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Review

Anabolic effects of vitamin D and magnesium in aging bone

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ABSTRACT

Decreased bone mass and an increased risk of bone fractures become more common with age. This condition is often associated with osteoporosis and is caused by an imbalance of bone resorption and new bone formation. Lifestyle factors that affect the risk of osteoporosis include alcohol, diet, hormones, physical activity, and smoking. Calcium and vitamin D are particularly important for the age-related loss of bone density and skeletal muscle mass, but other minerals, such as magnesium, also have an important role. Here, we summarize how optimal magnesium and vitamin D balance improve health outcomes in the elderly, the role of magnesium and vitamin D on bone formation, and the implications of widespread deficiency of these factors in the United States and worldwide, particularly in the elderly population.

1. Osteomalacia and vitamin D

In the 19th century, the children's bone disease rickets, which is caused by an inability to mineralize bone matrix proteins, was increasing in industrialized cities. In 1919, vitamin D was first used to treat adult and children with rickets [1], but it was unclear at the time whether vitamin D supplementation was directly associated with rickets or a general prophylactic. Between 1930 and 1950, there were reports of vitamin D toxicity in patients treated for hypoparathyroidism, and vitamin D was poorly mixed in supplemented foods for general consumption [2]. In adults, rickets is known as osteomalacia. In the 1970s, a hip fracture study revealed that vitamin D deficiency may be associated with increased risk of femoral fracture [3], and hip fracture patients often had low vitamin D levels [4]. A seasonal variation in the severity of osteomalacia suggested that osteomalacia may be linked to levels of vitamin D [3]. Since that time, numerous studies have linked low vitamin D levels to increased risks of fracture and osteomalacia, particularly in women [5–7]. Osteomalacia is characterized by deficient bone mineralization histology [8], and in animal models this condition can be reversed by an enriched calcium and phosphorous diet [9,10]. Furthermore, while there is a bona fide relationship between low vitamin D levels and an increased risk of hip fracture in the elderly [11], there are reports that only a minority of these patients have osteomalacia as gauge by detailed histomorphometric measurements [5,12]. Instead, most hip fracture patients have an alternative bone histology condition called osteoporosis. Osteoporosis is associated with a normal ratio of mineral to osteoid (rather than a lack of mineralization as in osteomalacia) and an overall reduced amount of bone mass [13].

2. Cellular events of osteoporosis

Osteoporosis is a disorder in which the loss of bone mass leads to the gradual weakening of bone and an increased risk of bone fractures. Bone weakness can occur because the bone does not achieve sufficient strength during bone formation, owing either to excess bone resorption that results in loss of bone mass, or to a failure to replace lost bone during bone turnover. Bone remodeling involves specialized cells called osteoblasts, osteoclasts as well as bone marrow cells. Activation of osteoclasts induces a brief resorption and reversal phase that lowers bone mass. This is followed by osteoblast activation, which results in the formation of bone matrix and flat lining cells that become embedded in the bone as osteocytes [14]. Several studies have examined the role of magnesium in osteoporosis, mainly in postmenopausal women [15]. Oral supplementation of magnesium increases bone mineral density in patients with osteoporosis [16], but other minerals, such as calcium, were included and the study used a small number of patients, which makes interpretation difficult. Other studies have also found similar effects of magnesium on bone mineral density with similar caveats [17,18]. Therefore, a large-scale prospective study is needed to

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conclude whether magnesium supplementation has any effect.

Studies in post-menopausal women have revealed a critical role for estrogen in the pathogenesis of osteoporosis [19,20]. Accelerated bone resorption rather than a loss of new bone formation is responsible for much of the bone loss from estrogen deficiency, and estrogen supplementation in older women can delay this decline [19]. Estrogen treatment decreases the rate of bone remodeling and reduces the amount of bone loss during each bone remodeling cycle. Estrogen acts primarily through estrogen receptor α in osteoblasts [21], though it may also act through estrogen receptor β [22,23]. Estrogen also promotes osteoclast turnover and affects cytokine production in T cells, which is important for initiating bone remodeling through the cytokine transforming growth factor beta (TGFβ) [24,25]. Estrogen enhances magnesium utilization and uptake by soft tissues and bone, which may partly explain the resistance to heart disease and osteoporosis in young women [26]. Thus, the role of estrogen in osteoporosis in aging women may, in part, be a result of inefficient use of magnesium in the body.

3. Vitamin D

Vitamin D is the common name for a group of secosteroids that can be found in fortified dairy products like milk, egg yolks, liver, meat as 25-hydroxyvitamin D [25(OH)D] [27], and fish oils used by the body when these foods are consumed. Vitamin D can also be formed in the skin from sun exposure [28]. Vitamin D is essential for the body's absorption of compounds like calcium from food into the blood serum. Optimal calcium balance is vital to cell survival and bone health. Studies conducted over the last 20 years have demonstrated a link between higher serum 25(OH)D concentrations and better outcomes for several chronic diseases [29,30]. The ideal levels of vitamin D for healthy function, are based on an optimal serum 25(OH)D concentration [29]. Guidelines focused on bone health recommend a serum 25(OH)D concentration of 20 ng/mL and vitamin D doses of 400–800 IU on a daily basis, depending on age [29]. A concentration of 30 ng/mL, and daily vitamin D doses of 400 and 2000 IU per day, dependent on age, weight and health status are recommended to maximize the pleiotropic effects of Vitamin D [29].

Vitamin D is transported through the body by vitamin D-binding protein (VDP). The enzyme CYP2R1 hydroxylates vitamin D to 25(OH)D in the liver; 25(OH)D is the major circulating form of vitamin D, and 25(OH)D is measured in serum as an indicator of one's vitamin D status [28]. It is then transported via VDP to the kidney. In the kidney it is hydroxylated by CYP27B1 to form 1,25-dihydroxyvitamin D [$1,25(OH)_2D_3$], which is the biologically active form of vitamin D. Mutations of CYP27B1 can result in vitamin D deficiency because the active form of the vitamin is not able to be formed. Deficiency in biologically active vitamin D can result in pathologies, such as rickets type 1 [28]. Magnesium deficiency also reduces the levels of $1,25(OH)_2D_3$, which has been implicated in magnesium-dependent vitamin D–resistant rickets [31]. In two cases of vitamin D-resistant rickets, supplementation with magnesium reversed the resistance to vitamin D treatment [32]. These studies suggest that vitamin D supplementation alone may not be sufficient to reverse bone mineralization defects, and may likely require magnesium to elicit beneficial effects to maintain bone homeostasis.

4. Magnesium

Magnesium is the second most abundant intracellular cation after potassium with a typical concentration of 10–30 mM in the human body [33], and is found naturally in most whole foods such as green leafy vegetables, nuts, and legumes [34]. When magnesium is abundant in drinking water, it is associated with a lower risk of coronary heart disease [35]. Magnesium is essential for hundreds of cellular processes including energy production, synthesis of DNA, RNA, and proteins; and cell cycle control. Therefore, magnesium is an important factor for cell proliferation, growth and survival [36]. Magnesium is also involved in the exchange of calcium and potassium ions across cell membranes, which is important for neuronal activity and muscle contractions.

There are low levels of magnesium in populations, such as the United States, that consume processed foods that are high in refined grains, sugars, and fats [37]. Magnesium deficiency may result from the decreasing amount of magnesium in soil used for agriculture, and the magnesium content of fruits and vegetables has declined by 20–30% over the last 60 years [38]. Magnesium deficiency results in nausea, fatigue, and muscle weakness, which can later progress to numbness, muscle spasms, seizures, migraines, and heart failure [39,40]. Low intake of magnesium increases the risk of metabolic syndrome in older Americans [41], type 2 diabetes [42,43], stroke [44], cardiovascular disease [45], and colorectal cancer [46,47]. Low magnesium levels are also associated with depression [48–51] and may increase the risk of dementia [52]. Migraines have also been linked to low levels of magnesium in the serum and cerebrospinal fluid [53,54]. Magnesium downregulates neuronal N-methyl-D-aspartate (NMDA) receptor excitability, which is important for excitatory synaptic transmission and neuronal plasticity in learning and memory [55]. Thus, NMDA receptors become hyper-excitable in low magnesium conditions [56,57]. Decreased magnesium levels in cerebrospinal fluid (CSF) correlates with magnesium levels in the brain, which is associated with the development of seizures [58]. Migraine headaches are also linked to low levels of magnesium in blood and CSF [54,59], resulting from cortical spreading depression (CSD), which consists of neuronal membrane depolarization and repolarization [60]. CSD is blocked by NMDA receptor antagonists [61], which suggests that an increase in neuronal excitability due to low CSF magnesium levels may increase susceptibility to migraines. In addition, patients often have changes in diastolic blood flow before, during, and after a migraine episode [62]. This hypotension is mainly controlled through vasodilatory effects of nitric oxide (NO) [63], which stimulates soluble guanylate cyclase (sGC) to produce the intracellular second messenger cGMP [64]. The NO-sGC-cGMP signaling pathway activates cGMP-dependent protein kinase to decrease intracellular calcium levels and inhibit myosin light chain phosphorylation in smooth muscle cells. This results in vasodilation and reduced blood pressure. Low levels of magnesium inhibits the release of nitric oxide from the coronary endothelium [65], and magnesium supplementation may affect vasodilation independent of endothelial nitric oxide [66]. Regardless of the mechanism, magnesium supplementation has been successfully used as a prophylactic for migraine treatment in several clinical trials [67–69]. Adequate consumption of magnesium has other health benefits. For example, consumption of magnesium promotes cardiorespiratory function in healthy individuals and is important for optimal athletic performance [70]. Increasing brain magnesium can enhance learning abilities, working memory, and short- and long-term memory in rats [71].

The recommended daily allowance of magnesium varies between individuals according to age, sex, and nutrition status, but ranges between 310–360 mg and 400–420 mg for women and men, respectively [72,73]. More than 50% of the US population does not consume the required amount of magnesium [37]. That number increases to 80% of males and 50% of females aged 71 years or older according to the 2005–2006 NHANES survey and NHANES III survey [74]. However, the ratio of calcium to magnesium has been increasing in the United States since 1977 particularly for older women [75]. Dietary intake of magnesium is decreasing in the United States and is particularly poor in African American and Mexican American men and women compared to that in Caucasians [76], which may contribute to health disparities among different ethnicities.

The magnesium content in an adult human is approximately 24 g and approximately 0.3% is present in the blood [77]. The measurement of serum magnesium levels is clinically used for determining total body magnesium status including normal levels (1.2–1.9 mEq/L), hypomagnesemia (less than 1.2 mEq/L), and hypermagnesemia (more than

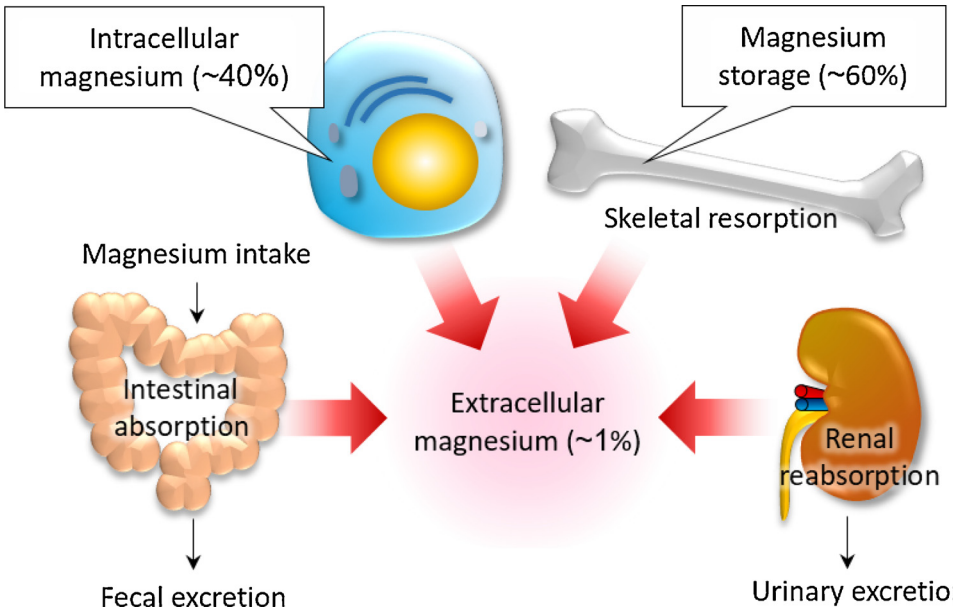

Fig. 1. Total body magnesium homeostasis is primarily maintained by a multi-organ cross-talk among intestine, kidney, and bone. Of clinical importance, less than 1% of total body magnesium is found in serum. Therefore serum magnesium concentration does not truly reflect total body magnesium content, and is also a poor predictor of intracellular magnesium content [93,94].

1.9 mEq/L) [78]. Magnesium is a physiological antagonist of calcium in cells because both are divalent cations, and the magnesium-to-calcium ratio affects the activity of calcium-dependent ATPases and calcium-transporting proteins [79]. Therefore, small changes in magnesium concentrations may disrupt calcium signaling or induce calcium toxicity.

Magnesium is regulated similar to that of calcium, both being absorbed by the small and large intestine and stored in bone [80]. Excess magnesium and unabsorbed magnesium by the gut are secreted by the kidneys or excreted as solid waste (Fig. 1) [81]. Magnesium absorption is not proportional to intake, but rather reflects the levels of intestinal magnesium – when intestinal magnesium is low, active transport increases absorption in the gut [82]. The level of serum magnesium, however, depends primarily on its excretion in urine through the kidneys. Serum magnesium is filtered through glomeruli in the kidneys; 95% is immediately reabsorbed and 3–5% is secreted in the urine. This reabsorption and secretion can be markedly altered in cases of magnesium deprivation or excess intake [80].

There are several tests to determine the levels of magnesium in the body, but no simple or reliable biomarker exists. The magnesium load test involves an intramuscular or intravenous loading of magnesium for a pre-determined amount of time, followed by collecting urine for 24–48 h after loading [83]. Healthy adults retain approximately 6% of the loaded magnesium with a range between 2% and 10% [84], which can vary based on lifestyle factors such as exercise or alcohol consumption [83]. Patients with a magnesium deficiency retain a much higher percentage of magnesium compared to that of healthy subjects in a magnesium load test [85]. In addition, patients with atrial fibrillation, other arrhythmias, hypertension, coronary artery disease, congestive heart failure, cerebrovascular events, gastrointestinal disorders, and diabetes, all have a higher retention rate of magnesium (10–35%) [84]. In patients with a retention rate greater than 20%, magnesium supplementation can significantly overcome this condition [85]. However, because there is a wide variation between individuals and because the test is time-consuming and involved, the load retention test cannot be used in patients with kidney disease or in the elderly individuals with declining renal function.

The alternatives to the magnesium load test for measuring magnesium levels include examining magnesium in the serum and urine. Serum magnesium may not be a reliable marker for magnesium status because there are individuals within the normal acceptable range from 0.6 to 0.84 mmol/L who may actually have insufficient amounts of magnesium. Urinary magnesium levels respond to changes in magnesium in diet or oral supplementation [86]. Urinary magnesium has been used to measure intestinal magnesium absorption, which serves as a reliable indicator for cardiovascular disease risk and hypertension [87]. In addition, urinary magnesium may be a more reliable indicator for ischemic heart disease than serum magnesium [88] and thus it has been successfully used as an indicator for the risk of heart disease [86]. A link between vascular calcification in CKD patients and the accumulation of uremic toxins such as indoxyl sulfate has been suggested by the results of a 2013 study of pre-dialysis patients [89]. In that study the use of the drug AST-120 and the neutralization of uremic toxins was associated with reduced aortic calcification compared to no treatment [90].

In addition to the challenges of interpreting different magnesium tests in patients with different disease conditions, the concentration of magnesium in mammals fluctuates in a circadian rhythm (24-hr) over the course of a day and also varies seasonally [91]. Magnesium concentration also has circadian variation in isolated cells [92]. Therefore, data on serum magnesium concentration or from other periodic measurements may not fully capture the true baseline level of magnesium in an individual.

5. Vitamin D, magnesium, and osteoporosis

Nutrients act in a coordinated fashion to maintain the physiologic functions of various organs, and thus, their abnormal balance could adversely affect organ functions [93–100]. Decreased calcium intake, impaired absorption of calcium from aging, disease, lifestyle factors, or vitamin D deficiency can cause secondary hyperparathyroidism, which results in an increased secretion of parathyroid hormone (PTH) and elevated serum calcium levels. The active form of vitamin D is necessary for optimal absorption of calcium, and vitamin D deficiency is common in elderly patients, especially those who are housebound or have insufficient sunlight exposure [101]. Secondary hyperparathyroidism accelerates bone loss, increases fragility, and impairs neuromuscular function, which increases the risk of falls. There is also a seasonal decrease in vitamin D and an increase in PTH levels and bone resorption during the winter, which is associated with an increased proportion of falls that result in increased risk of wrist and hip fractures [102]. In osteoporosis patients, there is a higher rate of magnesium deficiency in those without sufficient vitamin D compared to those with normal levels of vitamin D [103]. Magnesium deficiency particularly affects vitamin D levels in individuals at high risk for vitamin D

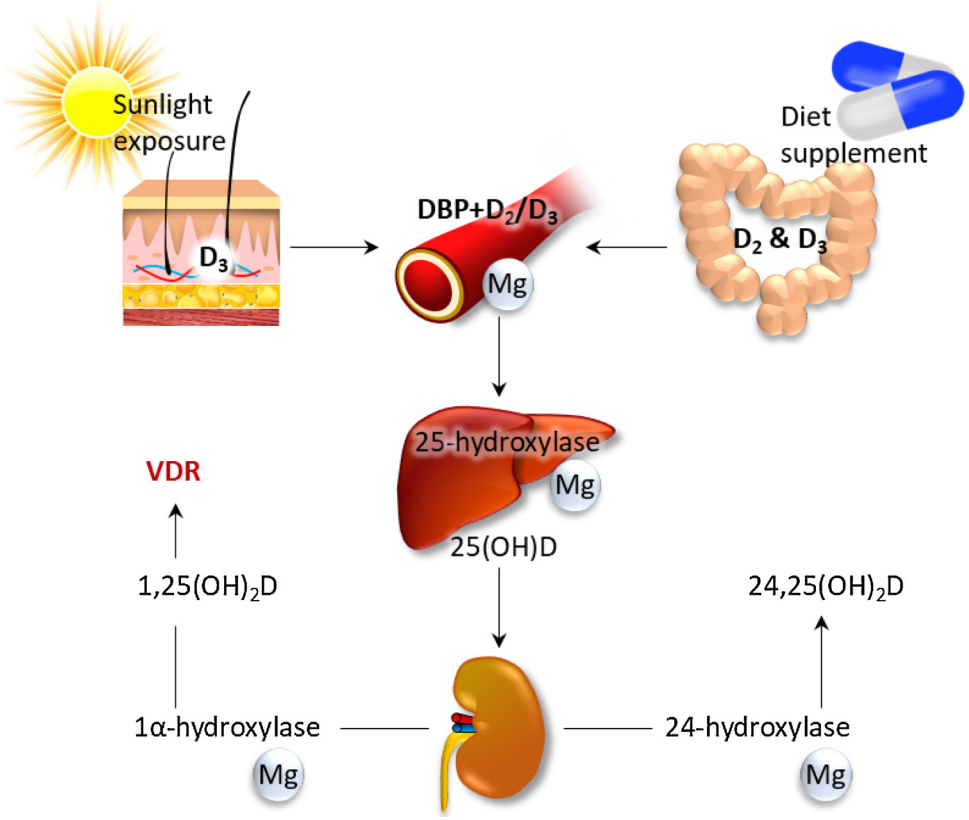

Fig. 2. Possible roles of magnesium in vitamin D synthesis. Please note that magnesium is involved in both activation and inactivation of vitamin D. [DBP: vitamin D binding protein; D_3 and D_2: vitamin D from animal and non-animal sources; VDR: vitamin D receptors; Mg: magnesium]; modified from reference [93,94].

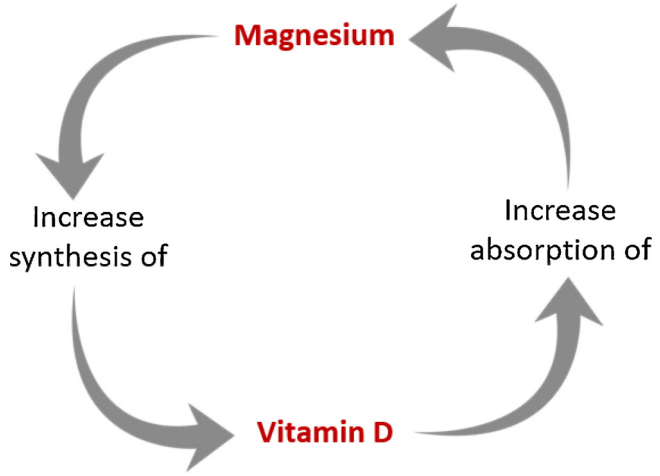

Fig. 3. Possible interactions between magnesium and vitamin D. Magnesium is an essential cofactor for vitamin D synthesis, and activated vitamin D, in turn, can increase intestinal absorption of magnesium, and therefore can form a feed-forward loop to maintain its homeostasis [93,94,129].

insufficiency, such as women, non-Hispanic African-Americans, obese, or individuals with the highest levels of circulating PTH [74]. These findings suggest an interaction between vitamin D and magnesium levels, particularly in the elderly and those with osteoporosis, which can have a major impact on human health.

Magnesium is needed to activate vitamin D because most of the enzymes involved in vitamin D metabolism and processing require magnesium [93]. Specifically, vitamin D is converted to the biologically active form $1,25(OH)_2D_3$ in the liver and kidneys via hydroxylation to 25(OH)D by the enzyme 25-hydroxylase, and 25(OH)D is further converted to $1,25(OH)_2D_3$ (Fig. 2) [104]. Both of these enzymes, hepatic 25-hydroxylase and renal 1α-hydroxylase require magnesium for activity. Furthermore, the synthesis of $1,25(OH)_2D_3$ was shown to occur in regions other than liver and kidney, such as the brain and testis, as well as other tissues. This was documented using a luciferase reporter linked to the promoter of the rate-limiting enzyme in $1,25(OH)_2D_3$ synthesis [105]. However, despite the widespread expression of enzymes involved in $1,25(OH)_2D_3$ synthesis, most serum $1,25(OH)_2D_3$ results from the processing of vitamin D metabolites in the kidney [106,107], and it is still unclear what role, if any, local generators of vitamin D might have in the body. $1,25(OH)_2D_3$ is a steroid hormone that activates the vitamin D receptor, a nuclear transcription factor, which results in the expression of vitamin D-responsive genes.

As mentioned above, magnesium deficiency reduces the levels of $1,25(OH)_2D_3$, which has been implicated in magnesium-dependent vitamin D–resistant rickets [31]. In two reported cases of vitamin D-resistant rickets, supplementation with magnesium reversed the resistance to vitamin D treatment [32]. In addition, serum $1,25(OH)_2D_3$ levels were substantially increased by supplementation with magnesium and vitamin D compared to that of vitamin D or magnesium alone [108]. Similarly, the serum levels of $1,25(OH)_2D_3$ in most magnesium deficient patients were unchanged after 5–13 days of parenteral magnesium therapy alone. Vitamin D is also transported in the blood via carrier proteins, which require magnesium for proper functioning [93]. Together, these studies suggest that magnesium and vitamin D interact to influence the levels of vitamin D [74], but more studies are needed (Fig. 3).

In animal studies, although vitamin D supplementation improves both calcium and magnesium absorption, it also increases magnesium excretion and reduces magnesium retention [109]. Levels of vitamin D are inversely related to PTH secretion and bone resorption [110]. 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 in osteoblasts and is modulated by the $1,25(OH)_2D_3$ [111]. In human studies, high magnesium intake is associated with reduced vitamin D deficiency [74]. High levels of magnesium may not only increase $1,25(OH)_2D_3$ by increasing the levels of 25-hydroxylase and vitamin D catabolites, but also by facilitating the transfer of vitamin D to target tissues through the vitamin D binding protein. This explanation is supported by studies showing that magnesium supplementation can reverse resistance to vitamin D treatment in magnesium-deficient patients [32]. However, it should be noted that while magnesium intake is associated with higher levels of vitamin D [74], magnesium supplementation alone cannot fully rescue vitamin D deficiencies [108]. These data suggest that there is a complex interplay between vitamin D and magnesium that requires further study.

6. Interaction between magnesium and calcium

Dietary factors can affect the age-related loss of bone density and skeletal muscle mass. Calcium is essential for bone health, but other minerals, such as magnesium, also have a role in the age-related loss of bone density. Dietary magnesium may slow the age-related loss of skeletal muscle mass, which is a risk factor for osteoporosis, falls, fractures, frailty, and mortality [112]. A decrease of magnesium in the food supply has likely contributed to inadequate consumption and chronic deficiencies, which is a direct result of lower levels of magnesium-rich soils and magnesium-poor vegetables, nuts, and legumes [113].

Calcium metabolism has a significant role in bone turnover, and deficiency of calcium and vitamin D leads to impaired bone deposition. Supplementation of calcium and vitamin D in clinical trials of older individuals can decrease bone resorption, increase bone density, decrease fractures, and decrease the risk of falling [101]. Secretion of the PTH is a reaction by the parathyroid glands to low calcium. This, in turn leads to increased bone resorption, ensuring sufficient levels of calcium in the blood. Calcitonin, a hormone generated by the thyroid, acts in an opposite manner to PTH by increasing bone deposition and decreasing ionic calcium levels in the serum, but its role in osteoporosis is less clear and probably not as dominant as that of PTH [14]. Magnesium can also reduce PTH secretion at low calcium concentrations [114], and restoring magnesium levels in a magnesium-depleted patient naturally corrected the low levels of calcium and intact parathyroid hormone (iPTH) without the need for additional supplementation with calcium [115].

PTH is secreted by chief cells in the parathyroid gland, acting as the key to unlock calcium stored in bone. Therefore, conditions that result in too much PTH or too little PTH, such as hyperparathyroidism or hypoparathyroidism, respectively, can result in calcium dysregulation and bone disease. Serum calcium levels negatively regulate the secretion of PTH, thereby indirectly regulating its own levels, by coupling to calcium-sensing receptors (CaSR) on the surface of chief cells. Calcium activates G-protein coupled receptors that act through intracellular messengers Inositol trisphosphate (IP3) and diacylglycerol (DAG) to raise the intracellular level of calcium in the cytoplasm, which inhibits the fusion of granules containing PTH on the cell membrane, thereby preventing their release [116,117].

The serum levels of PTH and magnesium are co-dependent; low levels of magnesium stimulate the secretion of PTH, but very low magnesium concentrations inhibit PTH secretion [118]. What is the mechanism by which these paradoxical blocks occur? Magnesium couples to the same calcium-sensing receptors as calcium on the surface of the chief cells, but has a weaker affinity for CaSR than that of calcium [119]. Therefore, when serum magnesium levels drop slightly, activation of CaSR decreases, which results in secretion of PTH similar to the effects of a decrease in serum calcium. However, the magnesium binding site on CaSR responsible for the inhibition of PTH secretion is not the same as the extracellular ion binding sites on CaSR. In support of this notion, CaSR mutants with increased or decreased affinity for calcium or magnesium do not affect CaSR activity at very low magnesium concentrations [120]. By contrast, mutation of the magnesium binding site on the alpha subunit of the heterotrimeric G-protein that binds to the receptor abolishes CaSR activation by magnesium. Magnesium inhibits guanine nucleotide exchange of the G alpha subunit by stabilizing guanine nucleotide binding, and therefore, the absence of magnesium increases the rate of GDP exchange of the G-alpha subunit. This results in constitutive activation of the CaSR receptor as well as other receptors that use G-alpha signaling [120]. Thus, magnesium directly and indirectly affects calcium levels through CaSR modulation and secretion of PTH, which have significant physiological impacts on bone health and the loss of bone density in older adults.

7. Overconsumption of magnesium and vitamin D

Hypermagnesemia is rare because the kidneys work to dispose of excess magnesium. However, hypermagnesemia can occur in people with kidney disease who are given magnesium supplements or drugs that contain magnesium, such as some antacids and laxatives. Elevated magnesium levels in people with end-stage renal disease might be beneficial because the additional magnesium delays the development of arterial calcifications [121]. Low serum magnesium is a risk factor for death in chronic kidney patients. Conversely, chronic kidney patients with mildly elevated magnesium levels have a survival advantage [122]. Therefore, patients need to be careful about both the underconsumption and overconsumption of magnesium because both lead to detrimental outcomes. An optimal amount of magnesium is the key for a patient's health. Elevated magnesium intake also improves overall survival following breast cancer in women, particularly for those who also have an increased calcium-to-magnesium intake ratio. However, elevated consumption of calcium alone does not have added benefit to prognosis [123]. Excess consumption of vitamin D may result in toxicity, with hypercalcemia and hyperphosphatemia [124] and an increase in kidney stones in post-menopausal women [125]. However, controlled trials of elevated doses of vitamin D (up to 100 μg per day for 2–5 months) in healthy adults did not reveal significant changes in serum calcium and urinary calcium excretion [126], and researchers presumed that normal doses of vitamin D (around 5 μg per day) are safe and effective [127]. However, it needs to be emphasized that phosphorus dysregulation, induced by exogenous vitamin D supplementation, may appear, even without developing hypervitaminosis D or changes in serum calcium level.

8. Conclusions

The micronutrient magnesium is essential for hundreds of essential cellular functions. Magnesium deficiency is associated with chronic diseases, including cardiovascular disease, metabolic syndrome, type II diabetes, and skeletal disorders. Osteoporosis is a particular concern among the elderly because insufficient intake of magnesium results in excess calcium release from bone, which further exacerbates bone fragility and increases the risk of fractures and falls. Dietary intake of magnesium in the US population is low, particularly among the elderly and ethnic minorities. Although the intake of calcium and vitamin D has been increasing in the United States for decades, there is relatively little information on the interactions between these three nutrients. High intake of calcium complicates the retention of magnesium, and low levels of magnesium can result in excess excretion of calcium. The optimal calcium-to-magnesium ratio is 2–2.8, but the increased consumption of calcium since the 1970′s in the United States has increased the ratio to above 3.0, which has coincided with an increased rate of diabetes [128].

Low vitamin D levels are also associated with chronic diseases worldwide. The interaction between vitamin D and magnesium contributes to the risk of cardiovascular disease and colorectal cancer.

Magnesium directly interacts with the enzymes that synthesize, transport, and activate vitamin D (Figs. 2 and 3). Although there are several studies on the effects of vitamin D or magnesium deficiency and supplementation alone, there are comparatively fewer studies on the interactions between vitamin D and magnesium for human health. Increasing vitamin D and/or calcium with supplements without a concomitant increase in magnesium intake may have unforeseen deleterious effects.

Measuring magnesium levels in the body is challenging because the magnesium load test is cumbersome and time consuming. It also may not be suitable for those with chronic kidney diseases or other complications. In addition, serum magnesium may not accurately reflect the available magnesium in tissues and may vary widely between individuals, time-of-day, and under different disease conditions. Thus, new non-invasive tests are needed to accurately measure magnesium status in blood, bone, and soft tissue in order to identify and effectively treat magnesium-deficient patients and those with chronic diseases, such as osteoporosis, depression, and chronic migraines that are affected by magnesium levels.

Finally, there is a profound lack of awareness of the insufficient intake of magnesium in the United States population and worldwide as evidenced by the stunning under-consumption of magnesium particularly in the elderly and ethnic minorities. Moreover, the dearth of magnesium in the food supply and agricultural soils and the decrease in magnesium content in processed foods and in newer varieties of grains, fruits, and vegetables poses a further challenge for adequate magnesium consumption. Poorer communities and food-insecure individuals are also disadvantaged in their ability to maintain an optimal magnesium balance. These disparities exacerbate health problems in diseases related to magnesium deficiencies and are a global health concern.

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