Review Article

Calcium-Magnesium Balance—Clinical Implications for Global Human Health

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Calcium (Ca) and magnesium (Mg) function as physiological opposites, and their ratio (Ca: Mg) is a key indicator of health status and disease risk. An imbalanced ratio—outside the optimal range of 1.7 to 2.6 —has been associated with conditions such as cancer, cardiovascular disease, dementia, and infections, including complications from COVID-19 and post-COVID syndrome. Obesity is both a cause and a consequence of Ca: Mg imbalance. While traditionally measured by dietary intake (mg/day), evaluating Ca: Mg levels in the blood as mmol/L provides a more physiologically relevant perspective. Mean values for ionized Ca and Mg yield iCa: iMg that aligns with this optimal physiological range. However, since Mg ions circulate in both RBCs and plasma versus Ca ions, a 3:2 intake ratio may better support homeostasis than the commonly recommended 2:1 ratio. As Mg is essential for vitamin D synthesis, maintaining the ideal Ca: Mg ratio may enhance the conversion of vitamin D_3 to 25(OH) D and the interaction of calcitriol with vitamin D receptors—potentially improving outcomes with lower vitamin D doses and significantly benefiting clinical outcomes and global health. However, the benefits of a balanced ratio extend well beyond that due to improved vitamin D efficacy. However, the benefits of a balanced ratio extend well beyond that due to improved vitamin D efficacy. Magnesium is crucial to the function of G-protein coupled receptors (GPCRs), critical to cell membrane signaling, CYP450 enzymes, activation of B vitamins, methylation of the epigenome, glucose metabolism, and to delay age linked oxidative stress and inflammaging. Magnesium deficiency may directly contribute to the global epidemic of type 2 diabetes and its symptoms overlap those of aging. Laboratory reference ranges, NHANES data, and pertinent recent peer reviewed reports offer objective support to speculative conclusions that require clinical validation.

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Highlights

- The optimal Ca: Mg ratio (1.7–2.6) prevents major chronic diseases.
- Imbalances are linked to cancer, heart disease, dementia, infections, and COVID-19 severity.
- Proper Ca: Mg ratio enhances vitamin D metabolism and improves health outcomes.
- A 3:2 Ca to Mg ratio intake may better support mineral balance than the traditional 2:1.
- Mg deficiency compromises PTH-dependent Ca absorption and the synthesis of all forms of vitamin D

Introduction

Much has been written about the global decline in health, with widespread micronutrient deficiencies playing a central role. Among the most overlooked are calcium (Ca) and magnesium (Mg)—the body's most abundant cations after sodium and potassium. Although deficiencies in both minerals are well documented, the benefits of supplementing one in isolation remain unclear. In recent years, greater emphasis has been placed on the Ca: Mg ratio rather than absolute levels. In 1989, Durlach proposed an ideal intake ratio of 2:1 by weight [1][2], but the optimal method for measuring and calculating this ratio—whether through dietary intake or blood levels—remains debated. This mini-review introduces a novel approach using laboratory reference ranges from healthy populations, comparing total serum Ca and Mg (mmol/L), ionized Ca and Mg, and RBC Mg to define optimal physiological balance.

Physiological Roles Cell Signaling to Cell Death: Calcium (Ca) and Magnesium (Mg)

Ca^{2+} and Mg^{2+} are essential divalent cations that play critical—and often opposing—roles in cellular physiology, ranging from signal transduction to apoptosis. Intracellular Ca is a ubiquitous second messenger, regulating numerous processes, including muscle contraction, neurotransmitter release, gene expression, enzyme activation, and programmed cell death [3]. In contrast, Mg acts as a natural Ca antagonist, stabilizing ATP, modulating ion channels, and maintaining membrane potential and genomic integrity [4].

While transient intracellular Ca^{2+} spikes initiate essential cellular responses, prolonged elevation can induce oxidative stress and activate both caspase-dependent and -independent apoptotic pathways [5]. By buffering Ca^{2+} influx, Mg^{2+} regulates mitochondrial permeability transition pores and protects against

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calcium-induced cytotoxicity and cell death. The precise balance between these ions is critical: disruptions in their ratio contribute to a range of pathologies, including cardiovascular diseases, neurodegeneration, and metabolic disorders [6]. Understanding the dynamic interplay between Ca^{2+} and Mg^{2+} provides valuable insights into cellular fate decisions and offers potential avenues for therapeutic intervention.

Importance of maintaining a balanced Ca: Mg ratio for overall health

Magnesium (Mg^{2+}) deficiency and an elevated calcium-to-magnesium (Ca^{2+}: Mg^{2+}) ratio are increasingly recognized as contributors to chronic low-grade inflammation and oxidative stress—key drivers of a process known as inflammaging [7]. Inflammaging, characterized by systemic, age-related inflammation in the absence of infection, is closely linked to the pathogenesis of numerous age-related diseases. Research has shown that low Mg^{2+} levels can trigger the release of pro-inflammatory cytokines and increase oxidative stress markers [8]. These responses accelerate cellular aging and dysfunction, directly associating an elevated Ca^{2+}: Mg^{2+} ratio with conditions such as cardiovascular disease, type 2 diabetes, and neurodegenerative disorders like Alzheimer's disease [9][10].

An imbalanced Ca^{2+}: Mg^{2+} ratio has been directly linked to the onset and progression of cardiovascular risk [11] and mortality [12][13], cancer, autoimmune disorders, infections, dementia [14][15], and obesity [16][17]. Although both Ca and Mg are essential minerals, their physiological actions are often antagonistic, making their balance vital for homeostasis. Excess Ca intake without sufficient Mg can promote uncontrolled cell proliferation—a hallmark of cancer—while Mg deficiency may impair DNA repair mechanisms and increase oxidative DNA damage [18]. However, the relationship between Ca, Mg, and cancer remains inconsistent [8], partly due to variations in study populations, dietary intake, methodologies, and the lack of consideration for their interactive effects [19]. Thus, greater emphasis should be placed on the Ca^{2+}: Mg^{2+} ratio rather than individual mineral levels when assessing disease risk and developing dietary guidelines.

Physiology of Calcium and Magnesium

Calcium is a vital mineral in human physiology, essential for maintaining the structural integrity of bones and teeth, supporting neuromuscular signaling, enabling blood coagulation, and facilitating hormone secretion. It also serves as a key intracellular messenger, regulating various cellular functions, including muscle contraction, neurotransmitter release, and enzyme activity. Intracellular Ca^{2+} levels are controlled tightly by calcium-binding proteins, membrane channels, and organelles such as the endoplasmic reticulum and mitochondria to prevent cytotoxic overload [20]. Extra-cellular Ca concentrations are maintained within a narrow range through hormonal regulation involving parathyroid hormone, calcitonin, and active vitamin D (calcitriol), thereby preserving physiological balance and homeostasis [21].

Magnesium, the second most abundant intracellular cation, is a critical cofactor in over 600 enzymatic reactions, particularly in ATP metabolism, DNA replication, and protein synthesis [22]. It plays a central role in stabilizing nucleic acids, modulating ion channels, and mitigating calcium-mediated excitotoxicity. Mg^{2+} is also essential for cardiovascular, neuromuscular, and immune function while maintaining cellular electrical gradients and mitochondrial integrity [23][24]. Magnesium homeostasis is regulated primarily through intestinal absorption and renal excretion. Mg^{2+} deficiency—often underdiagnosed—can result in neuromuscular disorders, arrhythmias, insulin resistance, and chronic inflammation, highlighting its indispensable physiological functions [25].

Calcium

Ca^{2+} and Mg^{2+} are vital to human physiology. Although there is some functional overlap, they primarily occupy opposite roles and have different counteracting functions. Ca^{2+} is predominantly extra-cellular, with a concentration of four orders of magnitude greater than that within the cell [1]. Nevertheless, Ca^{2+} and Ca/Mg ratio function as a second messenger from the circulation to cells and within cells, particularly those with calcium-sensing receptors (CaSRs), such as parathyroid cells, renal tubular cells, etc. Its primary extra-cellular role is the maintenance of skeletal and dental health. It is also vital for muscle contraction and nerve transmission.

Serum Ca^{2+} is the primary determinant of parathyroid hormone (PTH) secretion and the release of calcitonin in response to calcium stress situations [1]. Additionally, the intrinsic clotting cascade is highly dependent on Ca^{2+}. Although Ca^{2+} is primarily extra-cellular, its intracellular concentration is linked to signaling, inflammaging, and oxidative stress [7]. Half of the circulating plasma calcium is bound to protein, primarily albumin, while the other half exists in the ionized form. Laboratory reports often provide a corrected serum value when blood albumin is low; however, this is unnecessary [26].

Magnesium

Magnesium's intracellular versus extra-cellular concentration varies by cell type but is typically more than three times higher intracellularly. Meanwhile, the high 1:10,000 gradient for Ca^{2+} is maintained with the aid of Mg-dependent ATP. The latter also maintains the 30:1 gradient for intracellular potassium [27] and the 1:50 gradient for extra-cellular sodium [28]. Consequently, it would be challenging to maintain intracellular potassium levels or sustain normocalemia in the face of a Mg shortfall.

Hypermagnesemia: It leads to cardiovascular complications, such as hypotension and bradycardia. In extreme cases, it can cause cardiac arrest due to the inhibitory effect of Mg on Ca-mediated cardiac conduction pathways [29]. Elevated Mg^{2+} levels may lead to depressed central nervous system activity, including respiratory depression or even coma [30]. Consequently, severe hypermagnesemia (>6.0 mg/dL) is a medical emergency that may require interventions, including intravenous Ca gluconate and short-term renal replacement therapy to reduce Mg levels rapidly [31]. The key is recognizing early with prompt interventions to prevent life-threatening clinical outcomes [32].

Hypomagnesemia: Magnesium is essential for many physiological functions, including enzymatic activity, hormone synthesis and release, neuromuscular function, cellular energy balance, and receptor activation [33][34]. Thus, it is unsurprising that it can seriously affect human health. Examples include muscle weakness, cramps, tremors, and fatigue [32]. Magnesium is crucial for maintaining proper heart rhythm and regulating potassium and Ca ions in cardiac tissues; thus, hypomagnesemia can lead to cardiac arrhythmias [35].

Chronic hypomagnesemia contributes to several long-term health problems, such as the increased risk of falls, osteoporosis and fractures, insulin resistance, and hypertension. Nevertheless, the circulatory Mg concentrations do not accurately reflect tissue Mg levels [36]. As with higher levels, the lower tissue Mg can lead to cardiac arrhythmia, nerve conduction defects, and muscle weakness [34]. It also impairs parathyroid gland functions, simulates hypoparathyroidism, and exacerbates conditions such as diabetes and metabolic syndrome [35]. In severe cases, it can lead to life-threatening complications, such as respiratory distress and seizures [37]. Early diagnosis and management, through dietary adjustments or supplementation, are crucial to prevent adverse outcomes and restore Mg balance in the body [38][39].

Hypomagnesemia also disrupts hormone synthesis, release, and vitamin D activity (see below) [40]. It is associated with decreased synthesis and activation of vitamin D and VDR interactions, increased

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oxidative stress, and exacerbated cytotoxic activity in T lymphocytes, promoting the cytokine storm [41][42]. In addition, hypomagnesemia can cause endothelial dysfunction [43][44] and impaired myocardial contractility, hence increasing the risk of developing heart failure [45]. Those with hypomagnesemia with severe SARS-CoV-2 infection [46][47][48] or following COVID-19 vaccines can experience serious adverse effects [49][50].The physiological and biological functions of Mg are numerous. The renal outer medullary potassium channel (ROMK) is an Mg-dependent ATP channel that recycles potassium. Mg^{2+} is critical in inhibiting ROMK potassium channels in the principal cells of collecting tubules and ducts. When magnesium levels drop, ROMK channels become hyperactive—another mechanism of hypokalemia in hypomagnesemia.

Magnesium and Healthy Aging

Most enzymes that involve ATP/GTP, ADP/GDP, or cAMP/cGMP require physiological concentrations of Mg^{2+} [33][51]. Mg serves many disparate functions, some of which impact aging:

1. G-protein coupled receptors (GPCRs) are Mg-dependent (GTP), including those for Ca/Mg (CaSR), PTH, and insulin secretion [52]. Although VDR (vitamin D receptor) on the nuclear membrane is well known, there is another VDR like membrane receptor 1,25D3-MARRS (membrane associated, rapid response steroid-binding) on the cell membrane [53]. It is also a GPCR and potentiates immune function, e.g., breast cancer prevention [54].
2. Mg dependent cAMP (second messenger) intracellular signaling is also involved in VDR activation. Thirty-four per cent of FDA approved drugs target GPCRs [55]. Not surprisingly, decreased efficiency of GPCR signaling is linked to age-related disease [56]. TRH (thyrotropin releasing hormone) and TSH (thyroid stimulating hormone) are ligands for Mg dependent GPCRs. Iodination of T4 to form T3 is Mg dependent.
3. All CYP450 enzymes require Mg as a cofactor, some of which are involved in synthesizing vitamin D [57] (see Figure 1). CYP450 activity declines with age [58].
4. Another CYP450 enzyme, Mg dependent 11β-hydroxysteroid dehydrogenase, degrades cortisol [59], tightly linked to cognitive decline and dementia [60].

Figure 1 illustrates the crucial role of magnesium in the biochemistry of vitamin D synthesis.

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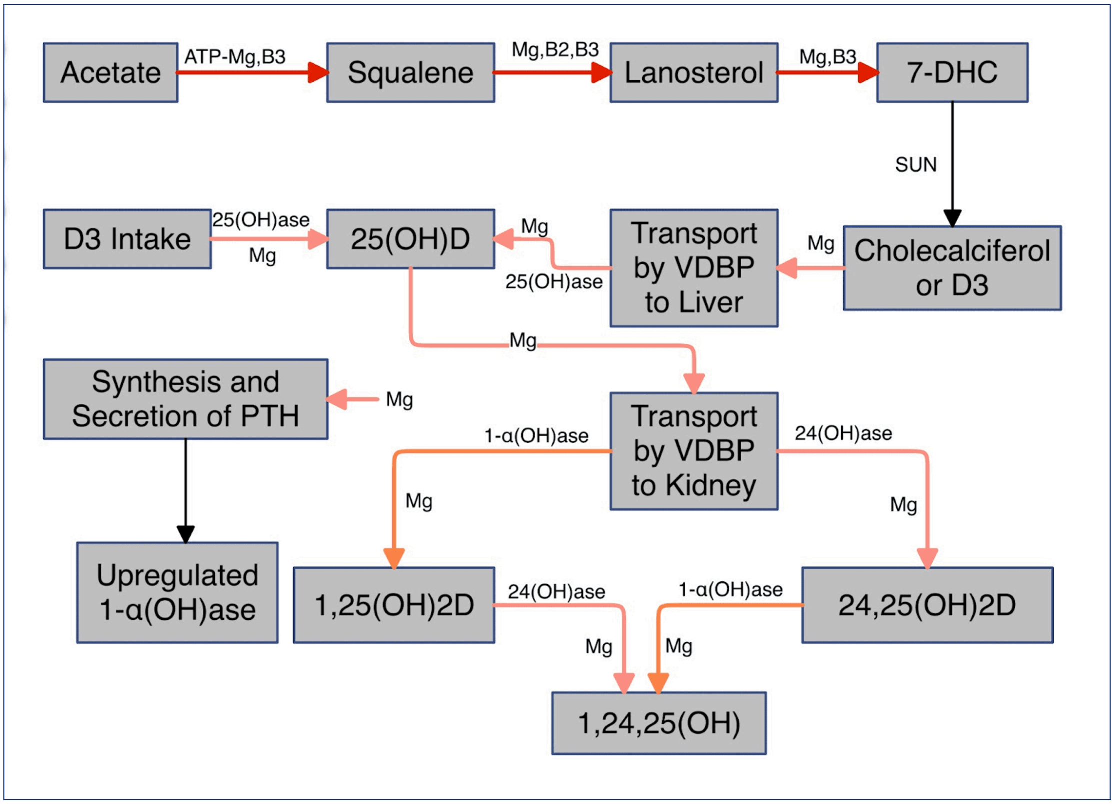

Figure 1. ATP-Mg, cofactor Mg, and Mg-dependent B2 and B3 are required to produce not only 7-dehydrocholesterol [19][61], the substrate for UVB-dependent production of D_3, but also the storage (25(OH) D) and active (1,25$(OH)_2$D) metabolites of vitamin D. The figure was created from fundamentals discussed by Han Y., et al., 2025 [61] and Chambers P. (2025) [19].

In addition to optimal GPCR function, CYP450 enzymes, and vitamin D synthesis, Mg is a required cofactor for most glycolytic and Krebs cycle enzymes. Many phosphorylation reactions are also Mg dependent, e.g., activation of vitamins B1 (thiamine to thiamine pyrophosphate) [62] B2 (riboflavin to FAD) [63], B3 (niacin to NAD) [64], B5 (pantothenate to coenzyme A) [65] and B6 (pyridoxine to pyridoxal phosphate) [51]. Methylation reactions are also Mg dependent, e.g., activation of B9 (folate to methyl folate) and B12 (cyanocobalamin to methylcobalamin) [66], require Mg as a cofactor [33][51]. All but biotin (B7) require Mg dependent activation and their deficiencies accelerate aging [67]. DNA methylation protects the genome and decreased DNA methylation is a hallmark of aging. [68]. Differential DNA methylation has recently been reported in cancer [69], dementia Yang T, C, Wei Q, Cheng Y, Xiao Y, Shang methylation in

Alzheimer's disease [70], cardiovascular disease (CVD) [71], and autoimmune disease [72], including Covid-19 severity and post-COVID syndrome [73].

Magnesium-dependent enzymes account for 80% of known metabolic functions [74]. Figure 1 illustrates the crucial roles of Mg, including synthesizing the substrate for D3 and all forms of vitamin D[19][61][75]. Low levels of vitamin D are linked with age-related disease, e.g., immunosenescence and inflammaging [76]. Mg is also essential for a healthy gut microbiome [77] and a healthy gut microbiome promotes healthy aging [77]. The above-mentioned Mg dependent functions support the view that Mg deficiency may drive the physiologic hallmarks of aging [9]. Mg deficiency profoundly affects oxidative stress and inflammaging [78], linked to aging [79][80]. and increased intracellular Ca^{2+} [81]. This underscores the increased health risks associated with an imbalanced Ca^{2+}: Mg^{2+} ratio.

Interrelationship Between Calcium and Magnesium

Ca^{2+} and Mg^{2+} compete for the same calcium-sensing receptors (CaSRs) [82]. Although these receptors are found primarily in the parathyroid gland and kidneys, they are also present in other organs, including the alimentary canal [26]. Concomitant intake of Ca^{2+} and Mg^{2+} may lead to competition for these receptors. Mg is also required for the synthesis and release of parathyroid hormone (PTH). While the PTH response to plasma Ca^{2+} and Mg^{2+} is similar, it is much more sensitive to plasma Ca^{2+}. According to a 2018 study, any attempt to correct a high Ca^{2+}: Mg^{2+} ratio by increasing Mg intake may exacerbate the imbalance when circulatory 25(OH) D exceeds 30 ng/mL [83].

When 25(OH) D levels are below 30 ng/mL, the demands of Mg dependent 25(OH) D synthesis

surpass those of Mg dependent PTH synthesis. Hypomagnesemia reduces the release and synthesis of hormones, especially PTH [84]. As Mg intake is increased, serum 25(OH) D levels also increase, up to about 25(OH) D levels 30 ng/mL, together with upregulation of Mg-dependent PTH synthesis. Beyond that, a further increase of the cellular Mg concentration results in downregulation of 25(OH) D. Increasing D3 to attain circulatory levels of 25(OH) D above 50 ng/mL, without first addressing an elevated Ca: Mg intake, may result in loss of Mg. Mg is consumed during the activation process of vitamin D metabolites [83]. In this study, BMI for both the study group and the placebo group averaged 30 kg/m Consequently, fat cells may also have absorbed some 25(OH) D. All participants had Ca: Mg ratios well above 3.5 and would represent the right hypoparathyroidic wing of the bell curve (see Figure 2). This reflects the Western fast/processed food diet. These theoretical considerations are speculative and require clinical validation. Table 1 illustrates various combinations of Ca^{2+}: Mg^{2+} ratios.

Imbalance	Etiology	Reference
Hypocalcemia (low Ca: Mg)	Seen primarily with hypoparathyroidic conditions. Vitamin D deficiency, gut dysbiosis, and certain medications. Chronic kidney disorders (CKDs) that suppress glomerular filtration can elevate serum phosphate, a divalent anion, that binds Ca and induces hypocalcemia. Mg insufficiency retards the synthesis of PTH and causes hypoparathyroidism.	[85]
Hypercalcemia (high Ca: Mg)	Primarily caused by overactive parathyroid glands, certain cancers, dehydration, and possibly prolonged excessive vitamin D intake (greater than 10,000 IUs/d).	[86][87]
Hypomagnesemia (high Ca: Mg)	Non-genetic origin: primarily encountered in those with low dietary intake, gut dysbiosis, or excess loss (excretion), e.g., vomiting or diarrhea.	[40]
Hypermagnesemia (low Ca: Mg)	Linked to CKDs, the primary culprit (other than iatrogenic). The low Ca: Mg seen in those on a traditional Asian diet is predominantly due to low Ca, not high Mg. CKDs associated with loss of glomerular filtration rate may not be able to maintain Mg homeostasis with resultant hypermagnesemia.	[31][88]

Table 1. Abnormal Ca: Mg ratios and their clinical settings

Symptoms of magnesium deficiency and an elevated Ca^{2+}: Mg^{2+} ratio can manifest in all three types of muscle: cramps in skeletal muscle, palpitations in cardiac muscle, and migraines and pre-menstrual syndrome (PMS) in smooth muscle. These two disorders and PMS have been linked to normo-magnesemic magnesium deficiency, first reported by Mansmann [89]. Like Ca^{2+}, Mg^{2+} is also essential for neural transmission. However, for other cell types, their functions are antagonistic: in smooth muscle cells, Mg^{2+}, a Ca^{2+} channel blocker, induces relaxation, while Ca^{2+} induces constriction.

An optimal balance of Ca^{2+} and Mg^{2+} is recommended. Mg-dependent flavin adenine dinucleotide (FAD) and nicotinamide adenine dinucleotide (NAD), the active forms of vitamins B2 and B3, are vital to the electron transport chain in the Krebs cycle [90]. An elevated Ca^{2+}: Mg^{2+} ratio compromises glucose metabolism and increases mitochondrial dysfunction. Mitochondrial dysfunction, linked to inflammaging, involves an increase in intra-mitochondrial Ca^{2+} induced partly by the mitochondrial permeability transition pore [91].

Pathophysiology of Ca: Mg Ratio—its Clinical Relevance

The Western diet typically has a high Ca-to-Mg ratio. Supplemental Ca was popular, especially among women, but this changed significantly after the Women's Health Initiative study [92] and similar studies published in subsequent years. As a result, the intake ratio increased from less than 2.5 to over 3.0, which is considered unphysiological [8]. Since Ca and Mg are ligands competing for the same Ca-sensing receptor (CaSR) receptor, it is unsurprising that their pathological ratios can adversely affect humans. CaSR is a G-protein coupled receptor that detects extra-cellular Ca levels to maintain calcium homeostasis. Activation of the CaSR in parathyroid cells reduces the secretion of PTH, while activation in renal tubular cells promotes urinary excretion of Ca [93].

Considering the Ca: Mg ratio as a messenger (from the circulation to) target cells would make it easier to understand its biological actions. Particularly in target cells with high CaSR density, such as parathyroid cells, renal tubular cells, and the brain [94]. The calcium-to-magnesium (Ca: Mg) ratio is equally vital in maintaining systemic equilibrium [95]. A high Ca intake without adequate Mg can suppress PTH levels, negatively impacting bone remodeling and mineralization. An imbalanced Ca: Mg ratio can also exacerbate chronic conditions, including cardiovascular diseases, due to improper Ca deposition in arterial walls [96]. Ensuring a balanced ratio, ideally around 2:1 (Ca: Mg), is critical to optimizing the synergistic effects of these minerals on vitamin D_3 metabolism, bone health, and overall physiological well-being [97].

Other studies show that a high Ca: Mg ratio is associated with higher mortality in those with severe SARS-CoV-2 infections [98]. Others have reported that a high Ca: Mg ratio can be used as a biomarker of clinical outcomes for chronic disease, and rectifying would derive benefit [99]. Both high and low Ca: Mg ratios are associated with higher cardiovascular and all-cause mortality [13]. Ca/Mg ratios >3.5 and <1.70 are independently associated with increased risk of chronic conditions, like cardiovascular disease, cancer, metabolic syndrome, type 2 diabetes, as well as all-cause mortality [100].

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Optimal Calcium-to-Magnesium Ratio

The Ca^{2+}: Mg^{2+} ratio is typically discussed regarding intake recommendations by weight (measured in mg/day). However, the interaction between these molecules occurs on an electrostatic molar basis, not a weight basis. When laboratory data is involved, concentrations are usually converted from mg/dL to mmol/L to account for the molecular interactions. Determining ionized calcium (iCa^{2+}): ionized magnesium (iMg^{2+}) ratios is less straightforward, particularly in hospitalized patients, due to various factors influencing ionized levels. In addition, different methodologies are used in studies, leading to confusion in interpreting the Ca^{2+}: Mg^{2+} ratio. Journal articles addressing the Ca^{2+}: Mg^{2+} ratio via these varying approaches contribute to this complexity.

The National Health and Nutrition Examination Survey (NHANES) from the Centers for Disease Control and Prevention (CDC) uses a detailed food frequency questionnaire (FFQ) to assess the national median Ca^{2+}: Mg^{2+} intake in mg/day from a civilian, non-institutionalized population [101]. The CDC's selectee criteria are less stringent than those used to determine laboratory reference ranges. A ratio of 1.7-2.6 (weight-to-weight in mg/day) has been recommended based on increased all-cause mortality in those outside this range [102]. One study from China involving 75,000 females and 62,000 males determined a median ratio of 1.7, lower than that found by NHANES, where the ratio exceeds 3 [103].

Two recent Chinese studies reported that this national intake ratio translated to actual serum reference ranges in mmol/L for Ca: Mg in a healthy subset of this population between 2.4 and approximately 3.6 [104][105].These Chinese serum mmol/L levels, with 70% of Mg unbound and 50% of calcium unbound, translate to a Ca^{2+}: Mg^{2+} ratio between 1.7 and 2.5, closely replicating the recommended 1.7-2.6 weight-to-weight intake. Using accepted laboratory reference ranges for total serum Ca and Mg in mmol/L, the American mean for iCa^{2+}: iMg^{2+} is similar (1.66-2.51). By comparing the reference range values for total serum Ca and Mg with their reference ranges for iCa^{2+} and iMg^{2+}, it is apparent that for alignment, Ca^{2+} must make up about 50% of total serum calcium, and Mg^{2+} must make up about 70% of total serum magnesium. Therefore, the recommended 1.7-2.6 range for Ca^{2+}: Mg^{2+} intake (weight-to-weight, as determined by FFQs) closely approximates the recommended range for serum Ca^{2+}: Mg^{2+} (mmol to mmol).

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Calcium-Magnesium Balance in Disease States

Mg deficiency and an elevated Ca^{2+}: Mg^{2+} ratio are linked to inflammaging and oxidative stress [15][16][17]. Inflammaging and oxidative stress, in turn, are linked to cancer [106], dementia [107], cardiovascular [108], diabetes [109], autoimmune disease [110], and obesity [17]. Not surprisingly, the Ca^{2+}: Mg^{2+} ratio is linked directly to cancer, metabolic disease, infections, autoimmune diseases, and obesity. However, many reports on the relationship between Ca and cancer and Mg and cancer are contradictory. Nevertheless, when their balance is evaluated, these relationships become clearer. If the Ca^{2+}: Mg^{2+} ratio is balanced with euparathyroidism, Ca and Mg levels must also be sufficient (see hypothetical Figure 2).

Cancer and Ca^{2+}: Mg^{2+}

An imbalanced Ca: Mg increases cancer risks when Ca is low (decreased ratio) and Mg is low (increased ratio). Ca and Mg compete for the same Ca-sensing receptor (CaSR). Many clinical studies have documented this for cancers of the colorectum, esophagus, prostate, lung, breast, ovary, and pancreas. (see Table 2).

Ca: Mg	Clinical Outcomes	Reference
Increasing Ca intake when Ca: Mg is low	Decreases the risk of colorectal cancer	[111][112]
Increasing Ca intake when Ca: Mg is high	Does not decrease the risk of colorectal cancer	[112]
Increasing Ca intake when Ca: Mg is low (less than 1.7)	Decreases esophageal cancer risk	[113]
Increasing Mg intake when Ca: Mg is low (less than 1.7)	Increases esophageal cancer risk	[113]
Increasing Mg intake when Ca: Mg is high	Decreases the risk of prostate cancer	[103][114]
A high or low Ca: Mg	Increases the risk of lung cancer	[103][115]
A high Ca: Mg	Decreases survival in breast and ovarian cancer	[116][117]
Increasing Mg when Ca: Mg is high	Decreases breast cancer risks	[118]
Increasing Ca when the Ca: Mg is low	Decreased risks for pancreatic cancer	[119]
Increasing Mg when Ca: Mg is high	Decreases the risks of pancreatic cancer	[120]

Table 2. Examples of different combinations of Ca” Mg ratios and reported clinical correlations

Metabolic Disease and Ca^{2+}: Mg^{2+}

The balance between Ca^{2+} and Mg^{2+} plays a critical role in metabolic disease, with an imbalanced Ca^{2+}: Mg^{2+} ratio (either high or low) contributing to various metabolic disorders [121]. Elevated Ca^{2+} levels in the presence of low Mg^{2+} have been linked to insulin resistance, impaired glucose metabolism, and increased risk for type 2 diabetes [121]. Furthermore, the dysregulation of this ratio exacerbates inflammation and oxidative stress, which are common pathophysiological features in metabolic diseases, including obesity and cardiovascular conditions [122].

Research suggests that maintaining an optimal Ca^{2+}: Mg^{2+} ratio could help mitigate these conditions and improve metabolic function by enhancing insulin sensitivity and reducing systemic inflammation. For instance, studies have highlighted the protective effects of Mg in preventing metabolic syndrome, emphasizing the need for proper Mg^{2+} intake alongside Ca to maintain metabolic health [123][124]. Some specific examples are discussed below.

Insulin Resistance, Diabetes Mellitus, and Ca: Mg

The growing global incidence of insulin resistance plays a key role in the development of type 2 diabetes, cardiovascular diseases, and obesity-related conditions [125][126]. Serum Mg levels may contribute to this increasing prevalence. The laboratory reference range for total serum Mg is typically 0.75-0.95 mmol/L. A study involving 10,000 participants showed that the risk for diabetes mellitus increased by 20% when serum Mg was between 0.80-0.85 mmol/L and 50% when it was between 0.75-0.80 mmol/L [127]. Additionally, conditions like PMS and migraine headaches have been linked to normo-magnesemic Mg deficiency, also known as chronic latent magnesium deficiency (CLMD), which may correspond to levels in the 0.75-0.85 mmol/L range. Table 3 summarizes the risks and benefits of Ca to Mg ratios in common disorders [57][89].

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Disorder	Clinical Presentations
Cardiovascular Disease	Elevated dietary Ca: Mg intake increases the risk for CVD [11]. Other researchers have reported that elevated serum Ca: Mg predicts mortality in CVD [12][13]. Low or high Ca intake increases cardiovascular disease risks when Ca: Mg is outside 2.0-2.5 [128].
Dementia	Both low Ca and Mg are associated with cognitive decline [129] and dementia [130]. Low Ca in Chinese is linked explicitly to dementia [131], while low Mg in Americans is specifically linked to dementia [14][15]
Obesity	Low dietary Mg intake is associated with higher BMI and obesity [16]. Obesity induces a low-grade, diffuse, pro-inflammatory state [17].
Cancer	Risks for numerous cancers increase when Ca intake is low and Ca: Mg is low or when Mg intake is low and Ca: Mg is high. Similarly, risks decrease when Ca: Mg is low and Ca intake is increased or when Ca: Mg is high, and Mg intake is increased [18][113][114][116][117][118][119][120][132].
Autoimmune Disease	Mg deficiency increases the risk for post-COVID syndrome [133], recovery from infections [46], and rheumatoid arthritis and lupus [134][135].
Infectious Disease	Mg deficiency increases mortality risks for COVID-19 [46].

Table 3. Examples of disorders linked to an imbalanced Ca: Mg

Infectious and Autoimmune Diseases and Ca: Mg

Mg deficiency has been associated with T-cell dysfunction, which can impair resistance to viral and bacterial infections [136]. However, the impact of Mg deficiency on vitamin D synthesis may have an even more profound effect. Vitamin D receptors (VDRs) are present in virtually all cells, and Mg deficiency can hinder vitamin D activation, further contributing to immune system dysfunction. T-cell dysfunction is also closely linked to autoimmune diseases. Adequate dietary and supplemental Mg intake has been shown to reduce all-cause mortality in individuals with rheumatoid arthritis [137].

Mg deficiency has been shown to increase the risk of rheumatoid arthritis [134], and oral Mg supplementation has been found to reduce pathogenic autoantibodies and skin disease severity in

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murine lupus models [135]. Post-COVID syndrome, now recognized as an autoimmune condition by the Autoimmune Registry, also appears to be influenced by Mg levels. Total serum Mg level below 0.80 mmol/L increased COVID-19 mortality by 29% and the risk of developing post-COVID syndrome by 114% [46], potentially reflecting chronic latent magnesium deficiency (CLMD). In conclusion, Mg deficiency negatively affects immune regulation while exacerbating inflammation, infectious diseases, cancer, and metabolic/ autoimmune disorders [46][120][138]. A low calcium-to-magnesium (Ca: Mg) ratio has also been linked to increased sickle cell disease sickling.

Mechanisms Underlying Calcium and Magnesium Imbalance

Multiple factors contribute to an imbalanced calcium-to-magnesium (Ca: Mg) ratio, including deteriorating agricultural soil, reduced essential mineral content in vegetables, and the global rise in consumption of processed foods and phosphate-rich soft drinks [96][139]. These dietary patterns are also associated with compromised gut microbiome diversity and function, further impairing nutrient absorption and metabolism [96][140][141]. An imbalanced Ca: Mg ratio is frequently a surrogate marker for vitamin D insufficiency or deficiency, as Mg is essential for synthesizing and activating vitamin D [141][142]. Furthermore, Mg deficiency often goes undetected because routine serum Mg testing is uncommon and, even when done, fails to reflect total body stores, making it easy to overlook [99][143].

The situation is compounded further by socioeconomic disparities and cultural practices that influence diet [144][145], clothing habits that limit sun exposure, and uneven access to healthcare services [146][147][148]. Besides, individuals from low-income or traditional communities often face limited dietary diversity and reduced availability of nutrient-rich foods, heightening their risk for micronutrient imbalances [149]. Aging and elevated body mass index (BMI) contribute to chronic low-grade inflammation, insulin resistance [150][151], and micronutrient depletion, exacerbating the health consequences of an imbalanced Ca: Mg ratio [152]. A widespread lack of public awareness and the absence of routine clinical screening for Mg status obstruct early detection and effective prevention. Figure 2 illustrates the proposed mechanisms linking circulating 25(OH) D levels with Ca: Mg ratios.

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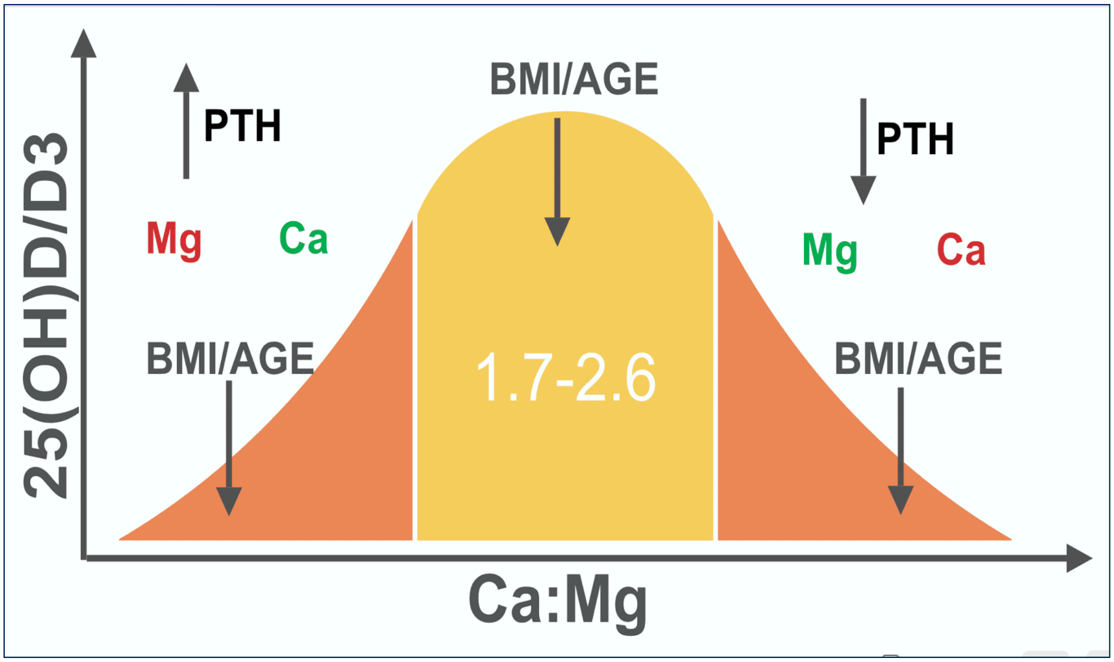

Figure 2. A hypothetical figure that illustrates improving Ca: Mg and BMI may enhance the efficacy of D_3. If Ca: Mg is optimal, attaining 25(OH) D >50 ng/mL may be theoretically possible with 2000 IUs of D_3 supplementation. Optimal Ca: Mg should also reflect euparathyroid state and sufficiency of Ca and Mg. One study suggests that the upper limit of optimal Ca: Mg be reduced to 2.5 [128].

Notably, PTH regulates Ca and Mg similarly, but Ca is the primary determinant of PTH level. Besides, Ca and Mg are antagonists in many ways, e.g., Mg is a Ca channel blocker and both compete for the same CaSR. The left side of the bell curve in Figure 2 represents the established inverse relationship between serum 25(OH) D and parathyroid hormone (PTH). A diet low in Ca, thus, a low Ca: Mg ratio—such as a traditional Asian diet—stimulates PTH secretion. However, increasing Ca intake to rectify the imbalance downregulates PTH/vitamin D synthesis and Mg absorption in those already D_3 deficient. This might increase the need for higher D_3 and Ca supplementation to achieve optimal 25(OH) D concentrations, probably at the expense of Mg.

In contrast, the right side of the bell curve in Figure 2 reflects scenarios common in Western diets, characterized by high Ca intake and routine D_3 supplementation without adequate Mg. In this context, Mg intake is often insufficient to support optimal PTH synthesis. Consequently, D_3 supplementation alone may downregulate Mg-dependent PTH, perpetuating a hypo-parathyroid state. This suggests that

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individuals with a suboptimal (high) Ca: Mg ratio may require even higher D_3 and Mg doses to achieve target 25(OH) D levels.

Complex pathophysiological interactions related to Ca: Mg ratios

As previously discussed, a 2018 study [83] reported that when baseline 25(OH) D exceeded 30 ng/mL, Mg supplementation (e.g., 200 mg/day) surprisingly reduced 25(OH) D synthesis [83]. However, PTH was not assessed in that study. Further analysis showed that Ca: Mg intake ratios (mg/d) were elevated at 3.9 and 3.7 in the placebo and treatment groups, respectively. Both groups were also overweight or obese [83]. These findings suggest that when Ca: Mg is elevated, Mg supplementation is first triaged to vitamin D synthesis and then to PTH synthesis. Another study supports this interpretation, proposing that in overweight and obese individuals with elevated Ca: Mg, increased Mg intake may first be directed toward restoring PTH synthesis [153]. The Ca: Mg ratio must normalize before additional Mg is available for 25(OH) D synthesis sufficient to attain 50 ng/mL.

These studies support the proposed bell curve in Figure 2, placing participants from both studies on the right wing [153] of the bell. Both findings suggest that near the lower limit of serum Mg^{2+} at 0.54 mmol/L, Mg^{2+} levels may be insufficient for adequate PTH synthesis. The lower reference value of total serum Mg at 0.75 mmol/L corresponds to a Mg^{2+} of approximately 0.52 mmol/L. Optimal allocation of Mg^{2+} for effective 25(OH) D synthesis may require Mg^{2+} levels approaching 0.60 mmol/L. Multiple studies recommend increasing the lower reference threshold for total serum Mg from 0.75 to 0.85 mmol/L [36][102][154], corresponding to a Mg^{2+} of approximately 0.60 mmol/L [155].

Clinical Implications and Recommendations

An optimal Ca: Mg ratio works synergistically with vitamin D. While a serum 25(OH) D level of 30 ng/mL may suffice for skeletal health, a target of 50 ng/mL is recommended to support extra-skeletal functions, which are predominantly intracellular. Intracellular Mg^{2+} concentrations consistently exceed those of extra-cellular Mg^{2+}. Both ionized Ca and Mg are integral to cellular signaling and are essential for regulating diverse cellular functions and enzymatic processes, including ion channel activity, metabolic pathways, and intracellular signaling mechanisms [156].

A study on FFQs in individuals not taking supplements found that a Ca: Mg ratio between 2.2 and 3.2 offered the greatest protection against osteoporosis [95]. While FFQ-derived data generally suggest an ideal Ca: Mg range of 1.7 to 2.6, the higher range recommended for skeletal (primarily, extra-cellular) health implies that additional Mg may be needed for extra-skeletal (intracellular) functions of target cells —such as intracellular signaling [157], including in cardiovascular and immune cells [158][159]. Adequate Mg is indispensable in this context, and a balanced Ca: Mg ratio enhances the effectiveness of 25(OH) D as well as key enzymatic processes (see Figure 2). Besides, Mg supplementation when Ca: Mg is elevated and 25(OH) D exceeds 30 ng/mL may be less effective [83].

A. Overlooked Physiological Roles of RBC Magnesium

Durlach's 2:1 weight-to-weight recommendation for Ca: Mg intake was first published in 1989 [1][2]. It is underpinned by the medical literature [79][82] and supported by the median laboratory reference range values for physiologic serum iCa and iMg. In addition, the molecular weight of Ca is nearly twice that of Mg [23][24]. However, unlike Ca, Mg occupies both intravascular compartments—plasma and RBCs, i.e., RBC Mg, a recent development. It is not reflected in what the laboratories measure in the serum. Recommended RBC Mg concentration (the reservoir maintaining plasma iMg homeostasis) is about three times that of plasma Mg [36]. Comparison of Chinese and American reference range means for whole blood Mg versus plasma Mg, support this multiple.

Mg dependent PTH responds more to circulating iCa than iMg, and because iCa and iMg are often competitors, a conflict of interest may develop. High Ca intake translates to low PTH, low endogenous D, and low Mg. Low Ca intake translates to high PTH and high endogenous D, but only if Mg is sufficient. Low Mg intake may compromise the healthful benefits of vitamin D. Perhaps the RBC reservoir of Mg was designed to counterbalance this. If one adjusts the 2:1 Ca: Mg weight to weight recommendation of Durlach for differential molar weights (40:24) and dissociation constants (50% v 70%), then this weight to weight ratio should be 2.33. But if Ca:Mg is balanced (euparathyroidism), then vitamin D should be optimized. Vitamin D enhances intestinal absorption/renal resorption of Ca. This might lower the intake ratio and more closely reflect Durlach's 2:1 recommendation. But is that ratio physiologically correct?

Using median laboratory reference range values for serum Ca (9.5 mg/dL), serum Mg (2.0 mg/dL) [36][82][132], and that recommended for RBC Mg (6 mg/dL) [36] and assuming 40% hematocrit and five liters blood volume, one can show that to maintain homeostasis (physiologic 2:1 ratio of serum iCa:iMg with adequate RBC reservoir), absorption of Ca:Mg should theoretically yield about 3:2 weight to weight (285 mg Ca:180 mg Mg). NHANES (FFQs) data through 2023 indicate that the intake ratio has well exceeded 3:1 since the year 2000.

However, determining the general Ca:Mg intake ratio required to meet this theoretical 3:2 need and to maintain Ca:Mg homeostasis/euparathyroidism is intake determined but absorption dependent. For example, if about 30% of Ca and 35% of Mg were absorbed, then intakes of 950 mg Ca and 514 mg Mg, nearly 2:1, would be required to meet the theoretical need. If sufficient vitamin D were aboard and absorption were equivalent, then intakes of 800 mg Ca and 514 mg Mg, nearly 3:2, would be required. Since they compete for the same CaSR absorption receptors, temporal separation of Ca and Mg intake should also impact absorption.

A 3:2 intake ratio of Ca: Mg seems optimal for vitamin D sufficient otherwise healthy individuals following a Western diet (hypoparathyroid). A 1:1 ratio might be initially considered for those with Ca: Mg > 2.6 (hypoparathyroid). Ca is often high in processed foods and carbonated colas, which are part of Western diets. Targeting a 2:1 intake ratio might be more appropriate in those on traditional Asian diets low in Ca (hyperparathyroid). The 3:2 ratio may also help address CLMD (e.g., pre-menstrual syndrome/migraines [89] and early insulin resistance [127], conditions prevalent among those consuming a Western fast-food diet. Much has changed since 1989. Deteriorating diets and lifestyle changes have conspired to compromise both intake and absorption. These conclusions, however, are theoretical and require clinical validation.

B. Physiological vs. Pathological Ca: Mg Ratios

Escalating BMI remains a central issue—sufficient attention to exercise and diet is necessary to lose weight [160][161]. A diet high in leafy greens, nuts, seeds, and legumes supports better Mg status, though supplementation is often necessary. To avoid the laxative effect—especially from Mg citrate—use varied forms in divided doses. Synbiotics may further support Mg absorption by improving gut microbiome health. Pyridoxal phosphate (active vitamin B_6) [162]—not its inactive form, pyridoxine—enhances Mg uptake. Excess pyridoxine can competitively inhibit pyridoxal phosphate [163]. Notably, elemental Mg typically constitutes no more than 10% of weight per tablet in most supplements.

Compared to CRP, Ca: Mg is a more specific and actionable indicator of inflammaging and oxidative stress, both linked to cancer, metabolic diseases, infections, autoimmune disorders like post-COVID syndrome, and obesity. While assessing dietary intake of either Ca or Mg is challenging, obtaining relevant laboratory data is relatively straightforward. Mg is essential for many physiological functions. Nevertheless, for over 50% of Americans intake is insufficient [36].

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Synthesis of D3/25(OH) D/1,25$(OH)_2$ and binding to VDBP require Mg [96]. Therefore, it is crucial to ensure that the recommended amount of Mg is consumed to optimize vitamin D benefits and support all body systems [83][96]. Unfortunately, measuring serum Mg is not routine, and it is not included in standard panels, requiring specific requests.

If Ca: Mg is balanced, then each is within normal limits: i.e., a euparathyroid state exists (see Figure 2). Human physiological demands have not changed. China and America share similar long-standing reference range limits for both Ca and Mg. Yet PTH laboratory reference ranges differ – 10-65 pg/mL in America versus 10-100 pg/mL in China [104].

This is due to the relative availability/intake of critical micronutrients influenced by cultural, agricultural, and food habits considerations. The shortfall in Mg is global, albeit much more so on a Western diet. However, wealthy Western countries are ingesting too much Ca, and the rest of the world is taking too little. The latter is better known, but the former is not so well known.

Conclusion

Maintaining an optimal calcium-to-magnesium (Ca: Mg) ratio is crucial for numerous physiological functions and for preventing chronic and infectious diseases. An imbalanced ratio—below 1.7 or above 2.6—has been linked to increased risks of cancer, cardiovascular disease, neurodegenerative disorders like dementia, autoimmune conditions such as post-COVID syndrome, and greater susceptibility to infections. These risks are further heightened by rising body mass index (BMI), which influences and is influenced by Ca: Mg imbalance. Some meta-analyses report no benefit from D3 supplementation, when 25(OH) D levels exceed 30 ng/mL. Unfortunately, these meta-analyses do not include Mg or Ca: Mg status.

If 30 ng/mL of 25(OH) D is sufficient for skeletal (endocrine) needs, despite Ca: Mg imbalance and parathyroid dysfunction [83][153], then additional supplemental D3 might provide even greater benefit, when 25(OH) D > 30 ng/mL and Ca: Mg is balanced with euparathyroidism. Optimum Ca: Mg optimizes extraskeletal health (see Tables 2,3). This feature is not dependent on the endocrine (hormonal) role of vitamin D but on its intracrine role, suppressing inflammaging and improving systemic immunity. This requires higher doses of D3, enough to attain 50 ng/mL 25(OH) D. Meta-analyses that refute this benefit overlook the key role Ca: Mg plays in the body's ability to synthesize and utilize vitamin D, whether from solar UVB exposure or supplementation with cholecalciferol (D3), impacting metabolic regulation.

Furthermore, outside this recommended Ca: Mg range, other benefits are lost, e.g., the anti-cancer benefits of physical exercise [164]. Symptoms of aging other than cancer, e.g., dementia, CVD, autoimmunity, infections, and obesity intensify. Many of these symptoms mimic those of Mg deficiency [9]. Given the complex roles of these minerals in health and disease, further research is needed to explore their interactions and establish evidence-based clinical guidelines for optimal intake and monitoring.

Statements and Declarations

Conflicts of Interest

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Data Availability

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References

1. a, b, c, d *Drake TM, G.V. "Calcium-Stat Pearls." StatPearls. https://www.ncbi.nlm.nih.gov/books/NBK557683/.*
2. a, b *Durlach J (1989). "Recommended dietary amounts of magnesium: Mg RDA." Magnes Res.* ***2****:195–203.*
3. ^ *Keller M, Pignier C, Santelli M, Vacher B, Niggli E, Egger M (2006). "Agonist specific L-type Ca (2+)-current stimulation in ventricular myocytes by a novel steroid-like compound." Cell Calcium.* ***39****:425–433. doi:10.1016/j.ceca.2006.01.006.*
4. ^ *da Silva Cunha TT, Silva RR, Rodrigues DA, de Sena Murteira Pinheiro P, Kronenberger T, Sant'Anna CMR, Noel F, Fraga CAM (2022). "Design, synthesis, and pharmacological evaluation of novel conformationally restricted N-arylpiperazine derivatives characterized as D (2)/D (3) receptor ligands, candidates for the treatment of neurodegenerative diseases." Biomolecules.* ***12****. doi:10.3390/biom12081112.*

5. ^Li Y, Johnson N, Capano M, Edwards M, Crompton M (2004). "Cyclophilin-D promotes the mitochondrial permeability transition but has opposite effects on apoptosis and necrosis." Biochem J. **383**:101–109. doi:10.1042/BJ20040669.

6. ^Swann K, Lai FA (2016). "Egg activation at fertilization by a soluble sperm protein." Physiol Rev. **96**:127–149. doi:10.1152/physrev.00012.2015.

7. a, bErmak G, Davies KJ (2002). "Calcium and oxidative stress: from cell signaling to cell death." Mol Immunol. **38**:713–721. doi:10.1016/s0161-5890(01)00108-0.

8. a, b, cRosanoff A, Weaver CM, Rude RK (2012). "Suboptimal magnesium status in the United States: are the health consequences underestimated?" Nutr Rev. **70**:153–164. doi:10.1111/j.1753-4887.2011.00465.x.

9. a, b, cDominguez LJ, Veronese N, Barbagallo M (2024). "Magnesium and the hallmarks of aging." Nutrients. **16**. doi:10.3390/nu16040496.

10. ^McCarty MF, DiNicolantonio JJ, Lerner A (2021). "A fundamental role for oxidants and intracellular calcium signals in Alzheimer's pathogenesis-and how a comprehensive antioxidant strategy May Aid Prevention of this disorder." Int J Mol Sci. **22**. doi:10.3390/ijms22042140.

11. a, bShahsavani Z, Masoumi SJ, Barati-Boldaji R, Shamshirgardi E, Kafipour R, Sohrabi Z, Babajafari S, Asadi AH, Behzadi M, Akbarzadeh M (2025). "Dietary calcium to magnesium ratio and Risk of cardiovascular diseases." Biological trace element research. doi:10.1007/s12011-025-04587-0.

12. a, bJiang Y, Luo B, Chen Y, Lu W, Peng Y, Chen L, Lin Y (2024). "Serum calcium-magnesium ratio at admission predicts adverse outcomes in patients with acute coronary syndrome." PLoS One. **19**:e0313352. doi:10.1371/journal.pone.0313352.

13. a, b, cLi Q, Chen Q, Zhang H, Xu Z, Wang X, Pang J, Ma J, Ling W, Li D (2020). "Associations of serum magnesium levels and calcium-magnesium ratios with mortality in patients with coronary artery disease." Diabetes & metabolism. **46**:384–391. doi:10.1016/j.diabet.2019.12.003.

14. a, bZhu X, Borenstein AR, Zheng Y, Zhang W, Seidner DL, Ness R, Murff HJ, Li B, Shrubsole MJ, Yu C, et al. (2020). "Ca:Mg ratio, APOE cytosine modifications, and cognitive function: Results from a randomized trial." J Alzheimers Dis. **75**:85–98. doi:10.3233/JAD-191223.

15. a, b, cTao MH, Liu J, Cervantes D (2022). "Association between magnesium intake and cognition in US older adults: National Health and Nutrition Examination Survey (NHANES) 2011 to 2014." Alzheimers Dement (N Y). **8**:e12250. doi:10.1002/trc2.12250.

16. a, b, cCastellanos-Gutierrez A, Sanchez-Pimienta TG, Carriquiry A, da Costa THM, Ariza AC (2018). "Higher dietary magnesium intake is associated with lower body mass index, waist circumference and serum gluco

se in Mexican adults." Nutr J. ***17****:114. doi:10.1186/s12937-018-0422-2.*

17. [a, b, c, d] *Khanna D, Khanna S, Khanna P, Kahar P, Patel BM (2022). "Obesity: A chronic low-grade inflammation and Its markers." Cureus.* ***14****:e22711. doi:10.7759/cureus.22711.*
18. [a, b] *Dai Q, Shrubsole MJ, Ness RM, Schlundt D, Cai Q, Smalley WE, Li M, Shyr Y, Zheng W (2007). "The relation of magnesium and calcium intakes and a genetic polymorphism in the magnesium transporter to colorectal neoplasia risk." Am J Clin Nutr.* ***86****:743–751. doi:10.1093/ajcn/86.3.743.*
19. [a, b, c, d] *Chambers P (2025). "Vitamin D, calcium to magnesium ratio, and the gut microbiome." Med Clin Res.* ***10****:1–14. doi:10.33140/MCR.10.02.04.*
20. [^] *Hoenderop JG, Nilius B, Bindels RJ (2005). "Calcium absorption across epithelia." Physiol Rev.* ***85****:373–422. doi:10.1152/physrev.00003.2004.*
21. [^] *Committee-DRI (2011). Dietary reference intakes for calcium and vitamin D. Washington DC, USA: National Academies Press.*
22. [^] *Lim HS, Lee B, Cho I, Cho GS (2020). "Nutritional and clinical factors affecting weight and fat-free mass loss after gastrectomy in patients with gastric cancer." Nutrients.* ***12****. doi:10.3390/nu12071905.*
23. [a, b] *Pilchova I, Klacanova K, Tatarkova Z, Kaplan P, Racay P (2017). "The involvement of Mg (2+) in regulation of cellular and mitochondrial functions." Oxid Med Cell Longev.* ***2017****:6797460. doi:10.1155/2017/6797460.*
24. [a, b] *Liu M, Jeong EM, Liu H, Xie A, So EY, Shi G, Jeong GE, Zhou A, Dudley SC Jr (2019). "Magnesium supplementation improves diabetic mitochondrial and cardiac diastolic function." JCI Insight.* ***4****. doi:10.1172/jci.insight.123182.*
25. [^] *Shimizu H, Fujita Y, Ito Y, Matsuo S (2008). "Disorders of calcium and magnesium metabolism: a diagnostic approach." Nihon Jinzo Gakkai Shi.* ***50****:91–96.*
26. [a, b] *Kenny CM, Murphy CE, Boyce DS, Ashley DM, Jahanmir J (2021). "Things we do for no reason: Calculating a "corrected calcium" level." J Hosp Med.* ***16****:499–501. doi:10.12788/jhm.3619.*
27. [^] *Zacchia M, Abategiovanni ML, Stratigis S, Capasso G (2016). "Potassium: From physiology to clinical implications." Kidney Dis (Basel).* ***2****:72–79. doi:10.1159/000446268.*
28. [^] *Gagnon KB, Delpire E (2020). "Sodium transporters in human health and disease." Front Physiol.* ***11****:588664. doi:10.3389/fphys.2020.588664.*
29. [^] *Nishikawa M, Shimada N, Kanzaki M, Ikegami T, Fukuoka T, Fukushima M, Asano K (2018). "The characteristics of patients with hypermagnesemia who underwent emergency hemodialysis." Acute Med Surg.* ***5****:222–229. doi:10.1002/ams2.334.*

30. [^]*Tosto F, Magro G, Laterza V, Romozzi M (2024). "Neurological manifestations of hypermagnesemia: a narrative review." Acta Neurol Belg. doi:10.1007/s13760-024-02653-3.*

31. [a, b]*Aal-Hamad AH, Al-Alawi AM, Kashoub MS, Falhammar H (2023). "Hypermagnesemia in clinical practice." Medicina (Kaunas). **59**. doi:10.3390/medicina59071190.*

32. [a, b]*Ayuk J, Gittoes NJ (2014). "Contemporary view of the clinical relevance of magnesium homeostasis." Ann Clin Biochem. **51**:179–188. doi:10.1177/0004563213517628.*

33. [a, b, c]*Fatima G, Dzupina A, H BA, Magomedova A, Siddiqui Z, Mehdi A, Hadi N (2024). "Magnesium matters: A comprehensive review of Its Vital role in health and diseases." Cureus. **16**:e71392. doi:10.7759/cureus.71392.*

34. [a, b]*Fanni D, Gerosa C, Nurchi VM, Manchia M, Saba L, Coghe F, Crisponi G, Gibo Y, Van Eyken P, Fanos V, et al. (2021). "The role of magnesium in pregnancy and in fetal programming of adult diseases." Biological trace element research. **199**:3647–3657. doi:10.1007/s12011-020-02513-0.*

35. [a, b]*Oost LJ, Tack CJ, de Baaij JHF (2023). "Hypomagnesemia and Cardiovascular Risk in Type 2 Diabetes." Endocr Rev. **44**:357–378. doi:10.1210/endrev/bnac028.*

36. [a, b, c, d, e, f]*Razzaque MS (2018). "Magnesium: Are we consuming enough?" Nutrients. **10**. doi:10.3390/nu10121863.*

37. [^]*Mawri S, Gildeh E, Joseph N, Rabbani B, Zweig B (2017). "Cardiac Dysrhythmias and Neurological Dysregulation: Manifestations of Profound Hypomagnesemia." Case Rep Cardiol. **2017**:6250312. doi:10.1155/2017/6250312.*

38. [^]*Wimalawansa SJ (1994). "Significance of plasma PTH-rp in patients with hypercalcemia of malignancy treated with bisphosphonate." Cancer. **73**:2223–2230. doi:10.1002/1097-0142(19940415)73:8<2223::aid-cncr2820730831>3.0.co;2-c.*

39. [^]*Cooper C, Li H, Wimalawansa SJ (1997). "Cancer-associated hypercalcemia and parathyroid hormone-related peptide: a new peptide with diverse roles." Reg. Peptide Letters. **7**:39–42.*

40. [a, b]*Hansen BA, Bruserud O (2018). "Hypomagnesemia in critically ill patients." J Intensive Care. **6**:21. doi:10.1186/s40560-018-0291-y.*

41. [^]*Suhail S, Zajac J, Fossum C, Lowater H, McCracken C, Severson N, Laatsch B, Narkiewicz-Jodko A, Johnson B, Liebau J, et al. (2020). "Role of oxidative stress on SARS-CoV (SARS) and SARS-CoV-2 (COVID-19) infection: A review." Protein J. **39**:644–656. doi:10.1007/s10930-020-09935-8.*

42. [^]*Vabret N, Britton GJ, Gruber C, Hegde S, Kim J, Kuksin M, Levantovsky R, Malle L, Moreira A, Park MD, et al. (2020). "Immunology of COVID-19: Current state of the science." Immunity. **52**:910–941. doi:10.1016/j.immuni.2020.05.002.*

43. ^Nagele MP, Haubner B, Tanner FC, Ruschitzka F, Flammer AJ (2020). "Endothelial dysfunction in COVID-19: Current findings and therapeutic implications." Atherosclerosis. **314**:58–62. doi:10.1016/j.atherosclerosis.2020.10.014.
44. ^Di Mario F, Regolisti G, Greco P, Maccari C, Superchi E, Morabito S, Pistolesi V, Fiaccadori E (2021). "Prevention of hypomagnesemia in critically ill patients with acute kidney injury on continuous kidney replacement therapy: the role of early supplementation and close monitoring." J Nephrol. **34**:1271–1279. doi:10.1007/s40620-020-00864-4.
45. ^Babapoor-Farrokhran S, Gill D, Walker J, Rasekhi RT, Bozorgnia B, Amanullah A (2020). "Myocardial injury and COVID-19: Possible mechanisms." Life Sci. **253**:117723. doi:10.1016/j.lfs.2020.117723.
46. a, b, c, d, eDominguez LJ, Veronese N, Guerrero-Romero F, Barbagallo M (2021). "Magnesium in infectious diseases in older people." Nutrients. **13**. doi:10.3390/nu13010180.
47. ^Gunay S, Caliskan S, Sigirli D (2021). "Relationship of magnesemia with myocardial damage and mortality in patients with COVID-19." Magnes Res. **34**:93–102. doi:10.1684/mrh.2021.0485.
48. ^Guerrero-Romero F, Micke O, Simental-Mendia LE, Rodriguez-Moran M, Vormann J, Iotti S, Banjanin N, Rosanoff A, Baniasadi S, Pourdowlat G, et al. (2023). "Importance of magnesium status in COVID-19." Biology (Basel). **12**. doi:10.3390/biology12050735.
49. ^Coman AE, Ceasovschih A, Petroaie AD, Popa E, Lionte C, Bologa C, Haliga RE, Cosmescu A, Slanina AM, Bacusca AI, et al. (2023). "The significance of low magnesium levels in COVID-19 patients." Medicina (Kaunas). **59**. doi:10.3390/medicina59020279.
50. ^Trapani V, Rosanoff A, Baniasadi S, Barbagallo M, Castiglioni S, Guerrero-Romero F, Iotti S, Mazur A, Micke O, Pourdowlat G, et al. (2022). "The relevance of magnesium homeostasis in COVID-19." Eur J Nutr. **61**:625–636. doi:10.1007/s00394-021-02704-y.
51. a, b, cDeshpande O, Mohiuddin SS. "Biochemistry, oxidative phosphorylation." StatPearls. https://www.ncbi.nlm.nih.gov/books/NBK553192/.
52. ^Cho YY, Kim S, Kim P, Jo MJ, Park SE, Choi Y, Jung SM, Kang HJ (2025). "G-Protein-Coupled Receptor (GPCR) Signaling and Pharmacology in Metabolism: Physiology, Mechanisms, and Therapeutic Potential." Biomolecules. **15**(2):291. doi:10.3390/biom15020291.
53. ^Kermpatsou D, Olsson F, Wåhlén E, Söderberg O, Lennartsson J, Norlin M (2024). "Cellular responses to silencing of PDIA3 (protein disulphide-isomerase A3): Effects on proliferation, migration, and genes in control of active vitamin D." J Steroid Biochem Mol Biol. **240**:106497. doi:10.1016/j.jsbmb.2024.106497.

54. ^Richard CL, Farach-Carson MC, Rohe B, Nemere I, Meckling KA (2010). "Involvement of 1,25D3-MARRS (membrane associated, rapid response steroid-binding), a novel vitamin D receptor, in growth inhibition of breast cancer cells." Exp Cell Res. **316**(5):695–703. doi:10.1016/j.yexcr.2009.12.015.

55. ^Zhang M, Chen T, Lu X, et al. (2024). "G protein-coupled receptors (GPCRs): advances in structures, mechanisms and drug discovery." Sig Transduct Target Ther. **9**:88. doi:10.1038/s41392-024-01803-6.

56. ^Santos-Otte P, Leysen H, van Gastel J, Hendrickx JO, Martin B, Maudsley S (2019). "G protein-coupled receptor systems and their role in cellular senescence." Comput Struct Biotechnol J. **17**:1265–1277. doi:10.1016/j.csbj.2019.08.005.

57. a, bMansmann H (1994). "Consider Magnesium Homeostasis: III: Cytochrome P450 Enzymes and Drug Toxicity*." Pediatric Asthma, Allergy & Immunology. **8**:7–28. doi:10.1089/pai.1994.8.7.

58. ^Konstandi M, Johnson EO (2023). "Age-related modifications in CYP-dependent drug metabolism: role of stress." Front Endocrinol (Lausanne). **14**:1143835. doi:10.3389/fendo.2023.1143835.

59. ^Schutten JC, Joris PJ, Minovic I, Post A, van Beek AP, de Borst MH, Mensink RP, Bakker SJL (2021). "Long-term magnesium supplementation improves glucocorticoid metabolism: A post-hoc analysis of an intervention trial." Clin Endocrinol (Oxf). **94**:150–157. doi:10.1111/cen.14350.

60. ^Ouanes S, Popp J (2019). "High cortisol and the risk of dementia and Alzheimer's disease: A review of the literature." Front Aging Neurosci. **11**:43. doi:10.3389/fnagi.2019.00043.

61. a, b, cHan Y, Huang Y, Israr M, Li H, Zhang W (2025). "Advances in biosynthesis of 7-dehydrocholesterol through de novo cell factory strategies." Bioresour Technol. **418**:131888. doi:10.1016/j.biortech.2024.131888.

62. ^Marrs C, Lonsdale D (2021). "Hiding in plain sight: modern thiamine deficiency." Cells. **10**. doi:10.3390/cells10102595.

63. ^Giancaspero TA, Colella M, Brizio C, Difonzo G, Fiorino GM, Leone P, Brandsch R, Bonomi F, Iametti S, Barile M (2015). "Remaining challenges in cellular flavin cofactor homeostasis and flavoprotein biogenesis." Front Chem. **3**:30. doi:10.3389/fchem.2015.00030.

64. ^Chandel NS (2021). "Nucleotide Metabolism." Cold Spring Harb Perspect Biol. **13**(7):a040592. doi:10.1101/cshperspect.a040592.

65. ^Leonardi R, Jackowski S (2007). "Biosynthesis of pantothenic acid and coenzyme A." EcoSal Plus. **2**. doi:10.1128/ecosalplus.3.6.3.4.

66. ^Costeira R, Evangelista L, Wilson R, Yan X, Hellbach F, Sinke L, Christiansen C, Villicana S, Masachs OM, Tsai PC, et al. (2023). "Metabolomic biomarkers of habitual B vitamin intakes unveil novel differentially methylated positions in the human epigenome." Clin Epigenetics. **15**:166. doi:10.1186/s13148-023-01578-7.

67. ^Mikkelsen K, Trapali M, Apostolopoulos V (2024). "Role of vitamin B in healthy ageing and disease." Subcell Biochem. **107**:245–268. doi:10.1007/978-3-031-66768-8_12.

68. ^Jung M, Pfeifer GP (2015). "Aging and DNA methylation." BMC Biol. **13**:7. doi:10.1186/s12915-015-0118-4.

69. ^Yang Y, Chen Y, Xu S, Guo X, Jia G, Ping J, Shu X, Zhao T, Yuan F, Wang G, et al. (2024). "Integrating muti-omics data to identify tissue-specific DNA methylation biomarkers for cancer risk." Nat Commun. **15**:6071. doi:10.1038/s41467-024-50404-y.

70. ^Yang T, Li C, Wei Q, Cheng Y, Xiao Y, Shang H (2024). "Blood-based sex-differential DNA methylation in Alzheimer's disease." Ageing Neur Dis. **4**:19. doi:10.20517/and.2024.28.

71. ^Krolevets M, Cate VT, Prochaska JH, Schulz A, Rapp S, Tenzer S, Andrade-Navarro MA, Horvath S, Niehrs C, Wild PS (2023). "DNA methylation and cardiovascular disease in humans: a systematic review and database of known CpG methylation sites." Clin Epigenetics. **15**:56. doi:10.1186/s13148-023-01468-y.

72. ^Kaczmarczyk B, de la Calle-Fabregat C, Conde A, Duarte AC, Mena-Vazquez N, Fernandez-Nebro A, Triguero-Martinez A, Castaneda S, Dos-Santos Sobrin R, Mera-Varela A, et al. (2025). "DNA methylome biomarkers of rheumatoid arthritis-associated interstitial lung disease reflecting lung fibrosis pathways, an exploratory case-control study." Sci Rep. **15**:15123. doi:10.1038/s41598-025-99755-6.

73. ^Hong P, Waldenberger M, Pritsch M, Gilberg L, Brand I, Bruger J, Frese J, Castelletti N, Gari M, Geldmacher C, et al. (2025). "Differential DNA methylation 7 months after SARS-CoV-2 infection." Clin Epigenetics. **17**:60. doi:10.1186/s13148-025-01866-4.

74. ^Workinger JL, Doyle RP, Bortz J (2018). "Challenges in the diagnosis of magnesium status." Nutrients. **10**. doi:10.3390/nu10091202.

75. ^Pinto JT, Cooper AJ (2014). "From cholesterogenesis to steroidogenesis: role of riboflavin and flavoenzymes in the biosynthesis of vitamin D." Advances in nutrition. **5**:144–163. doi:10.3945/an.113.005181.

76. ^Fantini C, Corinaldesi C, Lenzi A, Migliaccio S, Crescioli C (2023). "Vitamin D as a shield against aging." Int J Mol Sci. **24**. doi:10.3390/ijms24054546.

77. a, bLima FDS, Santos MQD, Makiyama EN, Hoffmann C, Fock RA (2025). "The essential role of magnesium in immunity and gut health: Impacts of dietary magnesium restriction on peritoneal cells and intestinal microbiome." J Trace Elem Med Biol. **88**:127604. doi:10.1016/j.jtemb.2025.127604.

78. ^Gielecinska A, Kciuk M, Kontek R (2024). "The impact of calcium overload on cellular processes: Exploring calcioptosis and its therapeutic potential in cancer." Int J Mol Sci. **25**. doi:10.3390/ijms252413727.

79. a, bNielsen FH (2018). "Magnesium deficiency and increased inflammation: current perspectives." J Inflamm Res. **11**:25–34. doi:10.2147/JIR.S136742.

80. ^Killilea DW, Killilea AN (2022). "Mineral requirements for mitochondrial function: A connection to redox balance and cellular differentiation." Free Radic Biol Med. **182**:182–191. doi:10.1016/j.freeradbiomed.2022.02.022.

81. ^Liu M, Dudley SC Jr (2020). "Magnesium, oxidative stress, inflammation, and cardiovascular disease." Antioxidants (Basel). **9**. doi:10.3390/antiox9100907.

82. a, b, c Smith SM (2010). "Magnesium activation of the calcium-sensing receptor, a mechanism to reduce infarction and vasospasm in subarachnoid hemorrhage." Crit Care Med. **38**:2083; author reply 2084-2085. doi:10.1097/CCM.0b013e3181e8ac36.

83. a, b, c, d, e, f, g, h Dai Q, Zhu X, Manson JE, Song Y, Li X, Franke AA, Costello RB, Rosanoff A, Nian H, Fan L, et al. (2018). "Magnesium status and supplementation influence vitamin D status and metabolism: results from a randomized trial." Am J Clin Nutr. **108**:1249–1258. doi:10.1093/ajcn/nqy274.

84. ^Rodriguez-Ortiz ME, Canalejo A, Herencia C, Martinez-Moreno JM, Peralta-Ramirez A, Perez-Martinez P, Navarro-Gonzalez JF, Rodriguez M, Peter M, Gundlach K, et al. (2014). "Magnesium modulates parathyroid hormone secretion and upregulates parathyroid receptor expression at moderately low calcium concentration." Nephrol Dial Transplant. **29**:282–289. doi:10.1093/ndt/gft400.

85. ^Goyal A, Anastasopoulou C, Ngu M, Singhm S (2003). "Hypocalcemia." StatPearls.

86. ^Goltzman G (2019). "Hypercalcemia." NIH.

87. ^Sadiq NM, Anastasopoulou C, Patel G, Badireddy M (2025). "Hypercalcemia." StatPearls.

88. ^Cascella M, Vaqar S (2025). "Hypermagnesemia." StatPearls.

89. a, b, c Mansmann H (2009). "Consider magnesium homeostasis: II: Staging of magnesium deficiencies." Pediatric Asthma Allergy & Immunol. **7**. doi:10.1089/pai.1993.7.211.

90. ^Yang Z, Liu J, Shah HA, Feng J (2022). "A novel hybrid framework for metabolic pathways prediction based on the graph attention network." BMC Bioinformatics. **23**. doi:10.1186/s12859-022-04856-y.

91. ^Miwa S, Kashyap S, Chini E, von Zglinicki T (2022). "Mitochondrial dysfunction in cell senescence and aging." J Clin Invest. **132**:e158447. doi:10.1172/JCI158447.

92. ^Cauley JA, Chlebowski RT, Wactawski-Wende J, Robbins JA, Rodabough RJ, Chen Z, Johnson KC, O'Sullivan MJ, Jackson RD, Manson JE (2013). "Calcium plus vitamin D supplementation and health outcomes five years after active intervention ended: the Women's Health Initiative." J Womens Health (Larchmt). **22**:915–929. doi:10.1089/jwh.2013.4270.

93. ^Tian L, Andrews C, Yan Q, Yang JJ (2024). "Molecular regulation of calcium-sensing receptor (CaSR)-mediated signaling." Chronic Dis Transl Med. **10**:167–194. doi:10.1002/cdt3.123.

94. ^Dimke H (2024). "New insights into renal calcium-sensing receptor activation." Curr Opin Nephrol Hypertens. **33**:433–440. doi:10.1097/mnh.0000000000000998.

95. a, bFouhy LE, Mangano KM, Zhang X, Hughes BD, Tucker KL, Noel SE (2023). "Association between a calcium-to-magnesium ratio and osteoporosis among Puerto Rican adults." J Nutr. **153**:2642–2650. doi:10.1016/j.tjnut.2023.05.009.

96. a, b, c, d, eDeng X, Song Y, Manson JE, et al. (2013). "Magnesium, vitamin D status and mortality: results from US National Health and Nutrition Examination Survey (NHANES) 2001 to 2006 and NHANES III." BMC Med. **11**:187. doi:10.1186/1741-7015-11-18797.

97. ^Rosanoff A, Dai Q, Shapses SA (2016). "Essential nutrient Interactions: does low or suboptimal magnesium status interact with vitamin D and/or calcium status?" Advances in nutrition. **7**:25–43. doi:10.3945/an.115.008631.

98. ^Guerrero-Romero F, Mercado M, Rodriguez-Moran M, Ramirez-Renteria C, Martinez-Aguilar G, Marrero-Rodriguez D, Ferreira-Hermosillo A, Simental-Mendia LE, Remba-Shapiro I, Gamboa-Gomez CI, et al. (2022). "Magnesium-to-calcium ratio and mortality from COVID-19." Nutrients. **14**. doi:10.3390/nu14091686.

99. a, bCostello RB, Rosanoff A, Dai Q, Saldanha LG, Potischman NA (2021). "Perspective: Characterization of dietary supplements containing calcium and magnesium and their respective ratio-Is a rising ratio a cause for concern?" Advances in nutrition. **12**:291–297. doi:10.1093/advances/nmaa160.

100. ^Escobedo-Monge MF, Barrado E, Parodi-Roman J, Escobedo-Monge MA, Torres-Hinojal MC, Marugan-Miguelsanz JM (2022). "Magnesium status and Ca/Mg ratios in a series of children and adolescents with chronic diseases." Nutrients. **14**. doi:10.3390/nu14142941.

101. ^Zipf G, Chiappa M, Porter KS, Ostchega Y, Lewis BG, Dostal J (2013). "National health and nutrition examination survey: plan and operations, 1999-2010." Vital Health Stat 1. 1-37.

102. a, bCostello RB, Rosanoff A, Dai Q, Saldanha LG, Potischman NA (2021). "Perspective: Characterization of aietary supplements containing calcium and magnesium and their respective ratio-is a rising ratio a cause for concern?" Advances in nutrition. **12**:291–297. doi:10.1093/advances/nmaa160.

103. a, b, cDai Q, Shu XO, Deng X, Xiang YB, Li H, Yang G, Shrubsole MJ, Ji B, Cai H, Chow WH, et al. (2013). "Modifying effect of calcium/magnesium intake ratio and mortality: a population-based cohort study." BMJ Open. **3**. doi:10.1136/bmjopen-2012-002111.

104. a, bZhang H, Cao Y, Song P, Man Q, Mao D, Hu Y, Yang L (2021). "Suggested reference ranges of blood Mg and Ca level in childbearing women of China: analysis of China adult chronic disease and nutrition surveillance (2015)." Nutrients. **13**. doi:10.3390/nu13093287.

105. ^Yang J, Cao Y, Shan X, Zhang H, Feng J, Lu J, Yang L (2023). "The magnesium status and suggested reference ranges of plasma magnesium, calcium, and calcium/magnesium ratio in Chinese adults over 45 years old." Nutrients. **15**. doi:10.3390/nu15040886.

106. ^Greten FR, Grivennikov SI (2019). "Inflammation and cancer: triggers, mechanisms, and consequences." Immunity. **51**:27–41. doi:10.1016/j.immuni.2019.06.025.

107. ^Mekli K, Lophatananon A, Maharani A, Nazroo JY, Muir KR (2023). "Association between an inflammatory biomarker score and future dementia diagnosis in the population-based UK Biobank cohort of 500,000 people." PLoS One. **18**:e0288045. doi:10.1371/journal.pone.0288045.

108. ^Henein MY, Vancheri S, Longo G, Vancheri F (2022). "The role of inflammation in cardiovascular disease." Int J Mol Sci. **23**. doi:10.3390/ijms232112906.

109. ^Nedosugova LV, Markina YV, Bochkareva LA, Kuzina IA, Petunina NA, Yudina IY, Kirichenko TV (2022). "Inflammatory mechanisms of diabetes and Its vascular complications." Biomedicines. **10**. doi:10.3390/biomedicines10051168.

110. ^Santos-Moreno P, Burgos-Angulo G, Martinez-Ceballos MA, Pizano A, Echeverri D, Bautista-Nino PK, Roks AJM, Rojas-Villarraga A (2021). "Inflammaging as a link between autoimmunity and cardiovascular disease: the case of rheumatoid arthritis." RMD Open. **7**. doi:10.1136/rmdopen-2020-001470.

111. ^Han C, Shin A, Lee J, Lee J, Park JW, Oh JH, Kim J (2015). "Dietary calcium intake and the risk of colorectal cancer: a case control study." BMC Cancer. **15**:966. doi:10.1186/s12885-015-1963-9.

112. a, bDai Q, Sandler R, Barry E, Summers R, Grau M, Baron J (2012). "Calcium, magnesium, and colorectal cancer." Epidemiology. **23**:504–505. doi:10.1097/EDE.0b013e31824deb09.

113. a, b, cShah SC, Dai Q, Zhu X, Peek RM Jr, Roumie C, Shrubsole MJ (2020). "Associations between calcium and magnesium intake and the risk of incident oesophageal cancer: an analysis of the NIH-AARP Diet and Health Study prospective cohort." Br J Cancer. **122**:1857–1864. doi:10.1038/s41416-020-0818-6.

114. a, bDai Q, Motley SS, Smith JA Jr, Concepcion R, Barocas D, Byerly S, Fowke JH (2011). "Blood magnesium, and the interaction with calcium, on the risk of high-grade prostate cancer." PLoS One. **6**:e18237. doi:10.1371/journal.pone.0018237.

115. ^Doan LN, Hu C, Zhang Z, Shannon J, Bobe G, Takata Y (2023). "Dairy product consumption and lung cancer risk: A prospective analysis." Clin Nutr ESPEN. **57**:423–429. doi:10.1016/j.clnesp.2023.06.040.

116. a, bTao MH, Dai Q, Millen AE, Nie J, Edge SB, Trevisan M, Shields PG, Freudenheim JL (2016). "Associations of intakes of magnesium and calcium and survival among women with breast cancer: results from Western New York Exposures and Breast Cancer (WEB) Study." Am J Cancer Res. **6**:105–113.

117. [a, b]Gong TT, Wei YF, Li XY, Liu FH, Wen ZY, Yan S, Qin X, Gao S, Li XQ, Zhao YH, et al. (2022). "Pre-diagnostic dietary consumption of calcium and magnesium and calcium-to-magnesium intake ratio and ovarian cancer mortality: results from the ovarian cancer follow-up study (OOPS)." Eur J Nutr. **61**:3487–3497. doi:10.1007/s00394-022-02883-2.

118. [a, b]Huang WQ, Long WQ, Mo XF, Zhang NQ, Luo H, Lin FY, Huang J, Zhang CX (2019). "Direct and indirect associations between dietary magnesium intake and breast cancer risk." Sci Rep. **9**:5764. doi:10.1038/s41598-019-42282-y.

119. [a, b]Bahrami A, Mohammadzadeh M, Abdi F, Paydareh A, Khalesi S, Hejazi E (2024). "Calcium intake and the pancreatic cancer risk: A systematic review and meta-analysis of observational studies." Clin Nutr Res. **13**:284–294. doi:10.7762/cnr.2024.13.4.284.

120. [a, b, c]Dibaba D, Xun P, Yokota K, White E, He K (2015). "Magnesium intake and incidence of pancreatic cancer: the VITamins and Lifestyle study." Br J Cancer. **113**:1615–1621. doi:10.1038/bjc.2015.382.

121. [a, b]Gommers LM, Hoenderop JG, Bindels RJ, de Baaij JH (2016). "Hypomagnesemia in Type 2 diabetes: A vicious circle?" Diabetes. **65**:3–13. doi:10.2337/db15-1028.

122. [^]Masenga SK, Kabwe LS, Chakulya M, Kirabo A (2023). "Mechanisms of oxidative stress in metabolicsyndrome." Int J Mol Sci. **24**. doi:10.3390/ijms24097898.

123. [^]Dibaba DT, Xun P, Fly AD, Yokota K, He K (2014). "Dietary magnesium intake and risk of metabolic syndrome: a meta-analysis." Diabet Med. **31**:1301–1309. doi:10.1111/dme.12537.

124. [^]Moore-Schiltz L, Albert JM, Singer ME, Swain J, Nock NL (2015). "Dietary intake of calcium and magnesium and the metabolic syndrome in the National Health and Nutrition Examination (NHANES) 2001-2010 data." Br J Nutr. **114**:924–935. doi:10.1017/S0007114515002482.

125. [^]Hossain MJ, Al-Mamun M, Islam MR (2024). "Diabetes mellitus, the fastest growing global public health concern: Early detection should be focused." Health Sci Rep. **7**:e2004. doi:10.1002/hsr2.2004.

126. [^]Zyoud SH, Shakhshir M, Koni A, Abushanab AS, Shahwan M, Jairoun AA, Al Subu R, Abu Taha A, Al-Jabi SW (2022). "Mapping the global research landscape on insulin resistance: Visualization and bibliometric analysis." World J Diabetes. **13**:786–798. doi:10.4239/wjd.v13.i9.786.

127. [a, b]Grober U, Schmidt J, Kisters K (2015). "Magnesium in prevention and therapy." Nutrients. **7**:8199–8226. doi:10.3390/nu7095388.

128. [a, b]Huang JH, Tsai LC, Chang YC, Cheng FC (2014). "High or low calcium intake increases cardiovascular disease risks in older patients with type 2 diabetes." Cardiovasc Diabetol. **13**:120. doi:10.1186/s12933-014-0120-0.

129. ^Kravchenko G, Stephenson SS, Gutowska A, Klimek K, Chrzastek Z, Piglowska M, Kostka T, Soltysik BK (2024). "The concurrent association of magnesium and calcium deficiencies with cognitive function in older hospitalized adults." Nutrients. **16**. doi:10.3390/nu16213756.

130. ^Kieboom BCT, Licher S, Wolters FJ, Ikram MK, Hoorn EJ, Zietse R, Stricker BH, Ikram MA (2017). "Serum magnesium is associated with the risk of dementia." Neurology. **89**:1716–1722. doi:10.1212/WNL.0000000000004517.

131. ^Luo J, Zhang C, Zhao Q, Wu W, Liang X, Xiao Z, Mortimer JA, Borenstein AR, Dai Q, Ding D (2022). "Dietary calcium and magnesium intake and risk for incident dementia: The Shanghai Aging Study." Alzheimers Dement (N Y). **8**:e12362. doi:10.1002/trc2.12362.

132. a, bTakata Y, Yang JJ, Yu D, Smith-Warner SA, Blot WJ, White E, Robien K, Prizment A, Wu K, Sawada N, et al. (2023). "Calcium intake and lung cancer risk: A pooled analysis of 12 prospective cohort studies." J Nutr. **153**:2051–2060. doi:10.1016/j.tjnut.2023.03.011.

133. ^La Carrubba A, Veronese N, Di Bella G, Cusumano C, Di Prazza A, Ciriminna S, Ganci A, Naro L, Dominguez LJ, Barbagallo M, et al. (2023). "Prognostic value of magnesium in COVID-19: Findings from the COMEPA study." Nutrients. **15**. doi:10.3390/nu15040830.

134. a, bLi S, Chen Z, Yu H, Chang W, Zhou J, Wu G, Sun X, Sun H, Wang K (2024). "Association of magnesium deficiency scores with risk of rheumatoid arthritis and osteoarthritis in adults: a cross-sectional population-based study." Clin Rheumatol. **43**:3973–3982. doi:10.1007/s10067-024-07203-z.

135. a, bVerlato A, Laragione T, Bin S, Kim RH, Salem F, Gulko PS, Cravedi P (2024). "Revised version with tracked changes oral Magnesium reduces levels of pathogenic autoantibodies and skin disease in murine lupus." BMC Immunol. **25**:58. doi:10.1186/s12865-024-00650-y.

136. ^Bird L (2022). "Magnesium: essential for T cells." Nat Rev Immunol. **22**:144–145. doi:10.1038/s41577-022-00688-2.

137. ^Liu H, Zhang K, Xiong L (2024). "Dietary magnesium intake and rheumatoid arthritis patients' all-cause mortality: evidence from the NHANES database." J Health Popul Nutr. **43**:112. doi:10.1186/s41043-024-00597-1.

138. ^Ashique S, Kumar S, Hussain A, Mishra N, Garg A, Gowda BHJ, Farid A, Gupta G, Dua K, Taghizadeh-Hesary F (2023). "A narrative review on the role of magnesium in immune regulation, inflammation, infectious diseases, and cancer." J Health Popul Nutr. **42**:74. doi:10.1186/s41043-023-00423-0.

139. ^Razzaque M, Wimalawansa SJ (2025). "Minerals and human health: From deficiency to toxicity." Nutrients. **17**:454. doi:10.3390/nu17030454.

140. ^Rude RK, Gruber HE (2004). "Magnesium deficiency and osteoporosis: animal and human observations." J Nutr Biochem. **15**:710–716. doi:10.1016/j.jnutbio.2004.08.001.

141. a, bLu WW, Chen X, Ni JL, Zhu SL, Fei AH, Wang XS (2021). "The role of gut microbiota in the pathogenesis and treatment of acute pancreatitis: a narrative review." Ann Palliat Med. **10**:3445–3451. doi:10.21037/apm-21-429.

142. ^Wimalawansa SJ, Razzaque MS, Al-Daghri NM (2018). "Calcium and vitamin D in human health: Hype or real?" J Steroid Biochem Mol Biol. **180**:4–14. doi:10.1016/j.jsbmb.2017.12.009.

143. ^Costello R, Wallace TC, Rosanoff A (2016). "Magnesium." Advances in nutrition. **7**:199–201. doi:10.3945/an.115.008524.

144. ^Valsta LM, Tapanainen H, Kortetmaki T, Sares-Jaske L, Paalanen L, Kaartinen NE, Haario P, Kaljonen M (2022). "Disparities in nutritional adequacy of diets between different socioeconomic groups of Finnish adults." Nutrients. **14**. doi:10.3390/nu14071347.

145. ^Niessen LW, Mohan D, Akuoku JK, Mirelman AJ, Ahmed S, Koehlmoos TP, Trujillo A, Khan J, Peters DH (2018). "Tackling socioeconomic inequalities and non-communicable diseases in low-income and middle-income countries under the Sustainable Development agenda." Lancet. **391**:2036–2046. doi:10.1016/S0140-6736(18)30482-3.

146. ^Al-Daghri NM, Ansari MGA, Sabico S, Al-Saleh Y, Aljohani NJ, Alfawaz H, Alharbi M, Al-Othman AM, Alokail MS, Wimalawansa SJ (2018). "Efficacy of different modes of vitamin D supplementation strategies in Saudi adolescents." J Steroid Biochem Mol Biol. **180**:23–28. doi:10.1016/j.jsbmb.2018.02.002.

147. ^Wimalawansa SJ (2020). "Maintaining optimum health requires longer-term stable vitamin D concentrations." Int J Regenr Med. **3**:1–5. doi:10.31487/j.RGM.2020.03.03.

148. ^Wimalawansa S (2020). "Achieving population vitamin D sufficiency will markedly reduce healthcare costs." Euro J Biomed Pharma Sci. **7**:136–141.

149. ^Deshpande S, Mandlik R, Khadilkar AV, Bhawra J, Kinnunen TI (2024). "Micronutrient deficiency, dietary diversity, and sociodemographic and lifestyle determinants of dietary diversity among pregnant slum-dwelling women in Pune, India." BMC Nutr. **10**:108. doi:10.1186/s40795-024-00915-0.

150. ^Lopez-Candales A, Hernandez Burgos PM, Hernandez-Suarez DF, Harris D (2017). "Linking chronic inflammation with cardiovascular disease: From normal aging to the metabolic syndrome." J Nat Sci. **3**.

151. ^Frasca D, Blomberg BB, Paganelli R (2017). "Aging, obesity, and inflammatory age-related diseases." Front Immunol. **8**:1745. doi:10.3389/fimmu.2017.01745.

152. ^*Rosique-Esteban N, et al. (2018). "Magnesium intake, cardiometabolic risk, and mortality: current perspectives." Nutrients.* ***10****:1685.*

153. a, b, c*Cheung MM, DeLuccia R, Ramadoss RK, Aljahdali A, Volpe SL, Shewokis PA, Sukumar D (2019). "Low dietary magnesium intake alters vitamin D-parathyroid hormone relationship in adults who are overweight or obese." Nutr Res.* ***69****:82–93. doi:10.1016/j.nutres.2019.08.003.*

154. ^*Elin RJ (2010). "Assessment of magnesium status for diagnosis and therapy." Magnes Res.* ***23****:S194–198. doi:10.1684/mrh.2010.0213.*

155. ^*Rosanoff A, West C, Elin RJ, Micke O, Baniasadi S, Barbagallo M, Campbell E, Cheng FC, Costello RB, Gamboa-Gomez C, et al. (2022). "Recommendation on an updated standardization of serum magnesium reference ranges." Eur J Nutr.* ***61****:3697–3706. doi:10.1007/s00394-022-02916-w.*

156. ^*Romani AMP (2011). "Intracellular magnesium homeostasis." In Magnesium in the Central Nervous System. Vink R, Nechifor M, editors. Adelaide (AU).*

157. ^*Al Alawi AM, Majoni SW, Falhammar H (2018). "Magnesium and human health: Perspectives and research directions." Int J Endocrinol.* ***2018****:9041694. doi:10.1155/2018/9041694.*

158. ^*Wimalawansa SJ (2023). "Physiological Basis for Using Vitamin D to Improve Health." Biomedicines.* ***11****. doi:10.3390/biomedicines11061542.*

159. ^*Wimalawansa SJ (2022). "Rapidly Increasing Serum 25(OH) D Boosts the Immune System, against Infections-Sepsis and COVID-19." Nutrients.* ***14****. doi:10.3390/nu14142997.*

160. ^*Wimalawansa SJ (2015). "Obesity and type 2 disbees: Preveting complications." Journal of Diabetes, Metabolic Disorders & Control.* ***2****:47–50.*

161. ^*Wimalawansa SJ (2013). "Visceral adiposity and cardio-metabolic risks: Epidemic of Abdominal Obesity in North America." Research and Reports in Endocrine Disorders.* ***3****:17–30.*

162. ^*Abraham GE, Schwartz UD, Lubran MM (1981). "Effect of vitamin B-6 on plasma and red blood cell magnesium levels in premenopausal women." Ann Clin Lab Sci.* ***11****:333–336.*

163. ^*Vrolijk MF, Opperhuizen A, Jansen E, Hageman GJ, Bast A, Haenen G (2017). "The vitamin B6 paradox: Supplementation with high concentrations of pyridoxine leads to decreased vitamin B6 function." Toxicol In Vitro.* ***44****:206–212. doi:10.1016/j.tiv.2017.07.009.*

164. ^*Hibler EA, Zhu X, Shrubsole MJ, Hou L, Dai Q (2020). "Physical activity, dietary calcium to magnesium intake and mortality in the National Health and Examination Survey 1999-2006 cohort." Int J Cancer.* ***146****:2979–2986. doi:10.1002/ijc.32634.*

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