyvitamin D (biologically active form); 1,24,25(OH)3D, 1,24,25-trihydroxyvitamin D; 24,25(OH)2D, 24,25-dihydroxyvitamin D; 25(OH)D, 25-hydroxyvitamin D; UVB, ultraviolet B; DBP, vitamin D binding protein.

distal tubule. Transport of Mg in TAL is primarily passive (moving from the lumen to the interstitium) via the paracellular channels, due to a transepithelial gradient generated by the apical NaK2Cl cotransporter. The selectivity of the paracellular pathway is determined by claudins, which form a cation-selective tight junction whereby the Mg paracellular transport is done [14, 15]. Three claudin proteins, claudin-14, claudin-16, and claudin-19, make the cation-selective paracellular pathway for Ca and Mg. Claudin-16 and claudin-19 form the pores and claudin-14 inhibits the cation selectivity of that pore [16, 17].

The extracellular fluid volume modulates tubular Mg transport, as does calcium sensing receptors (CaSR) located in the basal pole of the tubular cells of the TAL, which are sensitive to serum Ca and Mg [18]. The activation of CaSR inhibits the NaK2Cl cotransporter, dissipating the positive transepithelial gradient and decreasing the passive Ca and Mg reabsorption, which leads to the increase of Ca and Mg urinary losses [14, 15]. CaSR also inhibits the phosphorylation of claudins (and unphosphorylated claudins are not expressed in tight junctions) reducing the tight junction permeability to Ca and Mg [18].

A small percentage of Mg is reabsorbed in the distal tubule through active transport via the apical TRPM6/TRPM7 pathway. With respect to the active mechanism of Mg transport, TRPM6 and TRPM7 channels are located in the apical membrane of the cells in the TAL of Henle loop. However, some evidence suggests the participation of a sodium-dependent exchange mechanism where Na^+/K^+ ATPase pump participates together with low concentrations of Na+ [13].

Hypomagnesemia stimulates loop Mg transport. On the contrary, hypermagnesemia inhibits loop transport, as well hypercalcemia, hypokalemia, hypophosphatemia, and metabolic acidosis, as shown in Fig. 2. Furthermore, intestinal absorption of Mg can also be influenced by Ca and vice versa. High intestinal Ca concentrations have been reported to reduce the absorption of Mg [18]. In addition, vitamin D may influence the intestinal absorption of Mg. High doses of $1,25(OH)_2$ D increase the absorption of Mg [19].

Mg plays an important role in adenosine triphosphate (ATP) production, DNA/RNA synthesis, and glucose metabolism. Mg is also a cofactor for hundreds of metabolic reactions throughout the body. As an example, Mg is essential for the regulation of blood pressure, cardiac excitability, and neuromuscular conduction [14]. Mg also interferes in the immunoregulation of the body, and it is critical to the natural and adaptive immunity, partly by influencing the activity of vitamin D metabolites [14, 20]. Immune cells such as macrophages contain all the machinery required to synthesize and respond to active vitamin D, $1,25(OH)_2$ D, and these functions are enhanced by challenge to the immune system. $1,25(OH)_2$ D stimulates innate (macrophage) immunity by enhancing bacterial killing, but it also modulates adaptive (lymphocyte) immunity to minimize Inflammation, and autoimmune disease [20]. The close relationship of Mg and vitamin D

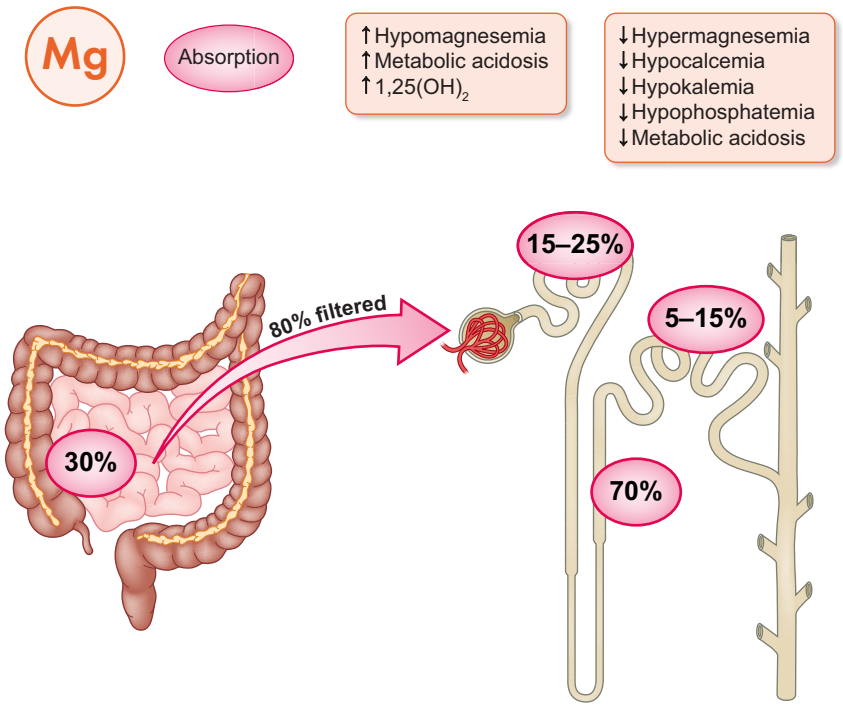


Figure 2: Magnesium absorption through intestine and kidney. 1,25(OH)2D, 1,25-dihydroxyvitamin D.

and the necessity of an optimal Mg status for the synthesis, transport, and activation of vitamin D suggest that the higher incidence of infectious diseases associated with vitamin D deficiency can be at least in part explained by a deficit of Mg. Even if most studies regarding the direct association between poor Mg status and poor immune system function are derived from animal models, human studies shown that Mg deficiency seems to be associated with a higher rate of infectious diseases, particularly when considering older people [21]. Mg transporter 1 (MAGT1) is an evolutionally conserved Mg^{2+}-specific ion transport facilitator found in all animals and has been shown to participate in the multienzyme complex responsible for enzymatic coupling of *N*-glycans onto peptide substrate. Recent studies demonstrate that humans lacking functional MAGT1 have a selective deficiency in both immune and nonimmune glycoproteins, and several critical glycosylation defects were also identified in important immune-response proteins and in the expression of genes involved in immunity, particularly CD28 [22].

Recommended daily allowance (RDA) for men is 5–6 mg/kg of body weight and for women is 4–5 mg/kg of body weight [23]. Dietary intake of Mg is inadequate in most adults because most of the Mg is lost during food processing [24]. Although drinking water accounts for 10% of daily Mg intake, food (spinach, nuts, and seeds) remain the richest source of Mg [24].

DEFINITION OF HYPOMAGNESEMIA AND CAUSES

The adult human body contains ~24 g of Mg, mostly (99%) contained in the bone, muscles, and soft tissues. Serum Mg concentration does not correlate with tissue pools, except for interstitial fluid and bone. Only 1% of total body Mg is present in extracellular fluids, and only 0.3% of total body Mg is found in serum, and so serum Mg concentrations are poor predictors of intracellular/total body Mg content [24].

What is considered the 'normal level' might actually be slightly too low, representing a mild Mg deficit present in the normal population [25]. In addition, there are individuals, in particular those with a subtle chronic Mg deficiency, whose serum Mg levels are within the reference range but who still may have a deficit in total body Mg [25]. In conclusion, a 'normal' serum Mg level (1.5–2.5 mEq/l) may be associated with a moderate to severe Mg deficiency [25, 26], which is known as the normomagnesemic magnesium depletion. Table 1 provide the normal and abnormal values for Mg in humans.

In the literature, patients with serum Mg concentrations <0.61 mmol/L (1.5 mEq/l) are considered hypomagnesemic [26]. Hypomagnesemia is common in hospitalized patients, with a prevalence ranging from 9% to 65%. A particularly high incidence of hypomagnesemia is observed in intensive care units [27]. Compartmental redistribution of Mg in severe illnesses like acute pancreatitis might be another cause of acute hypomagnesemia [26]. Furthermore, a significant association has been reported between hypomagnesemia and postoperative patients, particularly after esophageal surgery [28]. In these severely ill patients, nutritional Mg intake is probably insufficient.

Certain drugs have been associated with increased risk for acute hypomagnesemia. The main causes of drug-induced hypomagnesemia are: (i) promoting a shift of Mg into the cells (insulin therapy, epinephrine, salbutamol, terbutaline, rimiterol,

Table 1: Magnesium and Vitamin D normal and abnormal serum levels.

	Magnesium	Vitamin D–25(OH)D
Normal values	1.6–2.6 mg/dl 0.7–1.1 mmol/l 1.5–2.5 mEq/l	>20 ng/ml (>50 mmol/l)[a] >30 ng/ml (>75 mmol/l)[b]
High levels	>2.6 mg/dl (>1.1 mmol/l; >2.5 mEq/l)	Vitamin D toxicity >100 ng/ml (>250 mmol/l)
Low values	<1.6 mg/dl (<0.7 mmol/l; <1.5 mEq/l)	Vitamin D insufficiency 12–20 ng/ml[a] 15–30 ng/ml[b] Vitamin D deficiency <12 ng/ml (<30 mmol/l)[a] <15 ng/ml (<37.4 mmol/l)[b]

[a]National Academy of Medicine;
[b]National Osteoporosis Foundation; International Osteoporosis Foundation; American Geriatric Society; Kidney Disease Improving Global Outcomes.

theophylline, metformin, and rapid correction of metabolic acidosis with alkali therapy); (ii) increasing gastrointestinal Mg loss (laxative abuse, antibiotics, antineoplastic agents, metformin, proton pump inhibitors, and patiromer); and (iii) increasing urinary Mg excretion (antineoplastic agents such as carboplatin, cisplatin, cetuximab, and panitumumab, and mammalian target of rapamycin inhibitors, calcineurin inhibitors, aminoglycosides, amphotericin B, pentamidine, foscarnet, digoxin, and chronic use of loop and thiazide diuretics) [29]. Therefore, assessment of Mg status is advised, particularly in those who are critically ill and/or exposed to these medications.

Hypomagnesemia has also been linked to poor condition states and chronic illnesses such as malignant tumors, cirrhosis, or cerebrovascular disease [24]. Mg deficiency might arise from reduced intake caused by poor nutrition, from reduced absorption and increased gastrointestinal loss, such as in chronic diarrhea, malabsorption, or bowel resection/bypass [12, 26]. Heavy alcohol consumption is another frequent cause of hypomagnesemia because it reduces the absorption and increases the excretion of Mg [26]. Hypomagnesemia might also be triggered by increased Mg excretion in some medical conditions such as uncontrolled diabetes mellitus, renal tubular disorders, hypercalcemia, hyperthyroidism, hyperaldosteronism, or during excessive lactation [26]. When hypomagnesemia is detected, one should address, if identifiable, the underlying cause and try to reverse it.

Moreover, several inherited forms of renal hypomagnesemia exist. Gitelman syndrome is an autosomal recessive salt-losing renal tubulopathy that is characterized by hypomagnesemia, hypocalciuria, and secondary aldosteronism, which is responsible for hypokalemia and metabolic alkalosis. The prevalence is estimated at ∼25 per million and, accordingly, the prevalence of heterozygotes is ∼1% in Caucasian populations, making it one of the most frequent inherited renal tubular disorders [30]. Other less frequent inherited causes of renal hypomagnesemia are familial hypomagnesemia with hypercalciuria and nephrocalcinosis, familial hypomagnesemia with secondary hypocalcemia, autosomal dominant hypomagnesemia with hypocalciuria, and autosomal recessive hypomagnesemia [30].

Interestingly, taking large amounts of vitamin D supplements may also could induce a severe Mg depletion [31], since, as already mentioned, Mg seems to act as a cofactor in several enzymes of vitamin D metabolism consuming important quantities of Mg to be biologically active (Fig. 1).

MAGNESIUM AND VITAMIN D METABOLISM IN CHRONIC KIDNEY DISEASE

The kidney has a vital role in Mg homeostasis: regulation of Mg excretion is determined by filtration and reabsorption. The renal handling of Mg depends to a great extent on the plasma Mg concentration: in hypermagnesemia, the fractional excretion of Mg is high, while during hypomagnesemia it is low [32]. Because the renal excretion of Mg is so adaptable, impairment of renal function has long been recognized as a frequent prerequisite for the development of hypermagnesemia. However, in moderate CKD, the increase in the fractional excretion of Mg compensates for the loss of renal function, such that serum levels are maintained within in the normal range. Interestingly, there seem to be differences in diabetics and non-diabetics. When patients with and without diabetes (with creatinine clearance >30 ml/min) and not treated with diuretics were investigated, a serum total and ionized Mg levels, still in the normal range in both groups, were significantly lower in diabetics [33].

As renal function progresses to CKD Stages 4 and 5, the excretion of Mg tends to decrease and cannot be compensated any longer by an increased fractional excretion of Mg [32]. This first becomes apparent as creatinine clearance reduces to <30 ml/min and particularly to <10–15 ml/min [33]. Thus, overt hypermagnesemia develops frequently in patients with creatinine clearances <10 ml/min [32, 34].

Several mechanisms contribute to the decreased production of $1,25(OH)_2D$ during CKD. It was initially thought that decreased renal mass limits the amount of 1α-hydroxylase available to synthesize $1,25(OH)_2D$. The reduction in GFR, however, may also limit the delivery of 25(OH)D to the 1α-hydroxylase enzyme, thereby, limiting the ability of the kidney to produce $1,25(OH)_2D$. This occurs because circulating 25(OH)D is bound to the VDBP and is filtered at the glomerulus and absorbed into the proximal tubule by a receptor-mediated mechanism involving megalin. This mediates the endocytosis of 25(OH)D bound to its carrier protein, VDBP, and thus, regulates the delivery of 25(OH)D to the site of the 1α-hydroxylase in the mitochondria. This becomes problematic in CKD because low levels of circulating 25(OH)D are common in patients with CKD, particularly in those with proteinuria, when 25(OH)D, bound to VDBP is excreted in the urine. CKD has also been associated with reductions the expression of megalin in the kidney, which can further aggravate this process [35, 36]. The intestinal absorption of dietary or supplements of vitamin D could also be reduced in CKD subjects as suggested

by the results of experimental studies in uremic animals [37]. An additional factor, and potentially the major one, that contributes to decreased levels of $1,25(OH)_2D$ in CKD is the progressive increase in the levels of FGF23 that occur early in CKD. FGF23 directly suppresses the activity and expression of 1α-hydroxylase, and therefore, this is an important factor that contributes to the decreased ability of the failing kidney to maintain $1,25(OH)_2D$ production. In addition, FGF23 is also known to increase the expression of 24-hydroxylase, which is the enzyme responsible for the degradation of $1,25(OH)_2D$. Finally, the accumulation of 'uremic toxins' may limit the production and actions of $1,25(OH)_2D$ in CKD [35, 36].

INTERACTIONS BETWEEN MAGNESIUM AND VITAMIN D METABOLISM

Under normal physiologic conditions, 25(OH)D is derived primarily from endogenous synthesis via exposure of skin to sunlight, because few natural foods contain vitamin D except by fortification or supplementation. Vitamin D_3 or D_2 is transferred to the liver via VDBP and converted to 25(OH)D by 25-hydroxylase and subsequently carried to the kidney by VDBP and converted to $1,25(OH)_2D$ by 1α-hydroxylase enzyme. Both 25(OH)D and $1,25(OH)_2D$ can be converted by 24-hydroxylase to the 24,25-dihydroxyvitamin D or 1,24,25-trihydroxyvitamin D, respectively [1]. Therefore, $1,25(OH)_2D$ levels are primarily determined by VDBP, 25-hydroxylase, 1α-hydroxylase, and 24-hydroxylase activity, a fact that has recently been substantiated by a genome-wide association study [38]. Normal vitamin D levels are shown in Table 1.

As already mentioned, several steps in the vitamin D metabolism seems to depend on Mg as a cofactor, such as vitamin D binding to VDBP, 25(OH)D synthesis, $1,25(OH)_2$ D synthesis, 25-hydroxylase synthesis, and vitamin D receptor (VDR) expression for cellular effects [39]. Mg deficiency can also decrease PTH synthesis and secretion and can also decrease the number of available VDRs in target cells (Fig. 1) [40]. Some studies indicate that Mg status affects concentrations of cytochrome P450 (CYP) enzymes [41]. CYP enzymes include not only the vitamin D-activating enzymes [i.e. 25-hydroxylase (e.g. CYP2R1) and 1α- hydroxylase (i.e. CYP27B1)] but also vitamin D-deactivating enzymes [i.e. 24-hydroxylase (i.e. CYP24A1 and CYP3A4)]. These enzymes display similar properties including a requirement for Mg ions, molecular oxygen, and a source of reduced pyridine nucleotides [41].

On the other hand, it has been reported that $1,25(OH)_2$ D can stimulate intestinal Mg absorption, by up-regulating intestinal VDR [19]. However, most Mg is also absorbed independently of vitamin D and VDR. Claudins 2 and 12, which are involved in paracellular Ca transport are regulated by $1,25(OH)_2$ D [16]. Studies in animals showed that low and high dietary Mg affects Ca balance via the kidney (increased reabsorption and elimination, respectively). The mechanisms responsible for this fact are unknown, but some authors suggest that a regulatory role for the CaSR could explain this interaction between Mg and Ca and, its impact on vitamin D metabolism [12]. In conclusion, Mg seems to be an essential cofactor for vitamin synthesis, nevertheless activated vitamin D, in turn, can increase intestinal absorption of Mg, and therefore can form a feed-forward loop to maintain its homeostasis.

The effects of vitamin D supplementation in Mg circulating levels were investigated in 126 patients with type 2 diabetes. A significant increase in Mg levels was found after supplementation with vitamin D (cholecalciferol) (2000 IU/day) for 6 months [42]. We also performed a long-term study (5 years) of cholecalciferol supplementation in 97 hemodialysis patients and observed that Mg serum values increased significantly during the study, and that it was positively associated with 25(OH)D levels. In our study, with all patients submitted to a long period of cholecalciferol supplementation accordingly to 25(OH)D baseline levels, patients whose 25(OH)D levels did not increase all had diabetes and hypomagnesemia (Mg $<$ 0.61 mmol/l) [43].

National Health and Nutrition Examination Survey data analysis showed epidemiological evidence on this interaction between 25(OH)D and Mg [44]. According to the Institute of Medicine classification, circulating 25(OH)D, the generally accepted indicator of vitamin D status, was within the deficit range ($<$12 ng/ml) in 12% of participants and the insufficiency range (12 to 20 ng/ml) in 30% [44]. Mean energy-adjusted total Mg intake (dietary and supplemental) was clearly below the RDA [23]. High Mg intake was associated with reduced risk of vitamin D deficit or insufficiency [44]. Data also indicated an inverse association between circulating 25(OH)D and mortality, particularly cardiovascular mortality, among those with Mg intake above the median level. In conclusion, the authors showed that higher Mg intakes were associated with less 25(OH)D deficiency and that the association between low 25(OH)D levels and mortality may be present only in those with higher Mg intakes [44]. However, in this study only Mg intake was evaluated, and Mg serum levels were not measured and no confirmation of Mg deficiency in patients with low intake could be directly assumed. Further studies of vitamin D will likely need to account for Mg levels and Mg intake.

POTENTIAL EVIDENCE THAT CORRECTION OF MAGNESIUM DEFICIENCY CAN RESTORE VITAMIN D LEVELS

Hypomagnesemia has been implicated in the development of vitamin D-resistant rickets [45, 46]. For patients with Mg-dependent vitamin-D-resistant rickets, characterized by reduced $1,25(OH)_2D$ and impaired parathyroid response, intramuscular infusion with $\leq$600 000 IU vitamin D alone did not lead to any improvements in biochemical measures of vitamin D deficiency. However, Mg supplementation did substantially reverse the resistance to vitamin D treatment [46], as serum $1,25(OH)_2D$ levels were substantially increased by supplementation with Mg and vitamin D compared to that of vitamin D or Mg alone [45]. Rickets, thought to be secondary to vitamin D resistance, may heal with Mg therapy [1].

High levels of Mg increase $1,25(OH)_2D$ by increasing the levels of 25-hydroxylase and vitamin D catabolites, but also by facilitating the transfer of vitamin D to target tissues, such as bone, through VDBP. However, it should be noted that while Mg intake is associated with higher levels of vitamin D [42], Mg supplementation alone cannot fully rescue vitamin D deficiencies [45]. Similarly, the serum levels of $1,25(OH)_2D$ in critically Mg-deficient patients were unchanged after 5–13 days of parenteral Mg therapy alone [12]. Together, these studies suggest that Mg and vitamin D can interact to influence the levels of vitamin D, but more studies are needed.

Furthermore, Mg deficiency is more common in women, obese, CKD patients, and in those with higher levels of PTH, and all these situations are also more common in individuals at high risk for vitamin D insufficiency [45] These findings suggest an interaction between vitamin D and Mg levels, particularly in the

elderly and those with osteoporosis, which can have a major impact on human health.

A cross-sectional study, performed in the US general population (NHANES 2001–2006), showed that it is possible that Mg intake alone or its interaction with vitamin D intake may contribute to vitamin D status [44]. This study demonstrated that associations between serum 25(OH)D and risk of cardiovascular and possibly colorectal cancer mortality, which may be also modified by the intake level of Mg [44]. A Finnish cohort study also revealed that low serum 25(OH)D concentration was associated with a higher risk of death, and this association was most significantly among men with lower intake of Mg [47]. A recent randomized controlled trial in 180 patients found that Mg supplementation significantly affects vitamin D metabolism, dependent on the vitamin D status at baseline. Serum concentrations of both 25-hydroxyvitamin D_2 and 25-hydroxyvitamin D_3 increased with Mg supplementation only when baseline 25(OH)D were <30 ng/ml but decreased when baseline 25(OH)D was higher (from 30 to 50 ng/ml) [48]. Thus, emerging evidence suggests that adequate Mg levels seems to be necessary for adequate vitamin D function particularly in patients with vitamin D deficiency and that giving Mg itself can increase 25(OH)D in patients with low levels. Two small clinical trials of Mg-deficient patients [12, 49] found that Mg infusion alone led to a non-significant increase in $1,25(OH)_2D$ and 25(OH)D [12] whereas Mg infusion plus oral vitamin D significantly increased both serum 25(OH)D and $1,25(OH)_2D$ [49]. These findings suggest a potential interaction between vitamin D and Mg supplementation and a possible moderate effect of Mg on 25(OH)D status.

In animal studies, although vitamin D supplementation improves both Ca and Mg absorption, it also increases Mg excretion and reduces Mg retention [50]. In rats, the combined vitamin D and Mg deficiencies impairs the calcemic response to vitamin D, because of a diminished vitamin D-mediated intestinal Ca absorption in the Mg-deficient rats [46, 51].

POSSIBLE ROLE OF MAGNESIUM AND VITAMIN D IN BONE AND EXTRA-OSSEOUS CALCIFICATIONS

Decreased bone mass and an increased risk of bone fractures become more common with age and in CKD patients. This condition is often associated with low bone volume and is caused by an imbalance of bone resorption and new bone formation. Decreased Ca intake, impaired absorption of Ca from aging, CKD, or vitamin D deficiency (which is common in elderly and CKD patients) can cause an increased secretion of PTH to increase serum Ca levels. As the active form of vitamin D is necessary for optimal absorption of Ca, CKD patients can have persistent high levels of PTH [52]. Secondary hyperparathyroidism accelerates bone loss, increases fragility, and impairs neuromuscular function, which increases the risk of falls [52]. Many vitamin D-responsive genes are expressed in bone-forming osteoblast cells, and bone-resorbing osteoclasts cells including the tumor necrosis factor ligand family gene RANKL, which is involved in osteoclastogenesis and is modulated by the $1,25(OH)_2D$ [53]. In osteoporosis patients, there is a higher rate of Mg deficiency in those with vitamin D deficiency compared to those with normal levels of vitamin D [54]. Interestingly, a study conducted among osteoporotic patients showed much higher prevalence rates of Mg deficiency or insufficiency among people with insufficient 25(OH)D than those with sufficient 25(OH)D serum levels [55].

Several studies have shown that Mg inhibits vascular calcifications (VC) [56, 57]. *In vitro* studies demonstrate that Mg supplementation reduces phosphate-induced calcification of vascular smooth muscle cells through the inhibition of osteogenic transdifferentiation by Wnt/β-catenin signaling pathway [58]. Mg deficiency may accelerate VC and atherosclerosis, thus causing cardiovascular disease [57]. In uremic rats, Mg supplementation prevents aortic calcification together with an improvement in mineral metabolism and renal function [59]. Theoretically, Mg may be useful to prevent the progression of coronary artery calcification (CAC), which predicts cardiovascular events and mortality among CKD patients. In several epidemiological studies, circulating Mg is inversely associated with CAC [57]. In fact, a randomized trial showed that oral Mg oxide delayed CAC progression in patients with CKD stage 3–4 [60]. Another interesting study enrolling 142 069 hemodialysis patients had demonstrated that Mg can modified the mortality risk associated with hyperphosphatemia, as higher Mg levels decreased mortality, whereas lower Mg levels boosted hyperphosphatemia-related mortality [61].

A study using an animal model also showed the potential interaction between vitamin D and Mg [62]. This study revealed that combining Mg with active vitamin D (calcitriol) treatment can reduce hypercalcemia and yet similarly suppress PTH while protecting, at least in part, the vasculature from calcium and phosphate deposition. These results demonstrate that calcitriol can increase VC under certain circumstances, an effect that is attenuated in the presence of increased Mg. Importantly, the calcitriol-induced reduction in vascular TRPM7 protein expression was abrogated, at least in part, by Mg co-treatment [62]. Taken together, these data suggest that the benefit of the combined treatment likely involves (i) preventing reductions in TRPM7 expression and (ii) increasing the relative entry and availability of Mg (reducing Ca/Mg ratio) in the VC-susceptible microenvironment.

CONCLUSION

Because the intake of Mg is often inadequate and several other factors are also known to impair Mg supply (for example, diuretics use, diabetes mellitus, chronic alcohol consumption, stress factors), more attention should be paid in future to possible consequences of insufficient or deficient Mg supply in the general population. Vitamin D deficiency is also a growing global issue, particularly in CKD patients.

Mg is possible an important factor in vitamin D metabolism. The activities of the three major enzymes that determine 25(OH)D levels seems to be Mg dependent and there is also a potential relationship between Mg and VDBP. In clinical practice, when we have a patient who has 25(OH)D deficiency and despite high doses of vitamin D supplementation remains unresponsive, it is mandatory to exclude Mg deficiency.

Further studies on the interactions between Mg supply and vitamin D status should include a more detailed assessment of individual Mg status (for example, by measuring biochemical parameters of Mg status), a more complete investigation of different components of the vitamin D–PTH axis, clarification of the dose response relationship, and the realization of randomized controlled trials to verify whether oral Mg is indeed able to improve vitamin D status and survival.

KEY CONCEPTS

1. Mg homeostasis is maintained by the delicate interactions of the intestine, bone, and kidney.

2. Mg is possibly an essential cofactor for vitamin D synthesis and activation and vitamin D, in turn, can increase intestinal absorption of Mg and establish a feed-forward loop to maintain its homeostasis.
3. Dysregulation in either of Mg or vitamin D can be associated with various disorders, including skeletal abnormalities, cardiovascular disorders, and metabolic syndrome.
4. Mg levels seems to be necessary for adequate vitamin D function and giving Mg itself can increase 25(OH)D in patients with 25(OH)D deficiency.
5. In clinical practice, in a patient who, despite high doses of vitamin D supplementation, remains unresponsive, it is mandatory to exclude Mg deficiency.
6. A combined Mg and vitamin D treatment may be more effective in increasing 25(OH)D levels compared with vitamin D supplementation, particularly in patients with lower 25(OH)D concentrations such as obese and CKD patients.
7. A better understanding of how Mg supplementation might reduce the complications related to vitamin D deficiency is still needed and would help to improve patients' morbimortality.

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AUTHORS' CONTRIBUTIONS

P.M. conducted a literature search, interpreted the results, and drafted the manuscript. G.Á., A.C.F., I.L., and A.F. interpreted the results and revised the manuscript. All the authors read the manuscript and agreed to the submission of the final version.

CONFLICT OF INTEREST STATEMENT

Ana Carina Ferreira is member of the *CKJ* editorial board. The other authors have no conflicts of interest to declare.

DATA AVAILABILITY STATEMENT

The data underlying this article are available in the article itself.

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