Nutrition And Food Science Journal

SCIENTIFIC LITERATURE

Special Article Issue "Vitamin D"

Mini Review

Hypomagnesemia: A Hidden Cause of Persistent Vitamin D Deficiency

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ARTICLE INFO

Received Date: July 16, 2022
Accepted Date: August 15, 2022
Published Date: August 17, 2022

KEYWORDS

Magnesium
Mortality
Secondary hyperparathyroidism
Vascular calcifications
Vitamin D

Citation for this article: Patrícia Matias, Gonçalo Ávila, Ivo Laranjinha and Aníbal Ferreira. Hypomagnesemia: A Hidden Cause of Persistent Vitamin D Deficiency. Nutrition And Food Science Journal. 2022; 5(2):137

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ABSTRACT

Magnesium and vitamin D play important roles in most of the cells and organs of the body. Their deficient states may lead to several chronic medical conditions and increased cardiovascular and all-cause mortality. Some studies indicate that magnesium plays an essential role in the synthesis and metabolism of vitamin D, and that magnesium supplementation substantially reversed the resistance to vitamin D treatment, in patients with magnesium-dependent vitamin-D-resistant rickets. Recent observational studies found that magnesium intake significantly interacted with vitamin D status, and with the risk of mortality, particularly cardiovascular mortality. It is therefore essential to ensure adequate levels of magnesium to obtain the optimal benefits of vitamin D supplementation.

In this review, we discuss magnesium physiology, important findings concerning potential metabolic interactions between magnesium and vitamin D and its clinical relevance, as well as the possible role of magnesium supplementation in vitamin D levels.

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 in several countries and supplementation, some studies have observed that low vitamin D status is still relatively common while a large portion of the interpersonal variation in serum 25-hydroxyvitamin D (25(OH)D) levels is unexplained [8].

Magnesium (Mg) is the second most abundant intracellular cation and seems to play a critical role in the synthesis and metabolism of Parathyroid Hormone (PTH) and vitamin D [9,10]. Previous studies have shown that the activities of three major enzymes that determine 25(OH)D level [11] and Vitamin D Binding Protein (VDBP) [10] are Mg dependent (Figure 1). Magnesium deficiency, which leads to reduced 1,25-dihydroxyvitamin D ($1,25(OH)_2$ D) and impaired PTH response [10], has been implicated in "magnesium-dependent vitamin D-resistant rickets" [9].

In this article, we review Mg homeostasis, the critical role of Mg in vitamin D metabolism, how Mg deficiency can affect the response to vitamin D supplementation and the potential role of magnesium supplementation in restoring vitamin D levels.

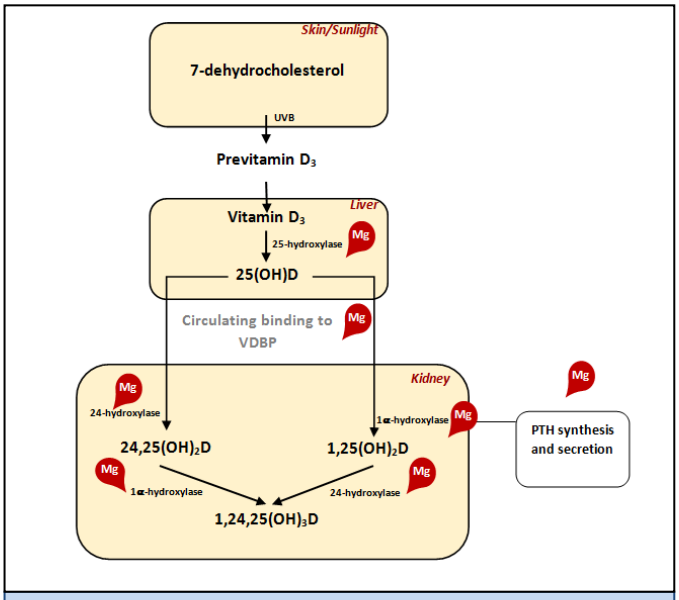

Figure 1: Potential interactions of magnesium in vitamin D metabolism - magnesium is involved in both activation and inactivation of vitamin D.

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

PHYSIOLOGY OF MAGNESIUM HOMEOSTASIS

Only approximately 30% of the total dietary Mg is absorbed in the small intestine, but higher absorption is possible in deficient states [12]. Mg excretion is mainly regulated by the kidney, where 70% of the filtered Mg is reabsorbed in the thick ascending limb of the loop of Henle. Mg is critical for Adenosine Triphosphate (ATP) production, DNA/RNA synthesis, and glucose metabolism. Mg also serves as a cofactor for hundreds of metabolic reactions in the body. Mg is essential for the regulation of blood pressure, cardiac excitability, nerve transmission, and neuromuscular conduction. Mg also plays a significant role 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 [12,13].

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 [14]. Dietary intake of Mg is inadequate in most adults because most of the Mg is lost during food processing [15]. Although drinking water accounts for 10% of daily Mg intake, food (spinach, nuts, and seeds) remain the richest source of Mg [15].

DEFINITION OF HYPOMAGNESEMIA AND CAUSES

The adult human body contains approximately 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 [13].

What is considered the "normal level" might actually be slightly too low, representing a mild Mg deficit present in the normal population. 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 [12]. In conclusion, a "normal" serum Mg level (1.5–2.5 mEq/L) may be associated with a moderate to severe Mg deficiency [13,15].

In the literature, patients with serum Mg concentrations < 0.61 mmol/L (1.5 mEq/L) are considered hypomagnesemic [16]. 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 [16]. Furthermore, a significant association has been reported between hypomagnesemia and postoperative patients, particularly after esophageal surgery [17]. In these severely ill patients, nutritional Mg intake is probably insufficient.

Certain drugs have been associated with Mg wasting (although the relationship between these factors remains unclear), putting those patients at an increased risk for acute hypomagnesemia. Such medications include chronic use of proton pump inhibitors, chronic use of loop and thiazide diuretics, aminoglycosides, cisplatin, digoxin, amphotericin B and cyclosporine A [12,17]. Therefore, assessment of Mg status is advised, particularly in those who are critically ill and/or exposed to these medications. When hypomagnesemia is detected, one should address, if identifiable, the underlying cause and try to reverse it.

Hypomagnesemia has also been linked to poor condition states and chronic illnesses, like malignant tumors, cirrhosis, or cerebrovascular disease [17]. Mg deficiency might stem from reduced intake caused by poor nutrition, from reduced

absorption and increased gastrointestinal loss, such as in chronic diarrhea, malabsorption, or bowel resection/bypass [12,13]. Deficiencies might also be triggered by increased Mg excretion in some medical conditions such as diabetes *mellitus*, renal tubular disorders, hypercalcemia, hyperthyroidism, hyperaldosteronism, during excessive lactation or use of diuretics. Compartmental redistribution of Mg in illnesses such as acute pancreatitis might be another cause of acute hypomagnesemia [13]. In addition, several inherited forms of renal hypomagnesemia exist [18].

Heavy alcohol consumption impairs the absorption and enhances the excretion of Mg [13]. Consuming large amounts of vitamin D supplements may also could induce a severe Mg depletion [15], since Mg is a cofactor in several steps of vitamin D metabolism (Figure 1).

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 [19]. Therefore, 25(OH)D 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 [20].

Based on *in vitro* studies, Mg status regulates both 1α-hydroxylase and 24-hydroxylase activity [11,21]. Previous studies indicated that both VDBP [10] and 25-hydroxylase [22,23] also appear to be Mg-dependent. In conclusion, several steps in the vitamin D metabolism 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 [24]. Mg deficiency can also decrease PTH synthesis and secretion and, also the number of available VDRs in target cells (Figure 1) [25].

On the other hand, it has been reported that $1,25(OH)_2$ D can stimulate intestinal Mg absorption, but Mg is also absorbed independently of vitamin D and the intestinal VDR [26]. In conclusion, Mg is an essential cofactor for vitamin synthesis, and activated vitamin D, in turn, can increase intestinal absorption of magnesium, and therefore can form a feed-forward loop to maintain its homeostasis (Figure 2).

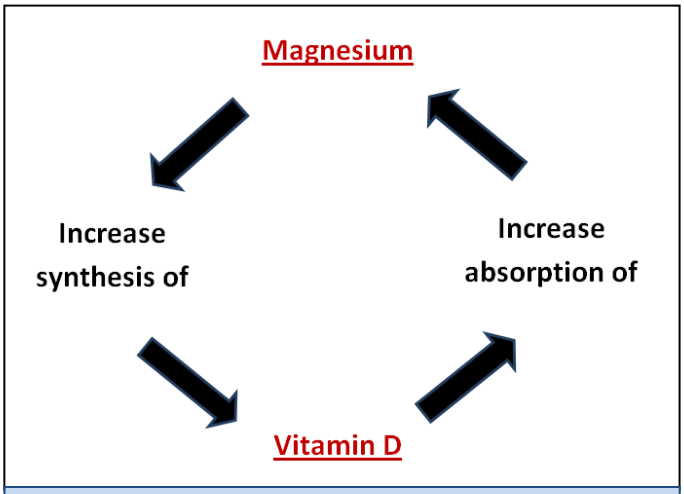

Figure 2: Feed-forward loop of the interaction between magnesium and vitamin D.

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 they were supplemented with vitamin D (cholecalciferol) (2000 IU /day) for 6 months [27].

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 they were positively associated with 25(OH)D levels. Patients whose 25(OH)D levels did not increase all had diabetes and hypomagnesemia (Mg < 0.61 mmol/L) [28].

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

Hypomagnesemia has been implicated for some time in the development of vitamin D-resistant rickets [26,29]. For patients with Mg-dependent vitamin-D-resistant rickets, characterized by reduced $1,25(OH)_2D$ and impaired parathyroid response, intramuscular infusion with ≤ 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 [29].

A cross-sectional study, performed in the US general population, showed that it is possible that Mg intake alone or its interaction with vitamin D intake may contribute to vitamin D status in NHANES 2001-2006. This study demonstrated that associations between serum 25(OH)D and risk of cardiovascular mortality and possibly colorectal cancer mortality may be also modified by the intake level of Mg [30]. A Finnish cohort study also revealed that low serum 25(OH)D concentration was associated with a higher risk of death, this association was most significantly among those men with lower intake of Mg [31].

A study using a mouse model, also showed the potential interaction between vitamin D and Mg [32]. 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 vascular calcifications (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 [32]. Taken together, these data suggest that the benefit of the combined treatment likely involves 1) preventing reductions in TRPM7 expression and 2) increasing the relative entry and availability of Mg (reducing Ca/Mg ratio) in the VC-susceptible microenvironment.

Some studies indicate that Mg status affects concentrations of cytochrome P450 (CYP) enzymes [33]. Cytochrome P450 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)]. 25-Hydroxylase synthesizes 25(OH)D from vitamin D_3 or vitamin D_2 in the liver, and then 1α-hydroxylase synthesizes active $1,25(OH)_2D$ from 25(OH)D in the kidney. 24-Hydroxylase metabolizes both 25(OH)D and $1,25(OH)_2D$ to inactive forms: 24,25-dihydroxyvitamin D and 1,24,25-trihydroxyvitamin D, respectively. Finally, CYP3A4 degrades 24,25-dihydroxyvitamin D and 1,24,25-trihydroxyvitamin D [34]. Both *in vitro* and *in vivo* studies have shown that 1α-hydroxylase and 24-hydroxylase are Mg-dependent [11,21] (Figure 1).

A recent randomized controlled trial in 180 patients found that Mg supplementation significantly impacts 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, with the increase of 25-hydroxyvitamin D_3 observed only in those patients with baseline 25(OH)D below 30 ng/mL [35]. Thus, emerging evidence suggests that adequate Mg levels seems to be necessary for adequate vitamin D function and that giving Mg itself can increase 25(OH)D in patients with low 25(OH)D levels.

An analysis of data from the National Health and Nutrition Examination Survey showed epidemiological evidence on this interaction between 25(OH)D and Mg [30]. According to the Institute of Medicine (IOM) classification [36], 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%. Mean energy-adjusted total Mg intake (dietary and supplemental) was clearly below the recommended daily allowance [14]. High Mg intake was associated with reduced risk of vitamin D deficit or insufficiency [30]. Data also indicates 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 [30]. Further studies of vitamin D will likely need to account for Mg levels and/or intake.

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 [37]. Two small clinical trials of Mg-deficient patients [10,38] found that Mg infusion alone led to a non-significant increase in 1,25(OH)2D and 25(OH)D [10] whereas Mg infusion plus oral vitamin D substantially increased both serum 25(OH)D and $1,25\ (OH)_2D$ [38]. These findings suggest a potential interaction between

vitamin D and Mg treatments and a possible moderate effect of Mg on 25(OH)D status.

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 in future be paid to possible consequences of insufficient or deficient Mg supply in the general population. In clinical practice, when we have a patient who, 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 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.

4. In clinical practice, in a patient who, despite high doses of vitamin D supplementation, remains unresponsive, it is mandatory to exclude Mg deficiency.

5. A better understanding of how Mg supplementation might reduce the complications related to vitamin D deficiency is still needed and would help to improve patient´s morbimortality.

STATEMENTS

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Funding Sources: The authors confirm that they had no funding sources for this review.

Author Contributions: Patrícia Matias conducted a literature search, interpreted the results, and drafted the manuscript. Gonçalo Ávila, Ivo Laranjinha and Aníbal Ferreira revised the manuscript. All the authors read the manuscript and agreed to the submission of the final version.

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