

Review Article

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

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A global shortfall in magnesium (Mg) is linked to long Covid (LC) and a shortened lifespan. Its efficacy is suppressed by an elevated Ca:Mg. Calcium (Ca) competes with Mg for the same receptor/channels for both transmembrane absorption and physiologic function. While developed countries (and cities) ingest too much Ca, the Third World ingests too little. An intake of Ca:Mg (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 recommendation. In 1990 global authorities on Mg (Seelig and Durlach) recommended 6-10 mg Mg/kg. Mean adult weight for Americans has grown from 75 kg in 1990 to 85 kg by the mid 2020s. Intestinal absorption and renal resorption are primarily (80-90%) paracellular and passive via tight junctions, not otherwise present in bone or soft tissue which possess 99% of total Mg. TRPM7s dictate mesenchymal cell entry of Mg. RBCs have no tight junctions and possess only TRPM7 channels. They also serve as a reservoir for Mg to maintain plasma Mg within a tight range. This puts RBC Mg at the nexus between plasma Mg and 99% of intracellular Mg. Furthermore, metabolically active iMg can be determined by comparing the upper and lower limits of the laboratory reference ranges for serum Ca and Mg with their reference ranges for their ionized counterparts. This enables convenient determination of serum iCa:iMg that reflects the intake ratio and general health status.

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Highlights

- Weight gain on an American type processed food diet suggests that the recommended Ca:Mg intake ratio weight to weight should be updated
- Recommendation of 2:1 Ca:Mg weight to weight intake in 1990 should updated to 3:2 in 2026
- Lab iCa:iMg in mM recapitulates Ca:Mg intake weight to weight
- RBC Mg reflects the status of serum Mg, intracellular Mg, and Mg intake by weight
- Serum iCa:iMg in mM determined from recommended lab reference ranges recapitulates Ca:Mg weight to weight intake range recommendations to minimize health risks

Introduction

Mg has long been recognized as critical to human health. Signs and symptoms of Mg deficiency (MgD) reflect those of aging ^[1]. 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 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 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 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 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, all CYP450 enzymes ^[6] and all GPCRs (require second messenger – cAMP). Of all FDA approved drugs 34% involve GPCR ligands ^[7]. Mg²⁺ 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 require Mg. Mg is a required cofactor for most glycolytic pathway and Krebs cycle enzymes. MgD is associated with insulin resistance involving both beta 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 reactions. 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 beta 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.

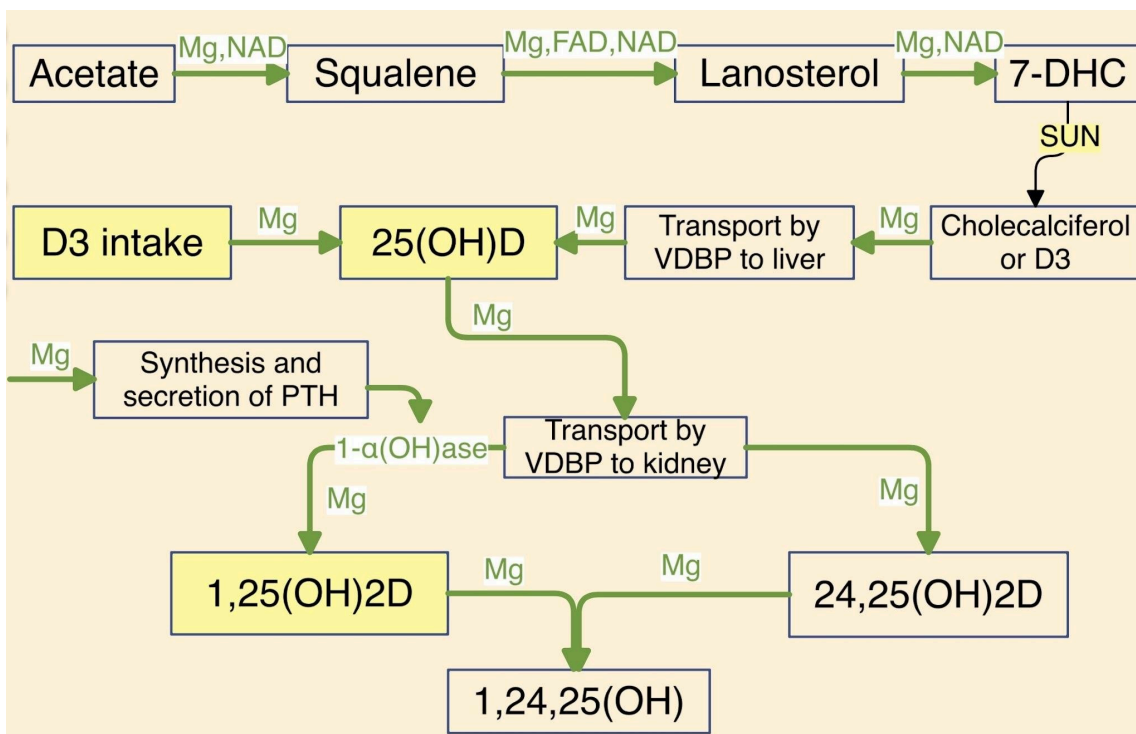


Figure 1. The intake, storage, and active forms of vitamin D are yellow. DHC is dehydrocholesterol, VDBP is vitamin D binding protein, FAD is flavin adenine dinucleotide, and NAD is nicotinamide adenine dinucleotide. Mg dependent B2 and B3 are crucial to synthesis of FAD and NAD and redox reactions to 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]. 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). IFN- γ is the defining cytokine of proinflammatory Th1 cells [13]. Any shortfall in circulating 25(OH)D translates to less available within immune cells to fulfill intracrine needs. Subsequently less immunomodulation of IFN- γ secretion may become problematic (see figure 2). All adverse human health consequences of vitamin D deficiency are associated with a low serum 25(OH)D level (intracrine) and not with low 1,25(OH)₂D (endocrine) [14].

Furthermore, Mg-dependent vitamin D down regulates mTOR [15], and up regulates AMPK [16] and autophagy [17]. The mTOR/AMPK directly reflects 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 displays this and the role of the IFN- γ , IDO, kynurenine, aryl hydrocarbon receptor, mTOR sequence in aging. Kynurenine and its metabolic products upregulate mTOR via AhR [21].

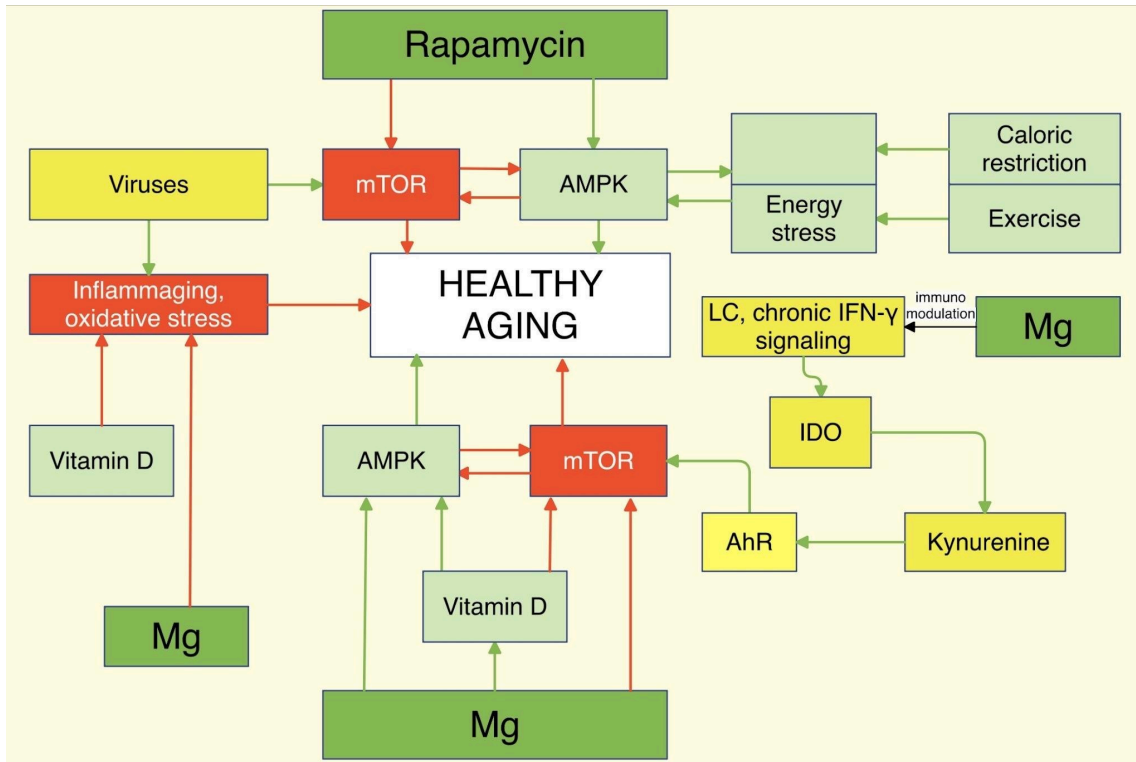


Figure 2. This figure demonstrates the biochemical pathways that link rapamycin and Mg to healthy aging. Rapamycin is top down and Mg is bottom up. It also demonstrates the sequence involving IFN- γ , IDO, kynurenine, and AhR. IFN is interferon, IDO is indoleamine dioxygenase, AhR is aryl hydrocarbon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

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 and endothelial 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).

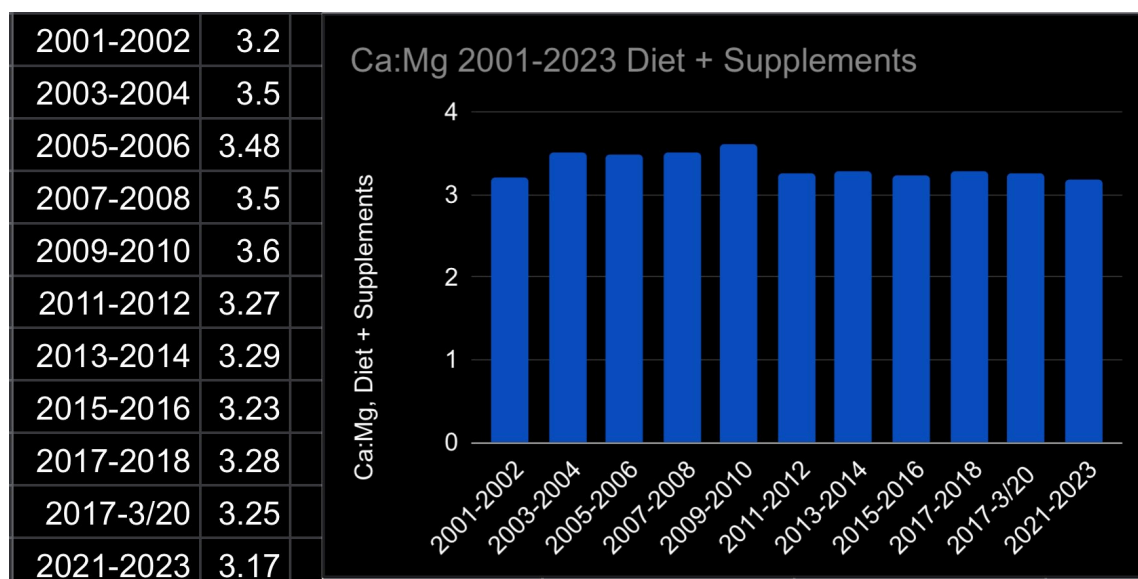


Figure 3. This figure, based on continuous NHANES data from 2000 through 8/2023, demonstrates the past 23 year history of the Ca:Mg intake ratio weight to weight in American males and females over 10 years of age.

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 renal Mg resorption and production of Mg dependent vitamin D. 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 and vitamin D synthesis ^[22].

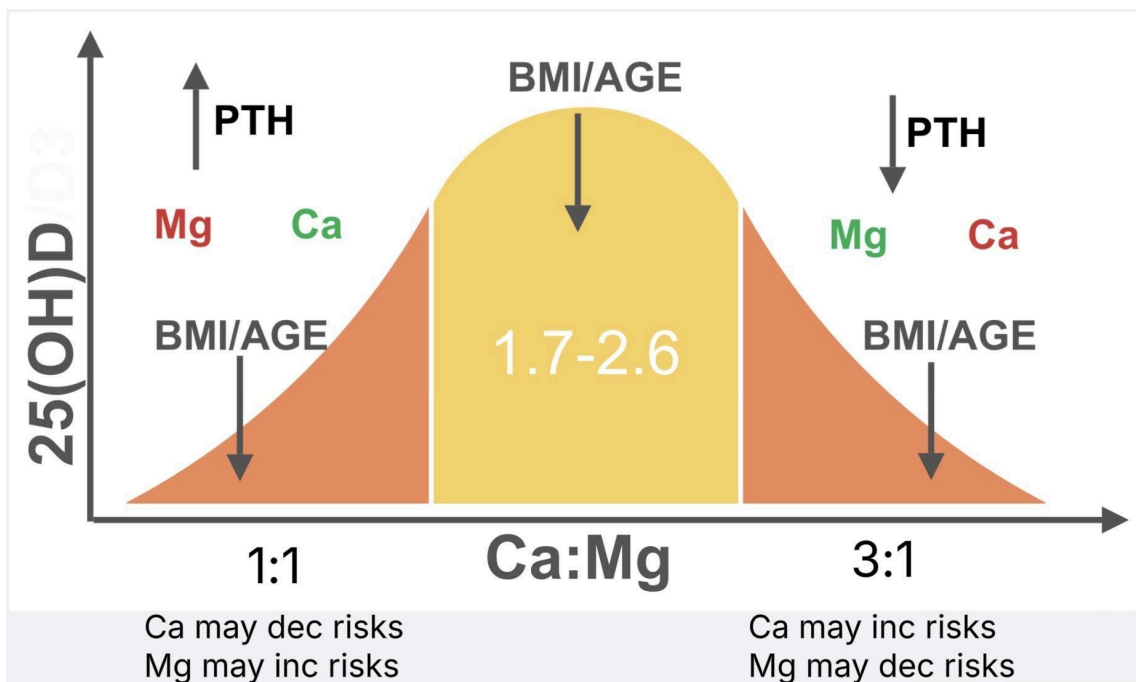


Figure 4. This figure demonstrates health risks linked to Ca:Mg intake weight to weight clinically determined (Chinese (left bell) and American (right bell))^[23]. An elevated intake of Ca suppresses PTH synthesis, $1,25(\text{OH})_2\text{D}$ production, and Mg absorption/resorption, while a low intake of Ca upregulates PTH, $1,25(\text{OH})_2\text{D}$, 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 ^[23], 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.

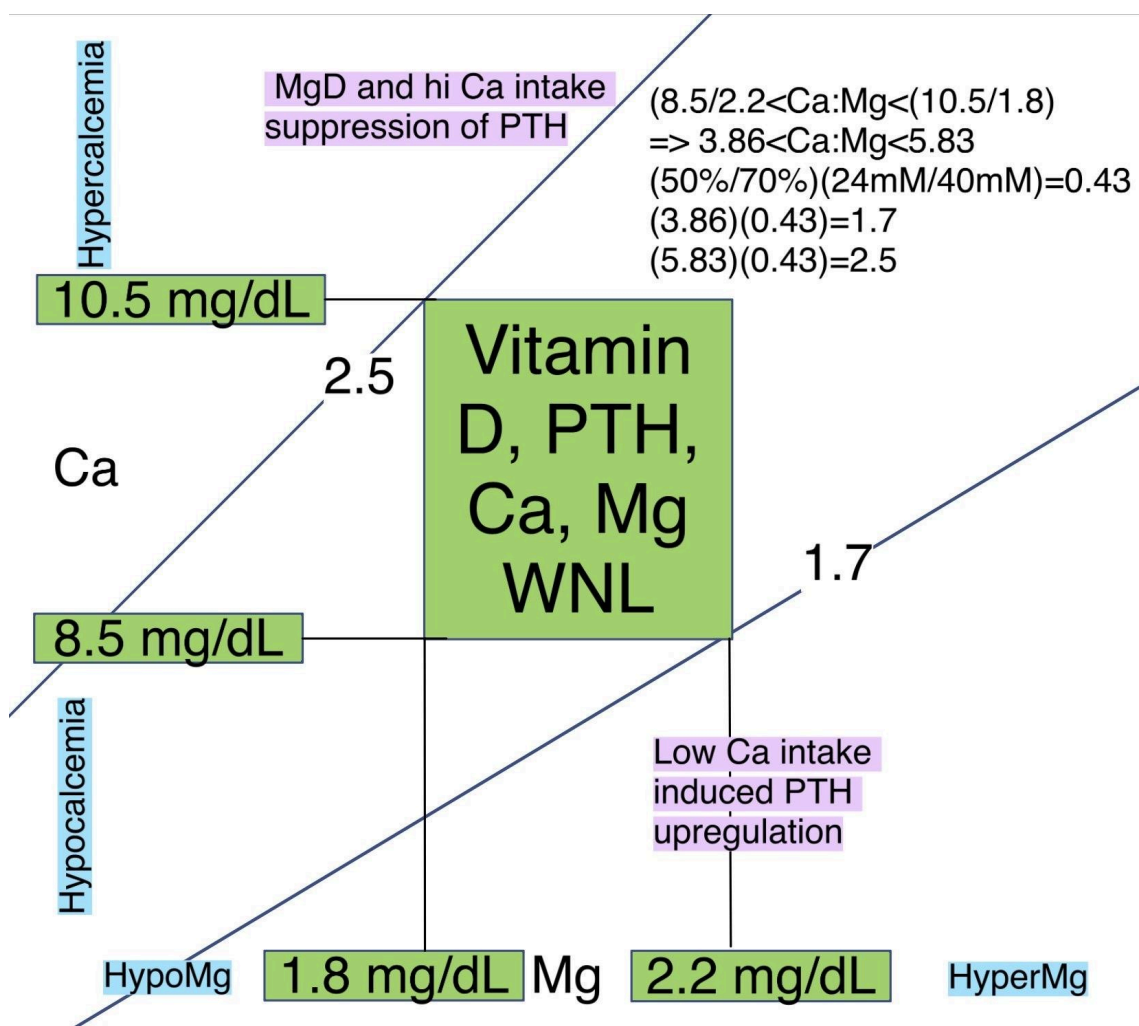


Figure 5. This figure demonstrates that the largest range for a healthy Ca:Mg is defined by minimum Ca:Mg (min Ca/max Mg) to maximum Ca:Mg (max Ca/min Mg). Converting this range from mg/dL to mmol/L and then to unbound or ionized forms yields $1.7 < \text{Ca:Mg} < 2.5$ (see upper right). Reference range limits and ionization rates for serum Mg in 1994 (70%) are used. If the ionization rate in 2023 (62%) is used, the range becomes 1.87-2.82, much worse, when it should be 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 [24]. Three decades later, using a very similar ion selective probe, Nova Biomedical's frequently used analyzer, determined 0.45-0.60 mmol/L to be the reference range for iMg [25]. Using the

present serum Mg range of 0.75-0.95 mmol/L, mean iMg:tMg has fallen from 72% in 1994 [24] to 62% in 2025 [25]. 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 mmoles Mg/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 [26][27] and Chinese [28] 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]. 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 the extracellular space, and to and from the intravascular space. On the other hand, transmembrane passage of Mg into epithelial cells (<10%) is predominantly via TRPM6 [29]. Transmembrane passage of Mg into endothelial cells (<10%) is predominantly via TRPM7 [30].

However, RBC membranes, like almost all mesenchymal cells (no tight junctions), contain TRPM7. TRPMs are the only Mg transporters for cellular influx that possess an extracellular domain (extracellular pore vestibule), which may sense extracellular Mg concentration [31][32][33]. 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 [31]. 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 channel, and maintain cell-specific intracellular Mg set points, optimal RBC Mg concentration (6.0 mg/dL) [34] should reflect optimal bone and soft tissue Mg (99% of total Mg), despite larger intracellular to extracellular Mg gradients. 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)^[23] 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) ^[34] 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. Vitamin D is critical to absorption of Ca and Mg, and Mg is critical to production of vitamin D. Most significantly absorption of both are critical to this determination. Absorption of ~25% was arbitrarily selected because:

1. Ca absorption plateaus at about 30%, when 25(OH)D exceeds ~32 ng/mL
2. Over time mean 25(OH)D levels have consistently fallen short of 30 ng/mL (see figure 3)
3. Mg absorption (less D sensitive) in general ranges from 30-40% or mean of 35%
4. Increased Ca:Mg suppresses Mg absorption, 35%->30%
5. Over time Mg intake has steadily decreased, compromising the amount absorbed, 30%->25%

Consequently, the calculations are subject to interpretation, but using 25%:

1. A daily Ca intake of $285 \text{ mg} / 25\% = \sim 1140 \text{ mg Ca}$ is needed yper day,

2. A daily Mg intake of $182 \text{ mg}/25\% = \sim 730 \text{ mg Mg}$ is needed per day, well above the 320 mg Mg RDA for females or 410 mg Mg RDA for males ($\text{Ca:Mg}, 1140/730=1.56$)

In 1964 Seelig recommended a daily minimum intake of 6 mg Mg/kg ^[35]. In 1971 she updated her recommendation to 6-10 mg Mg/kg ^[36]. Durlach published his recommendation of a “close to 2:1” intake ratio for Ca:Mg in developed countries in 1989 ^[37]. Mean weight for Americans in 1964 was $\sim 70 \text{ kg}$ (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 yields:

1. A mean daily Mg intake of $(8 \text{ mg/kg} \times 85 \text{ kg}) = \sim 730 \text{ mg Mg}$ (needed per day);
2. Absorption of 25% of 730 mg = 182 mg intake for the average American (see figure 6);
3. $\text{Ca:Mg} = 1140/730 = 1.56$ Seelig and Durlach (intake derived) versus $285/182 = 1.57$ Rosanoff and Razzaque (lab derived), assuming 25% absorption rates for both Ca and Mg.

So, from both recommended minimum 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 $\sim 72\%$ ^[24] (BMI and UPF was much lower). The Razzaque and Rosanoff recommendations were published decades later. The Mg RDA has never been updated. Seelig’s 1964 minimum $6 \text{ mg Mg/kg} \times 70 \text{ kg} = 420$ may have contributed to the Mg RDA of 420 mg per day. The seemingly excessive RDA for Ca may be based on lower absorption rates possibly due to the widespread shortfall in vitamin D.

A	B	C	D	E	F	G	H	I	J
	B=D/C			E=30xF	Serum Mg	Serum Ca	H=20xI	RBC Mg	J=E+H
		Absorp'n	absorbed	plasma	mg/dL	mg/dL	RBCs	mg/dL	Total
		25(OH)D	Amount	mg in 3L	(1.8-2.28)	(8.5-10.5)	mg in 2L	(4.2-6.8)	in
	RDA Ca 1000-1100, Mg 320-420, mean Ca:Mg 2.84							mg/dL	blood
Minimum recommended serum Mg and RBC Mg 2026									
Ca	1140 mg/day	25% <=	285 mg	285 mg	<= 9.5 (mean)				285 mg
Mg	728 mg/day	25% <=	182 mg	62.1 mg	<=2.07(min)		120 mg <= 6.0 (min)	182 mg	
Ca:Mg	1.57 (~3:2)(max)(2026)				Rosanoff et al.			Razzaque et al.	
Ca	1140	25% <=	285	285	<= 9.5 (mean)				285 mg
6-10 mg Mg/kg (Seelig recommendation 1971)									
Mg 1990	600 (8x75 US mean wt)	x 25% =>	150 v 182	<= 62.1	<=2.07 (min)		120	<= 6.0 (min)	182 mg
Mg 2026	680 (8x85 US mean wt)	x 25% =>	170 v 182	<= 62.1	<=2.07 (min)		120	<= 6.0 (min)	182 mg
Ca:Mg	rec'd intake 1140/600=1.9 (1990) v actual intake >3.0 (after 2000)								

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, Mg ref range 1.8-2.28 mg/dL (0.75-0.95 mmol/L), vitamin D<30 ng/mL => Ca absorption<30% ^{[38][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 ^[23] and a minimum RBC Mg of 6 mg/dL ^[34]. Seelig’s 1971 intake recommendations ^[36] 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 ^[23] and the recommended serum minimum of 6.0 mg RBC Mg/dL ^[34] are met, this homeostatic equilibrium suggests that either analyte might accurately reveal total body Mg status, all else being equal. RBC Mg reflects both intracellular Mg and serum Mg. Therefore, serum Mg of at least 2.04 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 ingested and absorbed. There’s now greater intake of Ca to compete with Mg for CaSRs and UPFs make dietary Mg intake less available. Unlike Seelig’s and Durlach’s recommendations, the RDAs do not adjust for weight (see figure 6). Individual serum Ca:Mg in mg/dL converted to molar concentration (x 24/40) and per cent unbound (x 51%/62%) yields iCa:iMg (see above). This is easily determined ^[39] 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% ^[40]. 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 ^[41] 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 ^[37] was framed as a maximum for developed countries. Given the increase in BMI, UFs, 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 ^[42], 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 ^{[43][44]}. Several recent articles have challenged this beneficial effect of B6 on Mg absorption ^{[45][46]}, 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 ^[47] and more Mg consuming chronic inflammation ^[48]. 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^[22].

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

Unfortunately the efficacy of RAP, like that of vitamin D, 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^[49]. 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 (mean 1050/mean 370 = 2.84), while the BMI in developed countries and cities grows ever larger.

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

1. Determine RBC Mg (should be at least 6.0 mg/dL)
2. or determine serum Mg (should be at least 2.04 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^[22])
7. Consider D3 supplementation and monitoring
8. Consider prebiotics and probiotics (synbiotics)
9. Consider butyrate (postbiotic)
10. Consider other supplements, if appropriate

Conclusion

RBC Mg sits at the nexus between intracellular Mg and serum Mg and is representative of both. RBCs, osteocytes, myocytes, and fibroblasts, the largest pool for intracellular soft tissue Mg, all possess membrane TRPM7. Mg dependent TRPM7 (chanzyme) is the primary determinant of passage into

mesenchymal cells. Other Mg transporters do not possess an extracellular pore vestibule to detect extracellular Mg. ATP-Mg can enable transmembrane passage against a 20:1 gradient. RBC Mg gradient is only ~3:1 (6.0/2.07). When its value is optimal at 6.0 mg/dL (minimum) [34], intracellular concentrations of Mg elsewhere should also be optimal. RBC Mg should be the first to register any Mg intake shortfall [12]. An optimal RBC Mg is linked to an optimal serum Mg, because RBC Mg also functions as a reservoir for serum Mg [34].

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. Serum iCa:iMg, easily determined from serum Ca:Mg, not only reflects Ca:Mg intake weight to weight but also the Ca:Mg weight to weight clinically correlated with disease, both in America and China [23].

Seelig's 1964 [34] and Durlach's 1989 minimum recommendation of 6 mg Mg/kg [37] and Seelig's 1971 updated recommendation of 6-10 mg Mg/kg [36] were based on physiologic needs. If Seelig's mean of 8 mg Mg/kg and the American mean weight were used ($8 \times 85 = 680$) (see figure 6), even the average RDA for Ca of 1050 mg would yield 3:2 (1050/680) or 1.54. Durlach's 1989 recommendation Ca:Mg of 2:1 weight to weight, a minimum for developed countries [24], 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 of their near 10 fold statistical error in 2014 [49].

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.

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