

Review Article

The Calcium to Magnesium Ratio: Create a Ratio that Deters Long Covid and Drives Healthy Aging

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A global shortfall in magnesium is linked to long Covid and a shortened lifespan. Its efficacy is suppressed by an elevated calcium to magnesium ratio. An intake of calcium to magnesium (weight to weight) close to 2:1 has been promulgated as the best measure of balance, but on an American type diet 3:2 might be a better target. In 1971 global authorities on magnesium (Seelig and later Durlach) recommended 6-10 mg magnesium/kg. Mean adult weight for Americans has grown from 70 kg in 1970 to 85 kg by the mid 2020s.

Absorption/resorption are primarily (80-90%) paracellular and passive via tight junctions. Transient receptor potential melastatin 6, a channel, determines intracellular entry for epithelial cells.

However, TRPM7 is the predominant determinant of mesenchymal cell (bone and soft tissue) magnesium influx. These cells represent 99% of total body magnesium and have neither TRPM6 nor tight junctions. RBCs also lack tight junctions and possess only the TRPM7 channel. They also serve as a reservoir for magnesium to maintain plasma magnesium within a tight range. This puts RBC magnesium at the nexus of plasma magnesium and intracellular magnesium.

Furthermore, metabolically active ionized magnesium can be determined by comparing the upper and lower limits of the laboratory reference ranges for serum calcium and magnesium with the reference ranges for their ionized counterparts. This enables determination of the serum ionized calcium to ionized magnesium ratio range (1.7-2.5 mmol to mmol) that is not only within normal limits but also reflects the Ca:Mg range (1.7-2.6 weight to weight) recommended for good health.

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Highlights

- Serum iCa:Mg mmol to mmol from recommended lab reference ranges (1.7-2.5) recapitulates the recommended Ca:Mg weight to weight (mg/day) intake range (1.7-2.6)
- RBC Mg should reflect the status of both serum Mg and intracellular Mg, due to the specificity of TRPM7
- The 1989 recommended 2:1 Ca:Mg intake ratio weight to weight should be updated to 3:2, given an American type diet, increasing BMI, and secondary hypoparathyroidism
- Mg dependent vitamin D and Mg immuno-modulate IFN- γ and the IFN- γ ->IDO->kynurenine->AhR->mTOR sequence with impact on long Covid and healthy aging

Introduction

Mg has long been recognized as critical to human health. Signs and symptoms of Mg deficiency (MgD) reflect those of aging ^[1]. Ca competes with Mg for the same channels that dictate transmembrane influx and the same membrane receptors that dictate physiologic function.

While the wealthy in developed countries (and cities) ingest too much calcium, the poor in the Third World ingest too little. Mg dependent vitamin D and Mg deficiency increase LC risk threefold ^[2]. Unfortunately, serum Mg is not considered representative of intracellular Mg and is not even offered on routine chemistry panels. Although RBC Mg is intracellular, the test has not been embraced as representative of Mg status within mesenchymal cells (bone and soft tissue), despite their shared transient receptor potential melastatin 7 (TRPM7) channels. RBC Mg also functions as a reservoir for serum Mg. However, given steady state conditions and homeostatic equilibrium, knowing both RBC Mg and serum Mg enables one to determine total blood Mg and to calculate Mg intake that might produce these lab values. However, the conversion is dependent on absorption, which is impacted by an elevated Ca:Mg. Pertinent interactions are complex and many are vitamin D dependent. The described calculations are only approximations and are based on upper/lower limits and on the means of recommended lab reference ranges determined from large test groups.

These points are discussed in detail and the implications for both intake and lab evaluation of Mg status are explored. Although this review is supported by the relevant human physiology, it is nonetheless an hypothetical approach. While intake recommendations for Ca and Mg are pondered and Mg continues

absent on routine lab chem panels, the escalating global epidemic of obesity, diabetes, chronic fatigue diseases, and those age related remains unaddressed.

I. Magnificent Magnesium

The hallmarks of aging include genomic instability, telomere attrition, epigenetic alterations, deregulated nutrient sensing, mitochondrial dysfunction, cellular senescence, disabled autophagy, dysbiosis, and chronic inflammation [1]. These aging hallmarks can be directly linked to shortfalls in phosphorylation and methylation [3], increased oxidative stress and mechanistic target of rapamycin (mTOR) activity, and inflammaging - all hallmarks of MgD. MgD even adversely impacts the gut microbiome [4], otherwise linked to healthy aging. Mg is required for more than 80% of all human metabolic functions [5]. These include all reactions that require ATP/GTP, ADP/GDP, cAMP/cGTP (Mg stabilizes all adenine/guanosine nucleotides), all CYP450 enzymes [6] and all G protein-coupled receptors (GPCRs, require a second messenger - cAMP). Of all FDA approved drugs 34% involve GPCR ligands [7]. Mg^{2+} itself can also function as a second messenger [8]. All redox reactions, including recycling of all anti-oxidants, and virtually all one carbon metabolic reactions (methylation) require Mg. Mg is a required cofactor for most glycolytic pathway and Krebs cycle enzymes. MgD is associated with insulin resistance involving both β cells and downstream receptors [9]. Vitamins B1,2,3,5,6 require Mg dependent phosphorylation for activation. All antioxidants that scavenge ROS by quenching their anions (reduction) must themselves be reduced for recycling. This requires FAD and NAD to facilitate electron transfer. Riboflavin (B2) and niacin (B3) must be phosphorylated to produce FAD and NAD and this requires the ATP-Mg complex. The primary function of B7 is ATP dependent carboxylation. B9 and B12 require Mg dependent methylation for activation. In short, the efficacy of all B vitamins require adequate Mg. One carbon metabolism (methylation) is vital to DNA stability and optimal function of the epigenome. Activation of vitamins A from β carotene and K from gut bacterial K2 (menaquinone) involve electron transfer; vitamin E, however, is obtained exclusively from dietary sources. Of all the fat soluble vitamins (A,D, E, and K) vitamin D is in a very special class. As demonstrated in figure 1, adequate Mg is critical to vitamin D synthesis.

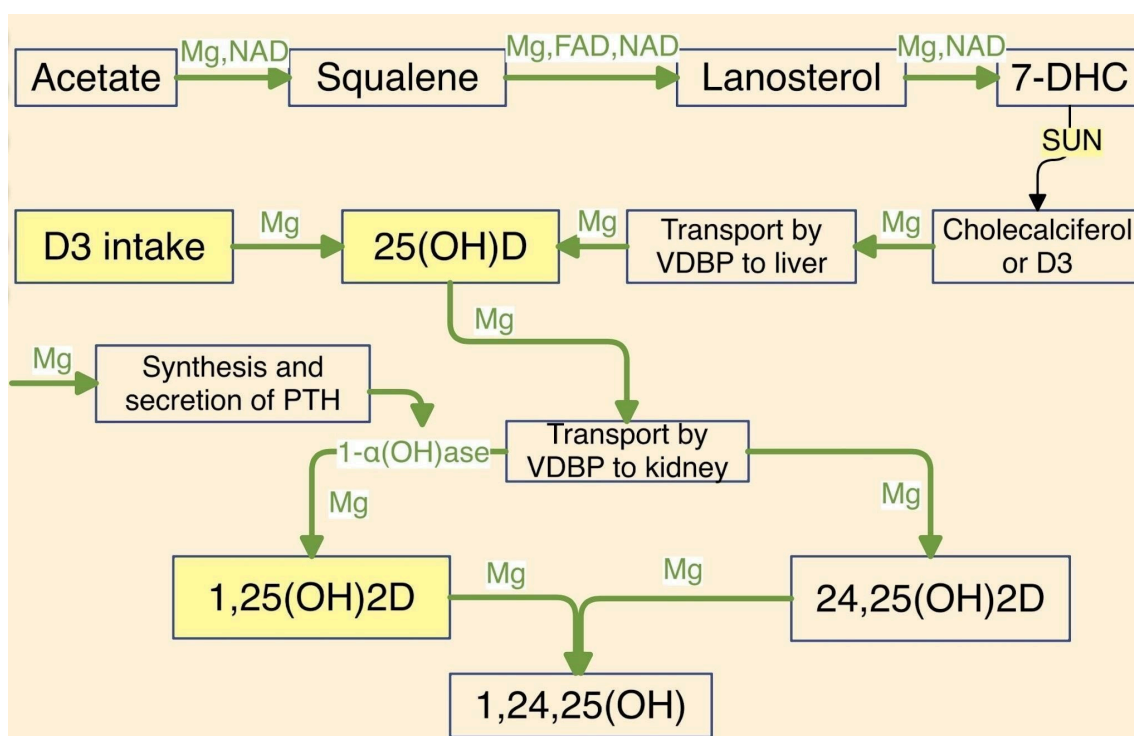


Figure 1. The intake, storage, and active forms of vitamin D are yellow. DHC is dehydrocholesterol, VDBP is vitamin D binding protein, FAD is flavin adenine dinucleotide, and NAD is nicotinamide adenine dinucleotide. Mg dependent B2 and B3 are crucial to synthesis of FAD and NAD and redox reactions to produce the required solar substrate.

The risk of long Covid is three times more likely if vitamin D and Mg deficiencies are present [2]. The majority of healthy adults worldwide are vitamin D deficient. This is especially true in females (57% v 44%) [10]. Approximately 61% of whites and 91% of blacks have less than 32 ng/mL of 25(OH)D, according to NHANES (2008) [11].

Vitamin D immunomodulates the immune response primarily via Th1 lymphocytes [12]. IFN- γ is the defining cytokine of proinflammatory Th1 cells [13]. Adequate 25(OH)D to fulfill this immune function (intracrine) appears to be much higher than 30 ng/mL, otherwise sufficient for skeletal needs (endocrine). Any shortfall in circulating 25(OH)D translates to less available within immune cells to fulfill intracrine needs. All adverse human health consequences of vitamin D deficiency are associated with a low serum 25(OH)D level (intracrine needs) and not with low 1,25(OH)₂D (endocrine needs) [14].

Furthermore, Mg-dependent vitamin D directly down regulates mTOR [15], and up regulates AMPK [16] and autophagy [17]. The mTOR/AMPK ratio over time reflects biological aging.

Direct suppression of this ratio and subsequent longevity by rapamycin has been demonstrated in yeast [18], flies, mice [19], and worms [20]. Figure 2 also displays the efficacy of Mg and vitamin D and the role of the IFN- γ ->IDO->kynurenine->AhR->mTOR sequence in aging. AhR is a promiscuous receptor, but when IDO upregulation is persistent and chronic, ill effects predominate. These include cancer, dementia, cardiovascular and autoimmune disease, diabetes, and obesity (bidirectional), all linked to altered tryptophan metabolism. IFN- γ sits at one end and mTOR at the other [21]. IFN- γ (pro inflammatory) and TGF- β (anti inflammatory) must be balanced and immunomodulators like Mg, Mg dependent vitamin D, and butyrate (biomarker for a healthy gut microbiome) enable this (see figure 2).

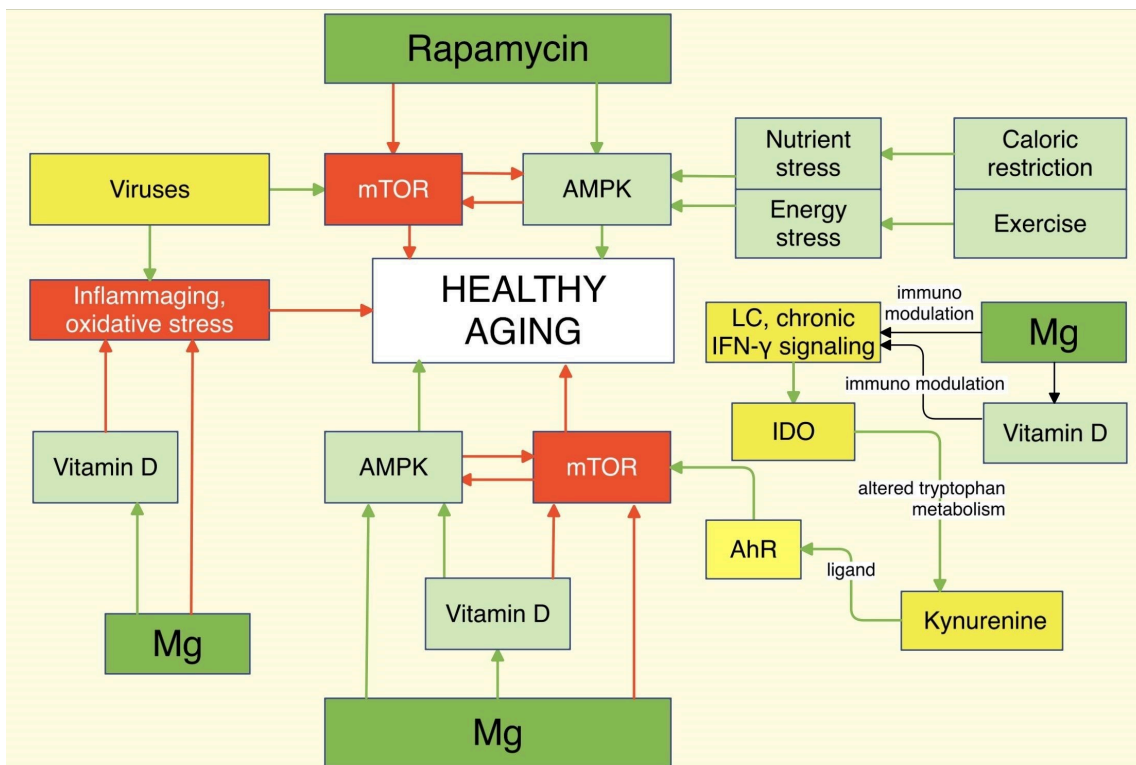


Figure 2. This figure demonstrates the biochemical pathways that link rapamycin and Mg to healthy aging. Rapamycin is top down and Mg is bottom up. Yellow demonstrates the critical sequence involving IFN- γ , IDO, kynurenine, AhR, and mTOR. IFN is interferon, IDO is indoleamine dioxygenase, AhR is aryl hydrocarbon receptor.

Aging is often linked with increasing mitochondrial dysfunction, further linked to mitochondrial calcification [22]. This may be due to the increasing incompetence of the mitochondrial permeability transition pore secondary to MgD, allowing influx of Ca [23]. Furthermore, oxidative stress and reactive oxygen species also accelerate this pore incompetence. So, not only does intracellular Mg directly inhibit opening of this mitochondrial pore, but Mg dependent FAD and NAD enable the electron transfer system required to reduce/recycle onboard antioxidants, directly combating oxidative stress. Loss of mitophagy due to downregulation of AMPK also exacerbates mitochondrial dysfunction linked with aging.

II. Ca:Mg Balance

The Ca:Mg ratio is critical, as both divalent cations compete for the same transmembrane receptor (CaSR), which determines physiologic function. CaSRs are present on parathyroid, kidney, bone, intestine, stomach, pancreas, brain, blood vessel and immune cells. The vast majority of intestinal absorption and renal reabsorption is passive and paracellular via tight junctions. Tight junctions are characteristic of epithelial and endothelial cells, but not strictly limited to them.

Mesenchymal cells, like osteocytes, fibroblasts, myocytes, have no tight junctions. RBCs also have no tight junctions. Transmembrane passage into epithelial cells is primarily via transient receptor potential melastatin (TRPM6). Transmembrane passage into mesenchymal cells (and RBCs) is primarily via TRPM7. TRPMs are called chanzymes, as they have both a channel component and a Mg dependent kinase.

An American type diet is characterized by ultraprocessed food (UPFs), simple sugars, and trans/saturated fats. All of these impact the Ca:Mg intake ratio. According to the NHANES, this weight to weight ratio, which should be no more than 2:1, has been significantly elevated for the past quarter century (see figure 3).

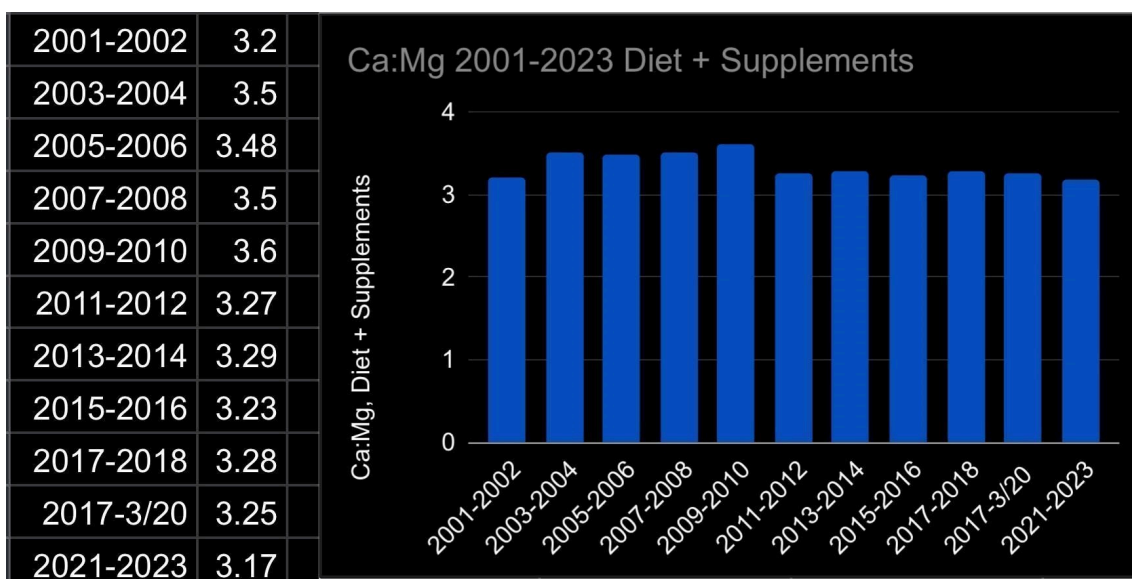


Figure 3. This figure, based on continuous NHANES data from 2000 through 8/2023, demonstrates the past 23 year history of the Ca:Mg intake ratio weight to weight in American males and females over 10 years of age.

Ionized Ca and to a lesser extent iMg dictate PTH secretion, regulating intestinal absorption and renal resorption of both elements. The American type diet induces secondary hypoparathyroidism (right side of bell in figure 4). An elevated Ca:Mg drives this, down regulating production of Mg dependent vitamin D, intestinal absorption, and renal Mg resorption. The abundant adipose tissue (elevated BMI) absorbs even more of onboard vitamin D with additional negative impact on Mg absorption/resorption. If an elevated Ca intake is not addressed first, additional Mg intake may further suppress PTH, vitamin D synthesis ^[24], and Mg absorption/resorption.

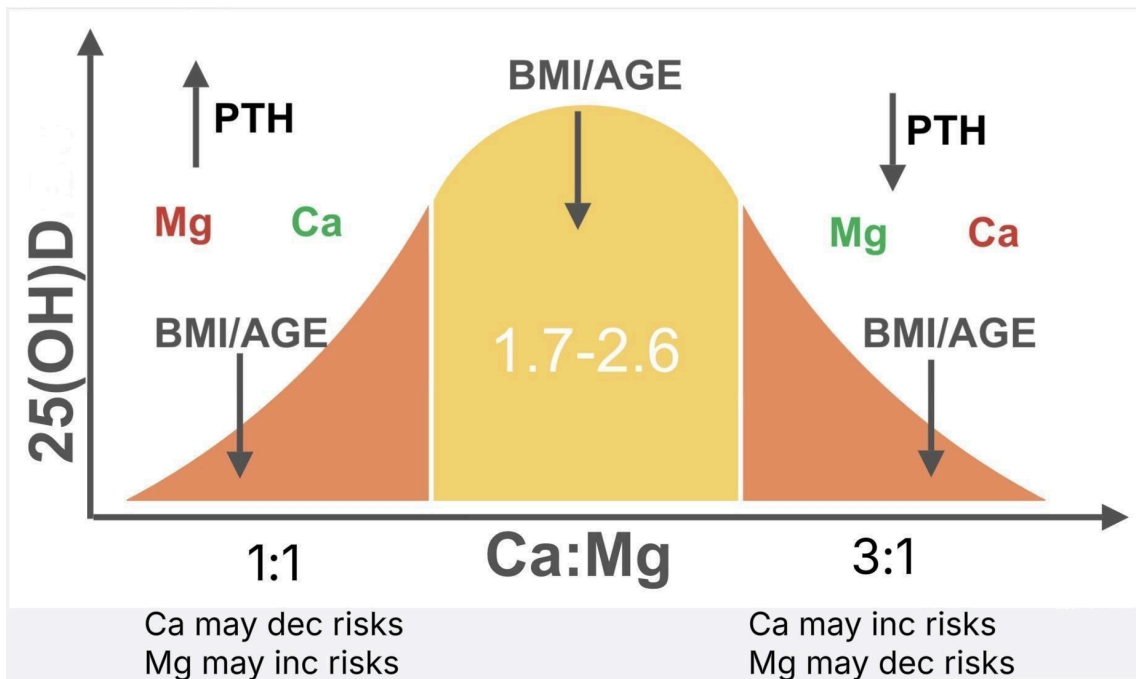


Figure 4. This figure demonstrates health risks linked to Ca:Mg intake weight to weight clinically determined (Chinese (left bell) and American (right bell))^[25]. An elevated intake of Ca suppresses PTH synthesis, 1,25(OH)₂D production, and Mg absorption/resorption, while a low intake of Ca upregulates PTH, 1,25(OH)₂D, and Mg absorption/resorption. Assuming steady state conditions and equal absorption rates, the alarming increase in BMI, UPFs, and Ca in the American type diet may have shifted the equivalence between iCa:iMg in mmol/L and Ca:Mg weight to weight from 2:1 to 3:2.

The Ca:Mg weight to weight intake range of 1.7-2.6 linked to better health ^[25], depicted in figure 4, conforms well to the iCa:iMg range derived from the reference ranges for serum Ca and Mg of 1.7-2.5, depicted in figure 5.

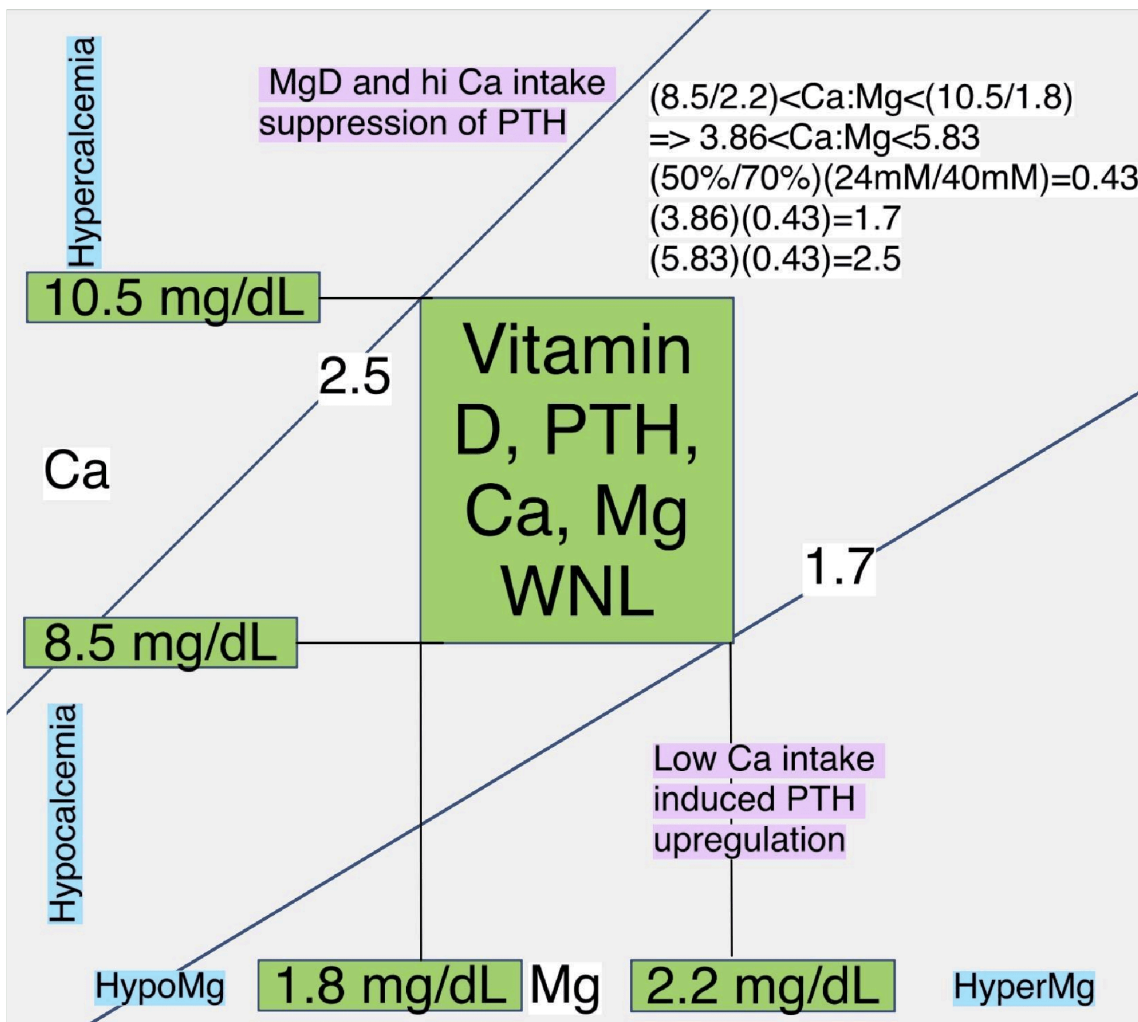


Figure 5. This figure demonstrates that the largest range for a healthy Ca:Mg is defined by minimum Ca:Mg (min Ca/max Mg) to maximum Ca:Mg (max Ca/min Mg). Converting this range from mg/dL to mmol/L and then to unbound or ionized forms yields $1.7 < \text{Ca:Mg} < 2.5$ (see upper right). Lines labeled 1.7 and 2.5 represent their slopes (change in Ca over change in Mg). Reference range limits and ionization rates in 1994 for serum Mg and Ca, 70% and 50% respectively, are used. If more recent upper reference range limits for Mg (2.28 mg/dL v 2.2 mg/dL) and Mg ionization rates (62% v 70%) are used, the endpoints balloon to 1.87-2.82, when it should be a maximum of 2.0 for those in developed countries. If the lower limit for Mg is raised to the recommended 2.07 mg/dL (0.85 mmols/L), the range becomes 1.7 to 2.18, much closer to 2.0.

The reference range limits for tMg, tCa, and iCa have changed very little over the last three decades. Consequently, iCa:tCa has remained at ~51% throughout. On the other hand, the reference range limits for iMg have changed significantly. In 1994 Burton et al (the next five authors were Nova technicians) developed the prototype ion selective electrode and determined that the reference range for iMg was

0.53–0.67 mmol/L [26]. Three decades later, using a very similar ion selective probe, Nova Biomedical's frequently used analyzer, determined a reference range of 0.45–0.60 mmol/L for iMg [27]. Using the present serum Mg range of 0.75–0.95 mmol/L, mean iMg:tMg has fallen from about 72% in 1994 [26] to about 62% in 2025 [27]. The continuing Ca driven secondary hypoparathyroidism might explain this drop in iMg over the past three decades.

According to the 2013–16 NHANES, 48% of Americans of all ages ingest less than the estimated average requirement (EAR) for Mg. Normal Mg serum values range from 0.75 to 0.95 mmol/L. Those from 0.75–0.80 are associated with a 50% greater risk for insulin resistance. Those between 0.80 and 0.85 are associated with a 20% greater risk for insulin resistance. Both American [28][29] and Chinese [30] studies have demonstrated this. Another study by Mansmann revealed the lower range of normal to be linked to pre-menstrual syndrome and migraines (normal serum Mg but low RBC Mg) [6]. Mansmann first labelled this normomagnesemic MgD. It is now called chronic latent MgD. Many less severe signs of chronic latent MgD are neuromuscular – cramps, constipation, and palpitations. Therefore, the true incidence of symptomatic MgD in Americans is probably well over 50%.

III. Intracellular Mg Versus Intravascular Mg

Ca and Mg compete for the same Ca sensing receptor (CaSR), but CaSRs are not involved in intestinal absorption or renal resorption. In fact 80–90% of the absorption/resorption of Ca and Mg by epithelial and endothelial cells is passive and paracellular via their tight junctions. This enables diffusion of Mg across intestinal epithelium and renal urothelium, into interstitial space, and to and from the intravascular space. On the other hand, transmembrane passage of Mg into epithelial cells (<10%) is predominantly via TRPM6 [31]. Transmembrane passage of Mg into endothelial cells (<10%) is predominantly via TRPM7 [32].

However, RBC membranes, like almost all mesenchymal cells, contain TRPM7 but not TRPM6 channels or tight junctions. TRPMs are the only Mg transporters for cellular influx that possess an extracellular domain (extracellular pore vestibule), essential to intracellular Mg biostasis [33][34][35].

Some cells, e.g., T cells, were thought to rely more on MAGT1 for Mg influx, but recent evidence favors TRPM7 as more significant in the regulation of intracellular magnesium biostasis [33]. TRPM7 channels control influx of Mg, inhibited by intracellular free Mg^{2+} and MgATP. Because erythrocytes, osteocytes, myocytes, and fibroblasts are exposed to the same extracellular Mg environment, employ the same

chanzyme, and maintain cell-specific intracellular Mg set points, optimal RBC Mg concentration (6.0 mg/dL) ^[36] should reflect optimal bone and soft tissue Mg (99% of total Mg). However, RBC Mg also functions as a reservoir to maintain plasma Mg within a tight range. Consequently RBC Mg sits at the nexus between plasma Mg and intracellular Mg throughout the body and should reflect both.

RBC Mg is much more dynamic (range 4.2-6.8 mg/dL) than serum Mg (range 1.8-2.28 mg/dL). Knowing both enables determination of total blood Mg (see figure 6). Assuming steady state and homeostatic equilibrium over time (input equals output), total circulating Mg should approximate absorbed intake of Mg and vice versa with steady state distribution from blood.

Specific intake and recommended blood minimums should reflect optimal intracellular efficiency.

The recommended laboratory data in figure 6 suggests that the optimal weight to weight intake ratio of Ca:Mg should approach 3:2. This figure demonstrates that:

1. If serum Mg = ~2.07 mg/dL (Rosanoff minimum)^[25] or ~21 mg/L, then, assuming hematocrit of 40%, in serum there are (21 mg/L)(3 liters) or ~62 mg Mg in plasma.
2. If RBC Mg = 6.0 mg/dL (Razzaque minimum) ^[36] or 60 mg/L, then, assuming hematocrit of 40%, in RBCs there are (60 mg/L)(2 liters) = 120 mg Mg in erythrocytes or ~182 (62+120) mg Mg total in circulation
3. If serum Ca = ~9.5 mg/dL (mean) or 95 mg/L, then, assuming hematocrit of 40%, in serum there are (95 mg/L)(3 liters) = 285 mg Ca in circulation.
4. Based on recommended minima, this approximation of a laboratory-determined Ca:Mg ratio of 285 mg Ca/182 mg Mg = 1.57 (an upper limit) is close to 3:2.

Determining the intake ratio that might support this lab derived 3:2 ratio recommendation is difficult. Mg is critical to the synthesis and secretion of parathormone. Parathormone is critical to the activation of vitamin D. Mg is critical to production of all forms of vitamin D (see figure 1).

And vitamin D is critical to absorption/resorption of Ca and Mg, critical to this determination.

Absorption of ~25% for both was arbitrarily selected because:

1. Ca absorption plateaus at about 30%, when 25(OH)D exceeds ~32 ng/mL
2. The majority of Americans have been vitamin D insufficient/deficient for the past ¼ century => 30%->25% Ca absorption
3. According to the NIH Mg fact sheet, Mg absorption normally ranges from 30-40% => mean of 35%

4. The prevalence of insulin resistance translates to less renal Mg resorption, suppressed by insulin => 35%->30% net Mg absorption
5. Increasing Mg intake, when Ca:Mg weight to weight is significantly elevated (see figure 3) may further suppress PTH/vitamin D and with it any additional Mg absorption (innocent bystander effect) => 30%->25% Mg absorption
6. Absorption rate only impacts the Ca:Mg intake calculation from iCa:iMg, if and only if the absorption rate for each divalent cation is significantly different

Consequently, the calculations (see figure 6) are subject to some interpretation, but using 25%:

1. A daily Ca intake of $285 \text{ mg}/25\% = 1140 \text{ mg Ca}$ is needed per day, not far from the RDA for Ca,
2. A daily Mg intake of $182 \text{ mg}/25\% = 728 \text{ mg Mg}$ is needed per day, well above the 320 mg Mg RDA for females or 420 mg Mg RDA for males ($1140/728=1.57$)

In 1964 Seelig recommended a daily minimum intake of 6 mg Mg/kg ^[37]. In 1971 she updated her recommendation to 6-10 mg Mg/kg ^[38]. Durlach published his recommendation for 6mg Mg/kg and an intake Ca:Mg ratio by weight “close to 2:1” in developed countries in 1989 ^[39].

Mean weight for Americans in 1964 was ~70 kg (75 for males and 65 for females) and 75 kg in 1990 (NHANES III). Presently mean weights in the US are 80 kg for females and 90 kg for males (mean of 85 kg). Using Seelig's mean of 8 mg Mg/kg and a mean Ca RDA of ~1000 mg yields:

1. A mean daily Mg intake of $(8 \text{ mg/kg} \times 85 \text{ kg}) = 680 \text{ mg Mg}$ (needed per day);
2. $\text{Ca:Mg} = 1000(\text{RDA})/680 = 1.47$ Seelig and Durlach (intake derived) versus $1140/728 = 1.57$ Rosanoff and Razzaque (lab derived), assuming 25% absorption rates for both Ca and Mg.

So, from both recommended minimum daily intakes by weight (mg Mg/kg) (Seelig and Durlach) and recommended minimum lab values (mmol/L) (Rosanoff and Razzaque) Ca:Mg intake should be about 3:2 (see figure 6). Durlach's 2:1 weight to weight intake recommendation was from 1989, when Mg ionization was ~72% ^[26] (BMI and UPF were much lower). The Razzaque and Rosanoff recommendations were published decades later. The Mg RDA of 420 mg for males may have been based on the Seelig and Durlach minimum recommendation of 6 mg Mg/kg for a 70 kg individual but never updated.

Ca and Mg intake based on recommended lab reference ranges

**Serum Ca ref range 8.5-10.5 mg/dL x 3L = 285 mg (mean) Ca in blood
=> 1140 mg Ca intake at 25% absorption**

Minimum recommended serum Mg 2.07 mg/dL x 3L = 62 mg Mg (25)

Minimum recommended RBC Mg 6.0 mg/dL x 2L = 120 mg Mg (36)

Plasma Mg + RBC Mg = 62 mg + 120 mg = 182 mg Mg in blood

=> 728 mg Mg intake at 25% absorption

Ca:Mg intake based on rec'd lab reference ranges= 1.57 (1140/728)

Ca and Mg intake based on body weight

2020 RDA Ca ~1000 mg, Mg 320-420 mg, mean Ca:Mg 2.7 (1000/370)

6-10 mg Mg/kg (Seelig recommendation 1970)

Mg 1970 560 mg (8mg/kg x 70kg mean)

Mg 2020 680 mg (8mg/kg x 85kg mean)

Ca:Mg intake based on body weight for Mg = 1.47 (1000RDA/680)

Figure 6. This figure approximates and interprets laboratory reference range data derived from “healthy” individuals. It assumes steady state homeostasis with hematocrit 40%, blood volume 5 liters, Ca ref range 8.5-10.5 mg/dL, vitamin D<30 ng/mL => Ca absorption<30% ^{[40][11]}, and Ca and Mg absorption rates of 25%. It suggests that a blood Ca:Mg (mmol/L to mmol/L) and a Ca:Mg intake (weight to weight) of about 3:2 might be the optimal target in 2026. This is based on a minimum serum Mg of 2.07 mg/dL or 0.85 mmol/L ^[25] and a minimum RBC Mg of 6 mg/dL ^[36]. Seelig’s 1971 intake recommendations ^[38] are used and support the 3:2 intake ratio.

Under steady state conditions absorption should approximate excretion. When the recommended serum minimum of 2.07 mg Mg/dL ^[25] and the recommended serum minimum of 6.0 mg RBC Mg/dL ^[36] are met, this homeostatic equilibrium suggests that either analyte might accurately reveal total body Mg status, all else being equal. RBC Mg should reflect both intracellular Mg and serum Mg. Therefore, serum Mg of at least 2.07 mg/dL implies adequate RBC and adequate intracellular mesenchymal Mg.

UPF in an American type diet has increased significantly since Durlach’s 1989 2:1 weight to weight recommendation. Less Mg is now both ingested and absorbed. There’s now relatively greater intake of Ca to compete with Mg for CaSRs and UPFs make dietary Mg intake less available. Unlike Seelig’s

recommendations, the RDAs do not adjust for weight (see figure 6). Individual serum Ca:Mg in mg/dL converted to molar concentration ($\times 24/40$) and per cent unbound ($\times 51\%/62\%$) yields iCa:iMg (see above). This is easily determined ^[41] and should be more accurate and less expensive than Mg depletion score, Ca and Mg intakes by weight, or urine Mg after Mg load.

The percent of food that has been ultraprocessed in developed countries, especially those English speaking, is close to 60% ^[42]. Not only does the milling and refining remove much of the Mg in our food but UPFs have also driven food choices from Mg rich foods/drinks to Mg poor substitutes. Soil depletion and ultra processing continue to challenge efforts to achieve Ca:Mg balance.

It is important to note that in the Third World the picture is even more complex. For example, in the Philippines the urbanite is more likely to be Mg deficient, while those in rural areas are more likely to be Ca deficient. A traditional Asian diet is more Ca depleted than Mg depleted ^[43] and vitamin D deficiency is even more prevalent in the Third World ^[10]. Other modifying factors not addressed include limited sun exposure, clothing practices, air pollution, skin pigmentation, and dietary patterns (cultural and genetic, e.g., lactose intolerance).

Durlach's 1989 2:1 weight to weight recommendation for Ca:Mg intake ^[39] was framed as a maximum for developed countries. Given the increase in BMI, UPFs, and dietary Ca since 1989, perhaps 3:2 should be the new target. The typical Asian diet lowers iCa:iMg and promotes secondary hyperparathyroidism (left side of bell in figure 4).

Mg supplementation can be complicated. Mg has laxative properties, especially Mg citrate. Exceeding bowel tolerance is counterproductive. Determination of the amount of elemental Mg ingested must be adjusted for serving size and whether each serving is reported as elemental Mg ("magnesium as") or the entire conjugate itself, where elemental Mg usually comprises only about 10% of the total. The laxative effect can be minimized by intermittent dosing, varying the forms, and combining absorption facilitators, like fructo-oligosaccharides ^[44], a prebiotic, and pyridoxal-5-phosphate, the active form of vitamin B6. Mg bioavailability is increased by the concomitant intake of its active form. Pyridoxal phosphate but not pyridoxine, appears to form a complex with Mg and may enhance absorption ^{[45][46]}. Several recent articles have challenged this beneficial effect of B6 on Mg absorption ^{[47][48]}, but both employed Magne, which is 300 mg Mg and 30 mg pyridoxine. Mg chelated with an amino acid like glycine or lysine is absorbed better than are inorganic Mg salts like Mg oxide. Glycine is the smallest

amino acid, enabling more passive, paracellular absorption (80–90% of total absorption/resorption) and passive distribution throughout the body to and from endothelial cells.

Many are resistant to the notion that MgD is linked to obesity and vice versa. Obese individuals tend to have lower Mg intake ^[49] and more Mg consuming chronic inflammation ^[50]. MgD is associated with inflammaging ^[1] and a higher Ca:Mg.

PTH and vitamin D are normally inversely related. However, synthesis and secretion of PTH require Mg and the overweight and obese require more vitamin D. Increasing Mg when Ca:Mg is elevated may further suppress PTH and decrease vitamin D ^[24].

Accordingly, the Ca:Mg imbalance must be addressed first by lowering Ca intake.

Unfortunately the efficacy of vitamin D, like that of rapamycin, may never be fully appreciated, due to the failure of randomized controlled trials or meta-analyses to adjust for an elevated Ca:Mg. Furthermore, the statistical error in the derivation of the RDA for D3 of 600–800 IUs (off by nearly an order of magnitude due to a statistical error uncovered in 2014) has remained unaddressed for a dozen years ^[51]. The highly respected Mg intake recommendations of Seelig and Durlach based on mg/kg and amplified by others, have languished for many decades, while the RDAs for Ca:Mg intake remain fixed (mean1000/mean370 = 2.7) and the BMI in developed countries and cities grows ever larger.

These recommendations are suggested for those unaware of their Ca:Mg on an American type diet (relative secondary hypoparathyroidism due to the low intake of Mg, higher intake of Ca, high BMI, high UPFs)

1. Determine RBC Mg (should be at least 6.0 mg/dL)
2. or determine serum Mg (should be at least 2.07 mg/dL or $\sim\frac{1}{3}$ of RBC Mg)
3. Determine 25(OH)D level (should be over 40 ng/mL and perhaps 50)
4. Determine serum Ca and Mg (mg/dL to mg/dL)
5. Calculate serum iCa:iMg by converting serum Ca:Mg from mg/dL ($\times 24/40$) to mmol/L and then to that ionized ($\times 50\%/62\%$) or serum Ca:Mg $\times 0.484 =$ iCa:iMg (should be less than 2:1)
6. If Ca:Mg is imbalanced consider increasing Mg intake only after decreasing Ca intake (vitamin D might drop otherwise ^[24])
7. Consider D3 supplementation and monitoring
8. Consider prebiotics and probiotics (synbiotics)
9. Consider butyrate (postbiotic, GLP-1 secretagogue)

10. Consider other supplements, if appropriate

Conclusion

In summary four primary observations are presented.

1. Serum iCa:iMg in mM determined from recommended lab reference ranges (1.7-2.5) recapitulates the recommended Ca:Mg weight to weight intake range (1.7-2.6) that minimizes health risks
2. RBC Mg should reflect not only the status of serum Mg, because it serves as a reservoir, but also the status of intracellular Mg, due to the specificity of the TRPM7 channel
3. Weight gain on an American type processed food diet suggests that the 1990 recommended 2:1 Ca:Mg intake ratio weight to weight should be updated to 3:2
4. Mg and Mg dependent vitamin D immuno-modulate IFN- γ and the IFN- γ ->IDO->kynurenine->AhR->mTOR sequence with impact on long Covid and healthy aging

So, RBC Mg sits at the nexus of intracellular Mg and plasma Mg and is representative of both. RBCs, osteocytes, myocytes, and fibroblasts, the largest pool for intracellular Mg, all possess membrane TRPM7 but not TRPM6 seen in epithelial cells. Mg-dependent TRPM7 (channel) is the primary determinant of passage into mesenchymal cells. Other Mg transporters do not possess a membrane channel gate (pore), opened by low intracellular Mg and essential to Mg biostasis [34]. When its value is optimal at 6.0 mg/dL (minimum) [36], intracellular concentrations of Mg elsewhere should also be optimal. RBC Mg should be the first to register any Mg intake shortfall [6]. An optimal RBC Mg is linked to an optimal serum Mg, because RBC Mg also functions as a reservoir for serum Mg [36].

Under steady state conditions and homeostatic equilibrium the recommended optimal intake of Ca:Mg weight to weight should fulfill the physiologic needs for intracellular Ca:Mg throughout the body. Individual serum iCa:iMg in mM, easily determined from serum Ca:Mg in mg/dL, not only reflects Ca:Mg intake weight to weight but also relative health risks, if outside the recommended range for Ca:Mg weight to weight (1.7-2.6), both in America and China [25]. Seelig's 1964 [36] and Durlach's 1989 minimum recommendation of 6 mg Mg/kg [39] and Seelig's 1971 updated recommendation of 6-10 mg Mg/kg [38] were based on physiologic needs. If Seelig's mean of 8 mg Mg/kg and present American mean weight were used (8x85=680) (see figure 6), even the average RDA for Ca of 1000 mg would yield 3:2 (1000/680) or 1.47. Durlach's 1989 recommendation Ca:Mg of 2:1 weight to weight, a minimum for developed countries [26], may be outdated.

BMI has steadily grown, vitamin D deficiency has increased globally ^[10], and the popularity and convenience of the American type UPF laden diet has assaulted Mg intake. Unfortunately 1/2 of Americans are Mg deficient and attempts to rectify this are hindered by its laxative effect, an imbalanced Ca:Mg, and lack of awareness of the actual content of elemental Mg in their supplements. The RDA for Mg has been too low for decades, despite the explicit recommendations of Seelig {m/1964,1971/} and Durlach (1989). The RDA for Mg dependent D3 is also too low, despite the revelation in 2014 of a near 10 fold statistical error by the National Academy of Sciences ^[51].

Lowering BMI and improving iCa:iMg and vitamin D status might be a worthy goal for those on an American type diet. Transitioning to a healthier one, slowly decreasing Ca intake, and slowly increasing Mg intake might gradually improve Ca:Mg weight to weight. Absorption of Ca and Mg might become more balanced, and a healthy BMI might make vitamin D more available. What has been proposed is theoretical and dependent on several reasonable physiologic assumptions. This proposal is not a structured methodical review but is based on disparate but seemingly related recent research. Nonetheless, the general approach is hypothetical and must be validated clinically.

Statements and Declarations

Funding

No specific funding was received for this work.

Potential Competing Interests

No potential competing interests to declare.

Author Contributions

P.C. was the sole author and is responsible for all aspects of the manuscript. All figures are original and created by the author.

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Declarations

Funding: No specific funding was received for this work.

Potential competing interests: No potential competing interests to declare.