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Review Article

Vitamin D, Magnesium and Their Interactions: A Review

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ABSTRACT

Multiple functions in our body require vitamin D and magnesium. Magnesium acts as a co-factor along with more than 600 enzymes, including enzymes that activate and inactivate vitamin D. In recent years, with the increase in consumption of processed foods, the consumption of magnesium has decreased. Magnesium deficiency can be associated with abnormal vitamin D function. Magnesium acts as a co-factor in the activation and inactivation of vitamin D. In addition, magnesium is required for the binding of vitamin D to its transporter protein and the expression of vitamin D receptors for cellular effects. On the other hand, vitamin D can affect the state of magnesium in the body. In this way, activated vitamin D in turn can increase the intestinal absorption of magnesium. Dysregulation in any of these nutrients can be associated with various disorders such as skeletal abnormalities, cardiovascular disorders and metabolic syndrome. It seems that considering magnesium along with vitamin D is a good approach to improve the function of vitamin D in the body.

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Introduction

Vitamin D and Its roles in the Body

Vitamin D is a fat-soluble steroid hormone that plays an important role in various physiological processes including calcium-phosphorus metabolism, bone turnover, and muscle contraction (1). In addition to skeletal roles, vitamin D has non-skeletal functions, such as prevention of cardiovascular disease, diabetes, cancer and autoimmune diseases (2-4). Serum 25(OH)D levels are used to assess vitamin D status. Serum levels of 25(OH)D less than 20 ng/mL (50 nmol/L) are defined as vitamin D deficiency and levels of 20-30 ng/mlL (50-70 nmol/L) are considered as vitamin D insufficiency (5). In a report published in 2011, the Institute of Medicine of the National Academies of the United States concluded that a concentration of 25(OH)D at 50 nmol/L (20 ng/mL) is sufficient for the needs of 97.5% of the general population (6). In low levels of sun exposure, daily intake of 800 IU of vitamin D is required to achieve a concentration of 50 nmol/L (20 ng/mL) in almost all individuals (6). Therefore, daily intake of 600-800 IU of vitamin D (calciferol or ergocalciferol) is recommended for adults who have no or very limited sun exposure (7). The natural sources of vitamin D in the diet are limited and the enrichment of foods with this vitamin is insufficient (8). Epidemiological studies showed that vitamin D intake in most people in the general population through diet and supplements is less than 200 IU per day, which in turn leads to a high prevalence of vitamin D deficiency (7). Besides, inadequate sunlight exposure, air pollution, and factors affecting the amount and efficiency of UVB, latitude and season are also reasons for vitamin D deficiency (8).

Magnesium and Its Roles in the Body

Magnesium is the second intracellular cation, which acts as a cofactor in more than 600 enzymatic reactions including energy and protein metabolism and nucleic acid synthesis. About half of the body's total magnesium is in the soft tissue and the other half is in the bones. Less than 1% of the total body magnesium is present in the blood (9). The role of magnesium in the development and progression of non-communicable diseases such as type 2 diabetes, hypertension, cardiovascular diseases, metabolic syndrome and osteoporosis has been recognized (10). The recommended daily allowance (RDA) of magnesium for men is 5-6 mg/kg body weight as a man of 70 kg needs 350-400 mg magnesium and it is 4-5 mg/kg body weight for women (11).

Foods such as spinach, nuts and seeds are the richest sources of magnesium. Other sources of magnesium include almond kernels, bananas, beans, broccoli, brown rice, peanuts, egg yolks, fish oil, flaxseed, green vegetables, milk, mushrooms, nuts, pumpkin seeds, oats, Sesame seeds, soy, sunflower seeds, sweet corn, tofu and whole grains. Magnesium is also available as a dietary supplement in antacids and laxatives (9, 11, 12). Although magnesium is found in a variety of foods; but according to the estimated average Estimated Average Requirement (EAR) requirement (255-265 mg/day for adult women and 330-350 mg/day for adult men), the population of numerous countries may be exposed to chronic latent magnesium deficiency and its severe health consequences (13). Recently, dietary magnesium intake has decreased mainly due to the consumption of processed foods (14). Serum magnesium levels are low in populations who eat modern processed food and diets that contain a large number of refined grains, fats, and sugars (15).

It was shown that consumption of magnesium-rich foods is inadequate in most adults because a plenty amount of magnesium is lost during food processing (11). Due to industrial agriculture and changes in eating habits, the consumption of magnesium from natural foods has decreased in the last few decades. Errors or discrepancies in measurement systems due to advances in technology may indicate such changes in magnesium content. But other reasons for the decrease in magnesium content are related to the removal of magnesium during food processing as well as changes in soil conditions (9). Magnesium restriction in the long-term diet can lead to magnesium depletion, before the onset of clinical signs and symptoms of magnesium deficiency. However, magnesium deficiency is difficult to diagnose only with clinical signs and symptoms, because these symptoms are associated with many other diseases (14).

Clinical tests for magnesium assay include assessment of total serum magnesium concentration, ionized serum magnesium concentration, and 24-hour urinary magnesium excretion (9, 10, 16). The reference range for serum and erythrocytes magnesium concentrations are 0.75-0.96 mmol/L and 1.65-2.65 mmol/L, respectively (13). Serum magnesium concentrations between 0.75 and 0.85 mmol/L are considered as chronic latent magnesium deficiency (14). Magnesium deficiency is one of the nutrient deficiencies in the US population (17). According to the report of NHANES in 1999–2000, 79% of US adults did not reach the recommended daily allowance (RDA) required for magnesium (13). The standard diet in the United States contains about 50% of the RDA for magnesium, and approximately three-quarters of the total US population consume a diet with insufficient magnesium content (9).

Low magnesium status leads to chronic diseases. For example, studies have shown that magnesium deficiency is related to a higher risk of type 2 diabetes, metabolic syndrome, cardiovascular diseases, chronic musculoskeletal disorders, obstructive pulmonary diseases and possibly some cancers. According to a global study of reported disease burden, these diseases impose high human and financial costs on society. Therefore, it is necessary to investigate the consequences of abnormal magnesium status in the population consuming processed diets (15).

Magnesium and Vitamin D Interactions

Vitamin D and magnesium are among the micronutrients that have been studied extensively because a deficiency in any of these nutrients has several negative consequences for general health. Magnesium and vitamin D are two essential nutrients and therefore, their balance is essential for maintaining the physiological functions of various organs (11, 18). Vitamin D helps regulation of the calcium and phosphorus balance to maintain bone function. Magnesium is essential for the stability of cell function, RNA and DNA synthesis and cell repair, as well as maintaining the antioxidant status of cells (19). Deficiencies in both nutrients are associated with skeletal abnormalities, cardiovascular diseases, and metabolic syndrome (18, 19). Magnesium is also an important cofactor needed to activate a variety of enzymes. It seems that all the enzymes that metabolize vitamin D need magnesium for their function. Magnesium also helps synthesis of the active form of vitamin D in the body. It acts as a cofactor in enzymatic reactions for vitamin D activation in the liver and kidneys (18, 19). Both *in vitro* and *in vivo* studies have shown that 1α-hydroxylase and 24-hydroxylase are dependent on magnesium (20, 21).

Magnesium status affects the concentration of cytochrome P450 (CYP) enzymes (22). Cytochrome P450 enzymes include vitamin D 25-hydroxylase-activating enzymes (CYP2R1) and 1α-hydroxylase (CYP27B1) enzymes, as well as vitamin D-24-hydroxylase-inactivating enzymes (CYP24A1 and CYP3A4). In the liver, the enzyme-25-hydroxylase helps the formation of 25(OH)D and then activated by 1α-hydroxylase in the kidney. 24-Hydroxylase converts metabolites 25(OH)D and 1, 25 $(OH)_2D$ to the inactive forms of 24,25- dihydroxy vitamin D and 1, 24, 25-trihydroxy vitamin D. Finally, 24,25-dihydroxy vitamin D and 1,24,25-trihydroxy vitamin D are degraded by CYP3A4 (23, 24).

In addition, magnesium is required for binding vitamin D to its transporter protein, and also the expression of vitamin D receptors (11, 18, 20). Magnesium deficiency leads to impaired parathyroid hormone (PTH) secretion and response, which can reduce the number of vitamin D receptors in the target cells (25, 26). In general, magnesium is a major co-factor for biosynthesis, transport and activation of vitamin D (9). It was shown that the risk of death due to vitamin D deficiency can be altered by magnesium intake, and when magnesium homeostasis is not maintained in the body, the effectiveness and clinical benefits of vitamin D are significantly reduced (9).

Studies Related to the Interaction between Vitamin D and Magnesium

In general, limited studies have been performed on the interaction of vitamin D and magnesium. Some studies have shown that a good magnesium level can affect vitamin D level, and magnesium supplementation can increase the serum vitamin D level. One study illustrated that magnesium injection along with vitamin D could improve 25(OH)D and 1,25(OH)2D levels better in comparison to magnesium or vitamin D injection alone (11, 27). According to National Health and Nutrition Examination Survey (NHANES) in 2001-2006, high magnesium intake declined the risks of vitamin D deficiency or insufficiency in the whole society (28). Also, magnesium plays an important role in the immune system by affecting the activity of vitamin D metabolites (9). For patients with "magnesium-dependent vitamin D-resistant rickets" characterized by a decrease in 25,1- dihydroxy vitamin D and impaired parathyroid response; intramuscular injection of 60,000 IU of vitamin D alone did not improve the biochemical parameters of vitamin D deficiency. However, magnesium supplementation significantly altered resistance to vitamin D therapy (25).

A study by Deng et al. showed that a significant increase in serum 25(OH)D occurs only with co-supplementation of vitamin D and magnesium (28). A prospective cohort study of 1,892 men aged 42-60 years found that those with the lowest levels of 25-hydroxyvitamin D had a 31% higher risk of death than those with the highest levels of 25-hydroxyvitamin D. When the analysis was categorized by magnesium intake, the risk was higher at lower magnesium intakes. In this cohort, the increased risk of mortality was seen in people with low serum concentrations of 25-hydroxyvitamin D and low magnesium intake (29).

Some studies also showed that adequate magnesium can keep vitamin D levels within the normal range and prevent vitamin D toxicity. For example, in a clinical study, magnesium supplementation significantly affected vitamin D metabolism in participants using a personalized dose regime adjusted for oral doses by participants. In this study, concentrations of 25-hydroxyvitamin D increased among those whose baseline concentrations were less than 30 ng/mL; but decreased among those with the concentration of 25-hydroxyvitamin D in the range of 30-50 ng/mL. These data provided evidence to support the notion that adequate magnesium status can directly improve vitamin D deficiency and control its side effects. In another study, co-supplementation of magnesium and vitamin D resulted in control of the side effects of vitamin D supplement, including vascular calcification. It was shown that a dose of calcitriol alone increased the prevalence of vascular calcification in rats; however, when calcitriol was used with magnesium, the severity of calcification decreased compared to the control group. Calcitriol treatment alone significantly reduced transient receptor potential cation channel, subfamily M, member 7 (TRPM7) protein compared with calcitriol and magnesium. In summary, magnesium prevents a decrease in TRPM7 and reduces the severity of vascular calcification and increases the bioavailability of magnesium in microvascular environments. These findings suggest that rectifying the side effects of calcitriol with magnesium may be an acceptable approach for patients with renal failure receiving calcitriol (30).

On the other hand, vitamin D can affect

magnesium status. 1,25(OH)$_2$D has been shown to stimulate magnesium uptake in the intestine. In a study by Al-Daghri *et al.* on the effects of vitamin D supplementation and magnesium blood level in patients with type 2 diabetes demonstrated a significant increase in serum magnesium level after taking 2000 IU/d of vitamin D3 supplement for 6 months (9, 16). In another study in obese patients, after vitamin D injection, a significant change was observed in serum magnesium concentration, while serum magnesium concentration in non-obese cases before and after the intervention was not significantly different. The mean increase in serum magnesium levels after vitamin D injection was greater among women who were deficient in magnesium than women who had sufficient magnesium. Women with serum magnesium above 2.1 meq/L showed a decrease in in serum magnesium level (31).

So there is a possible interaction between magnesium and vitamin D, which affect each other's condition. In addition, magnesium is required for the binding of vitamin D to its transporter protein, and the expression of vitamin D receptors for cellular effects. Given the role of magnesium in the synthesis and metabolism of vitamin D, it is likely that magnesium should be included in any vitamin D correcting regimens for optimal biological function. Therefore, in examining the status and role of vitamin D, the effects of some essential elements such as magnesium should be considered (32). Vitamin D deficiency is a common medical condition worldwide. Vitamin D supplementation has recently increased due to global awareness, but magnesium deficiency has been less discussed (11). It is worthwhile paying more attention to the possible consequences of magnesium deficiency in the general population. Although magnesium is well known; But its interaction with calcium and vitamin D has been less studied (15).

Conclusion

The interaction between magnesium and vitamin D is due to enzymatic pathways in which magnesium participates in the activation and inactivation of vitamin D as a cofactor. In addition, magnesium is required for the binding of vitamin D to its transporter protein and the expression of vitamin D receptors for cellular effects. Magnesium is an essential cofactor for the synthesis of vitamin D. Activated vitamin D in turn can increase intestinal absorption of magnesium. Available data in literature showed that magnesium supplementation can increase vitamin D level and that magnesium can maintain normal vitamin D level and prevent vitamin D toxicity. On the other hand, vitamin D supplementation can rise magnesium level, and of course, excessive supplementation may reduce serum magnesium.

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Conflict of Interest

None declared.

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