

Review Article

Magnesium and Rapamycin in Long Covid and Longevity: Mechanistic (Part A) and Therapeutic (Part B) Proposals

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A global shortfall in magnesium (Mg) is linked to long Covid and a shortened lifespan. The mTOR (mammalian or mechanistic target of rapamycin)/AMPK (AMP-activated protein kinase) ratio increases with age and these kinases are inversely related. A balanced mTOR:AMPK ratio, promoted by rapamycin (RAP), is linked to healthy aging. mTOR is anabolic and AMPK is catabolic. Mg and RAP are synergistic collaborators in suppressing this ratio. Mg is bottom up, while RAP is top down. Any inhibition of mTOR by RAP may upregulate kinases that activate mTOR via alternate pathways. Whether this occurs with low-dose, intermittent RAP is unknown. But Mg is perfectly placed to block this.

Efficacies may merge at the IFN- γ -> indoleamine dioxygenase (IDO) -> kynurenine -> aryl hydrocarbon receptor (AhR) sequence. Persistence of any intracellular pathogen, e.g., SARS CoV2, can prolong IFN- γ activation of IDO, e.g., LC. IDO metabolizes tryptophan (T) and upregulates the kynurenine (K) pathway. Elevated K/T and mTOR/AMPK are linked to cancer, autoimmune disease, cardiovascular disease, dementia, diabetes, and obesity. Furthermore, Mg-dependent vitamin D immunomodulates IFN- γ .

Calcium (Ca) competes with Mg for the same transcellular receptor (calcium sensing receptor) for physiologic balance. However, absorption, resorption, and diffusion to and from the vascular and extracellular spaces is predominantly paracellular through tight junctions. RBC Mg sits at the nexus between intracellular Mg and serum Mg. RBCs, like all mesenchymal cells, have no tight junctions but do have cell membrane TRPM7 channels (chanzymes) that sense extracellular Mg and respond appropriately. They also serve as a reservoir for Mg to maintain serum Mg within tight limits. This enables convenient determination of serum Ca:Mg that reflects their intake ratio, their intracellular ratios, and general health status, when converted from mg/dL to mmoles/L of iMg.

While developed countries (and cities) ingest too much Ca, the Third World ingests too little.

Unfortunately the maximum recommended Ca:Mg intake (weight to weight) of 2:1 was based on total body weight {m/1964-1989/}, but has encountered an American lifestyle. Mean American adult weight has grown from 70 in the mid 60s to 85 in the 2020s. Soil depletion and the increase in dietary UPFs have conspired to further compromise Mg intake. The ionized component of serum Mg has dropped from about 72% to about 62% over the last several decades. This component can be easily determined by comparing the reference range limits for serum Mg with their ionized counterparts. The discussion is technical, and in the interest of clarity the article is partitioned into Part A (proposed mechanism) and Part B (proposed therapeutics).

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Highlights

Part A

- An elevated mTOR/AMPK may represent the most common endpoint shared by human disease and aging
- The IFN- γ :IDO:kynurenine:aryl hydrocarbon receptor sequence may represent the predominant final common pathway to this endpoint
- The Ca:Mg, Kynurenine/Tryptophan, altered tryptophan metabolism, and altered NAD⁺ metabolism drive this sequence
- RAP suppresses mTOR/AMPK, while Mg downregulates this sequence

Part B

- Weight gain on an American type processed food diet over the past half century 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 1964 and 1989 should updated to 3:2 in 2026
- RBC Mg should reflect the status of serum Mg, intracellular Mg, and Mg intake by weight
- If Ca:Mg is balanced, the benefits of intermittent, low dose RAP might outweigh possible side effects, if any

PART A: Proposed Mechanism

Introduction

Mg has long been recognized as critical to human health. Signs and symptoms of Mg deficiency (MgD) reflect those of aging ^[1]. Furthermore, adequate Mg may offer health benefits that complement those of rapamycin (RAP) via many disparate pathways outside those directly involving mTOR (mechanistic or mammalian target of rapamycin). One of these may be RAP induced overactivation of the inflammatory kinase MAPK, linked to inflammaging, and up regulation of mTOR by an RAP independent pathway ^[2]. This may detract from RAP efficacy in those with MgD.

Because some human studies of RAP demonstrate limited evidence of tangible clinical benefit, some recommend against its use as an anti-aging drug, except under strict medical supervision. Unfortunately, the alternative to the reversible (and avoidable) side effects of RAP are the irreversible (and inevitable) effects of aging. For the vast majority of humans this includes cancer, stroke, dementia, and an early demise. Most potential adverse effects of RAP are minor. However, potential major adverse effects, e.g., significant immunosuppression, are unlikely, given the low, intermittent dosage regimen and given proven longevity benefits in yeast ^[3], flies, mice ^[4], and worms ^[5]. Indeed some balanced immunosuppression, aside that for organ transplants, may be beneficial ^[6]. Alzheimer's disease has no cure, but RAP has shown some benefit ^[7]. Although reports of efficacy for long Covid are anecdotal, SARS CoV2 is linked with overactivation of mTOR ^[8] and is one of many intracellular viral pathogens that do this ^[8].

Although this review is supported by the relevant human physiology, it is nonetheless a hypothetical approach. While time consuming randomized controlled trials are underway, the global epidemic of obesity, diabetes, chronic fatigue diseases, and those age related remains unaddressed.

I. mTOR:AMPK in LC/Longevity

mTOR promotes cell growth, protein synthesis, and anabolism when nutrients are abundant. AMPK, activated during low energy states (high AMP/ATP ratio) and low nutrient states, promotes catabolism. mTOR suppresses AMPK indirectly when energy and nutrients are plentiful. AMPK suppresses mTOR when energy and nutrients are low.

However, outside these functions other conditions can overactivate mTOR with deleterious consequences. These include manipulation of host-cell mTOR pathways by viruses to support viral replication [8][9], oxidative stress [10], neuronal damage due to prolonged glutamatergic NMDA receptor activity and associated excitotoxicity [11], and inflammatory pathways involving TNF- α [12].

An increased mTOR/AMPK is a biomarker for autoimmunity, cancer, obesity, aging [13], and dementia [14][15]. Overactivation of mTOR is also linked to T2DM [16], hypertension, LC [17], chronic fatigue syndrome [18], and post acute infection syndrome [8]. Respiratory syncytial virus and coronaviruses up-regulate mTOR [19], as does the influenza virus [20], hepatitis B virus [21], Epstein-Barr virus [22], Zika virus [23], cytomegalovirus [24], herpes simplex [25], human immune deficiency virus [26], and probably Lyme disease [27].

Mild MgD in immune cells tends to increase mTOR:AMPK, while more significant MgD should decrease this ratio [28]. Energy and nutrient stress upregulate AMPK. However, the anti-inflammatory immune response of IFN- γ can oppose and ironically upregulate mTOR instead. Females generally produce more IFN- γ than males [29], resulting in elevation of mTOR:AMPK. This can be aggravated by any MgD induced increase in oxidative stress and inflammaging. Reproductive age females are particularly prone to MgD (see figure 1)

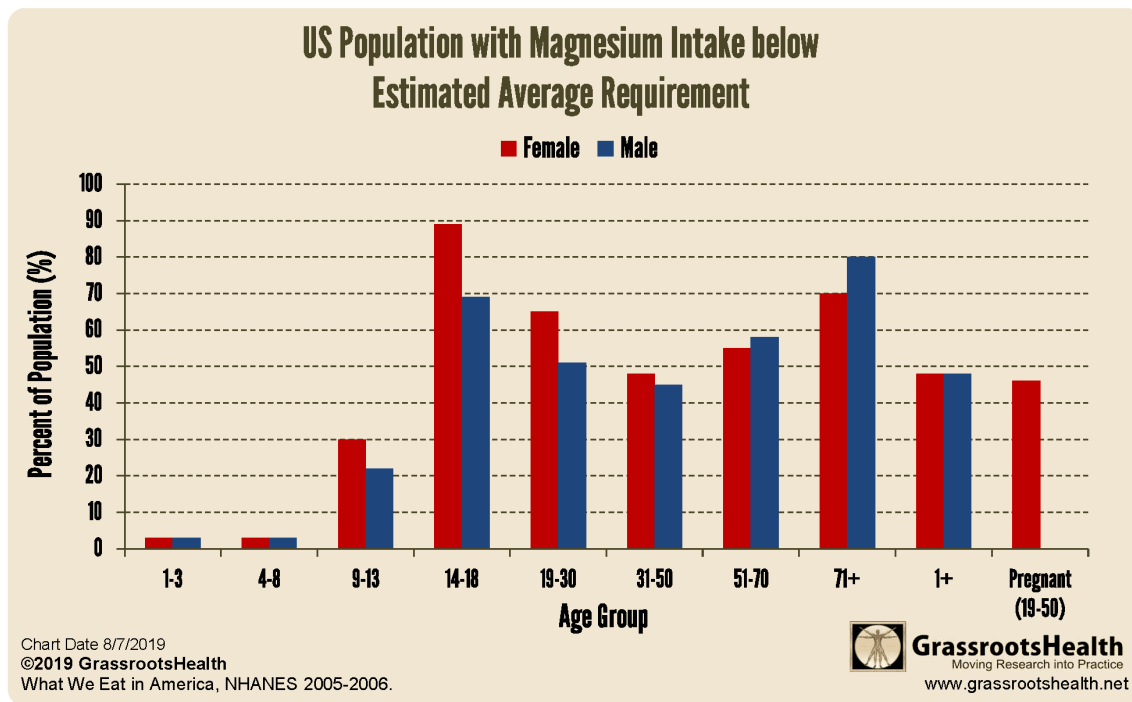


Figure 1. This figure from NHANES data demonstrates the low intake for Mg in females 9 to 50 years of age.

Premenopausal females may be more prone to long Covid and autoimmune disease, characterized by elevated mTOR [8]. Long haulers have difficulty absorbing seven of the nine essential amino acids. This is due to the dysfunction of ACE2 on enterocytes secondary to persistent SARS CoV2. These seven neutral amino acids primarily depend on BOAT1, their designated amino acid transporter [30][31]. BOAT1 requires ACE2, as a chaperone for tryptophan, methionine, and branched chain amino acid absorption [32][33]. This impact of ACE2 depletion on nutrient stress should increase AMPK and suppress mTOR/AMPK

However, many viral pathogens are known to cause fatigue and cognitive decline, but SARS CoV2 seems most adept. Increased IFN- γ , IDO, K/T, and AhR activity seem to be common features. Perhaps ACE2, uniquely targeted by SARS Cov2, plays a role in its inordinate impact. The loss of ACE2 increases angiotensin II signaling, oxidative stress, inflammation, and endothelial/mitochondrial dysfunction. These all increase mTOR and appear to overwhelm any effect of significant SARS CoV2 induced nutrient stress on AMPK.

II. RAP in LC/Longevity

RAP induces healthy aging via inhibition of mTOR [34].

Intermittent chronic feeding of low-dose RAP increases autophagy ^[35]. Such doses do not compromise muscle mitochondrial content or endurance ^[36]. RAP has been touted for Covid-19 ^[37] and anecdotally for long Covid. Its efficacy for chronic fatigue diseases has recently been reported ^[38].

Intracellular RAP allosterically inhibits mTORC1, but many of the subsequently generated interactions and pathways are unknown or incompletely understood. Although RAP and rapalogs have been predominantly beneficial as longevity and anticancer agents, recent research shows that mutations, cross-talk pathways, and negative feedback loops can compromise their benefits. MAPK may be activated as a consequence of mTORC1 inhibition at high doses in a mouse model ^[39]. MAPK may activate mTORC1 via other pathways and bypass RAP inhibition of mTORC1 ^{[40][41][42]}. Dysfunctional MAPK/ERK signaling is tumorigenic and its suppression is touted in cancer therapy ^[43]. The extent to which RAP independent activation of mTORC1 occurs, if at all, via MAPK/ERK signaling during low-dose intermittent RAP therapy in humans is unknown. However, Mg can indirectly immunomodulate MAPK/ERK signaling by suppressing oxidative stress, NF-κB signaling, inflammatory cytokines, and excess Ca signaling. These latter can both activate MAPK/ERK or be upregulated by the activation of MAPK/ERK, i.e., Mg has upstream and downstream immunomodulating impact on MAPK/ERK and mTORC1 activation.

In addition to its down regulation of mTOR and upregulation of AMPK, RAP has antifungal properties ^[44] and is toxic to *Candida albicans* ^[45]. *Candida* overgrowth is linked to LC ^[46]. This suggests an under-appreciated pathway for the efficacy of RAP in long Covid.

Intestinal tryptophan produced by microbiota is also antifungal and helps maintain the balance between bacteria and fungi ^[47]. So, RAP can directly suppress *Candida albicans*, linked to long Covid ^[48], and with it production of an IDO like enzyme produced by *Candida* ^[47], preserving tryptophan, a known biomarker for longevity ^[49].

III. Mg, Vitamin D, Benefiting Longevity Linked Molecules

The hallmarks of MgD induced 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 ^[50], increased oxidative stress and mTOR activity, and inflammaging – all hallmarks of MgD. MgD even adversely impacts the gut microbiome ^[51].

Mg is required for more than 80% of all human metabolic functions ^[52]. These include all reactions that require ATP/GTP, ADP/GDP, cAMP/cGTP, all CYP450 enzymes ^[53] and all GPCRs (require second messenger - cAMP). Of all FDA approved drugs 34% involve GPCR ligands ^[54]. Mg²⁺ itself can also function as a second messenger ^[55]. All redox reactions, including all anti-oxidant recycling, 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 ^[56]. 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. 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. So, activation of almost all fat and water soluble vitamins is Mg dependent.

Mg-dependent vitamin D down regulates mTOR ^[57], and up regulates AMPK ^[58] and autophagy ^[59]. All forms of vitamin D (D3, 25(OH)D, and 1,25(OH)₂D) require Mg (see figure 2).

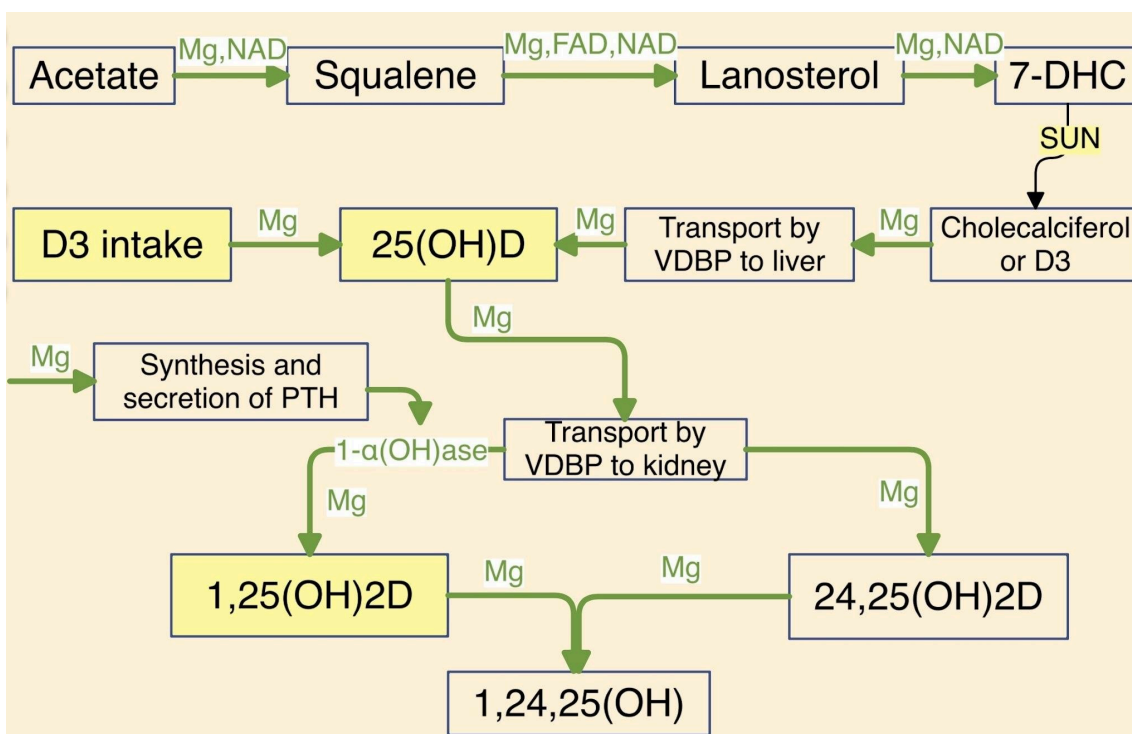


Figure 2. The intake, storage, and active forms of vitamin D are yellow. DHC is dehydrocholesterol, VDBP is vitamin D binding protein, FAD is flavin adenine dinucleotide, and NAD is nicotinamide adenine dinucleotide. Mg dependent B2 and B3 are crucial to synthesis of FAD and NAD and redox reactions to produce the required solar substrate.

Some tumor cells express VDRs that can be modulated by vitamin D, improving prognosis. These include colorectal cancer, prostate cancer, breast cancer, acute myeloid leukemia, and melanoma [60].

Mg dependent NAD⁺ deserves special attention (see figure 3). NAD⁺ levels decrease as we age [61], although NAD⁺ metabolites simultaneously increase. As we age, mitochondria become less efficient, inducing more oxidative stress. Inflammaging consumes more NAD⁺ and nicotinamide (NAM) is a biomarker for greater NAD⁺ turnover (see figure 3). One study on this involving several dozen men and women partitioned into three groups by age (20-40,40-60,60+) revealed no statistically significant changes across age in serum levels of nicotinic acid (NA), nicotinamide mononucleotide (NMN), and nicotinic acid mononucleotide (NAMN). These three metabolites that appear to be constant as we age are governed by enzymes that require Mg as a cofactor. On the other hand, NAM increases (turnover), while NAAD, NAD⁺, and NADP⁺ decrease with aging. These latter three are governed by ATP-Mg, which is much more susceptible to Mg deficiency than that involving its action as a cofactor.

Figure 3 demonstrates the three NAD⁺ synthetic pathways and the relationships between these metabolites [62][63][64].

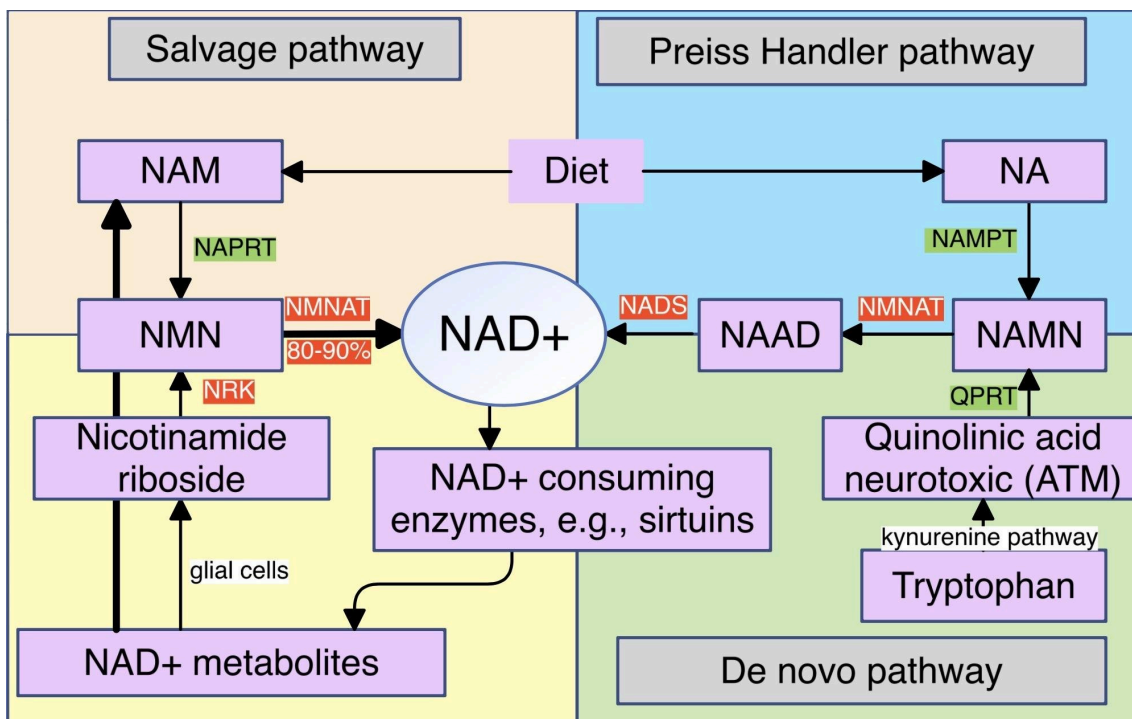


Figure 3. Figure demonstrates the synthetic and degradatory pathways of NAD⁺. Green enzymes indicate Mg cofactor required. Red enzymes indicate ATP-Mg required. Glial cells are dependent upon the nicotinamide riboside kinase (NRK) pathway to quell inflammation and boost mitochondrial function [65]. NAD is nicotinamide dinucleotide, NAM is nicotinamide, NA is nicotinic acid, NMN is nicotinamide mononucleotide, NAAD is nicotinic acid adenine dinucleotide, NAMN is nicotinic acid mononucleotide, NAMPT is nicotinamide phosphoribosyltransferase, NAPRT is nicotinate phosphoribosyltransferase, NMNAT is nicotinamide mononucleotide adenylyltransferase, ATM is altered tryptophan metabolism.

These Mg linked alterations in the extracellular plasma NAD⁺ metabolome are age related and underscore the association between the hallmarks of aging and the symptoms of a shortfall in Mg [1]. Figure 3 also reveals a mechanistic connection between neurodegenerative disease and Mg deficiency, altered tryptophan, and altered NAD⁺ metabolism [65][66].

This decline in NAD⁺ levels is linked causally to numerous age-associated diseases, including cognitive decline, cancer, metabolic disease, sarcopenia, frailty [66], cardiovascular disease [67], obesity, insulin

resistance [68], autoimmune disease, and inflammation [69]. The predominant source of NAD⁺ outside that from recycling (salvage pathway) is from tryptophan via the kynurenine pathway [70] (see figure 3).

A recent study on aging uncovered a prominent role for NAD⁺ in exercise induced longevity [71]. Exercise is cautioned for long haulers, given the frequency of fatigue and post exercise malaise in LC. However, significant efficacy of RAP in those with ME/CFS [38] holds promise for long haulers.

Other beneficiaries of adequate Mg include SIRT1, PGC-1 α , Klotho, and urolithin A. SIRT1 enhances ATP dependent mitochondrial biogenesis in adipocytes [72]. PGC-1 α , called the master regulator of energy metabolism, also drives ATP dependent mitochondrial biogenesis [73]. Synthesis of Klotho requires redox reactions and its intracellular signaling is also dependent on Mg dependent cAMP [74]. Secondary bile acids from gut microbiota also enhance longevity [75], but microbiota rely on Mg dependent 7- α dehydrogenase for their production of secondary bile acids [50]. Noteworthy antioxidants produced by gut bacteria or directly by the host include urolithin A, indoles, glutathione, melatonin, vitamins A, C, E, and selenium.

Vitamin C also increases lactose producing Bifidobacteria [76]. Lactogenic bacteria feed butyrogenic bacteria [77]. Deficiency in gut butyrogenic bacteria is linked to CFS [78] and LC [79]. Mg increases production of butyrate by gut microbiota [80]. Butyrate activates AMPK [81], immunomodulates IFN- γ [82], and downregulates IDO [83]. It also challenges obesity [84], which can raise estradiol and increase IFN- γ . mTOR activation enhances T-cell activation and differentiation (especially Th1/CD8⁺) and increases IFN- γ production [85].

IV. IFN- γ , IDO, Kynurenine, AhR, and Aging

This cytokine, enzyme, metabolite, and receptor form a group that sequentially defines a pathway that is a significant determinant of aging. When they are chronically activated, lifespan is shortened. RAP is top down (mTOR/AMPK) and Mg is bottom up (see figure 4). Mg modulates IFN- γ and its downstream effects on lifespan like Mg regulates HMG-CoA reductase and its statin-like downstream effects on cardiovascular disease [86].

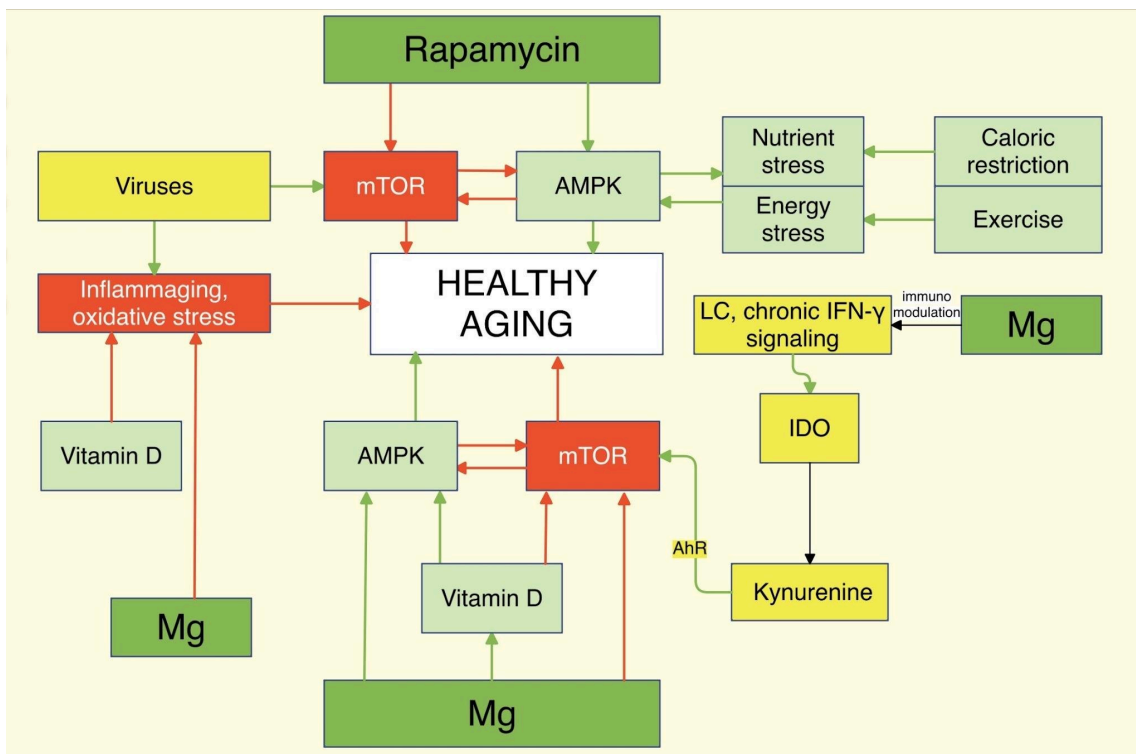


Figure 4. This figure demonstrates the biochemical pathways that link rapamycin (RAP) and Mg to healthy aging. RAP is top down and Mg is bottom up. It also demonstrates the sequence involving IFN- γ , IDO, kynurenine, and AhR. IFN is interferon, IDO is indoleamine dioxygenase, AhR is aryl hydrocarbon receptor.

A. IFN γ

Viral invasion initiates an innate immune response. Natural killer (NK) cells and CD8+ T cells produce the predominance of IFN γ [87].

Mg immunomodulates these cells [88] and attenuates any over-response, i.e., prevents inflammaging [89]. In addition to production of IFN- γ by host NK cells and CD8+ T cells, some cancer cells, e.g., certain T cell lymphomas and myeloid leukemias, can produce their own IFN- γ . For some cancers, including breast cancer [90] and glioblastoma [91], IFN- γ is tumorigenic. MgD and loss of IFN- γ immunomodulation may open the door for this. This anti-inflammatory cytokine is a potent stimulant of IDO. Inflammaging can further stimulate IDO activity. IFN- γ and IDO then become central players in upregulating the kynurenine pathway and “stealing tryptophan.” (see figure 5).

C. Kynurenine

IDO converts tryptophan to kynurenine, stealing tryptophan that otherwise would have been available for the more beneficial indole and serotonin pathways. Indeed elevated serum tryptophan is a biomarker of longevity ^[49]. Many of the kynurenine pathway metabolites are neurotoxic; K/T and longevity are inversely related. Kynurenine may inhibit autophagy via pathways beyond inhibition by upregulated mTOR ^[98]. Impact of this on the efficacy of RAP is unknown. Kynurenine pathway metabolites are the most prominent endogenous AhR activating ligands ^[99].

D. AhR

However, the AhR is a promiscuous receptor. Some indole derivatives and secondary bile acids are AhR ligands that counteract the effects of kynurenine and exogenous toxins ^{[100][101][102]} and enhance longevity. A healthy gut microbiome produces these longevity agents – secondary bile acids, indoles, and short-chain fatty acids ^[103]. Each triggers the secretion of GLP-1 ^[104], which may assist in the beneficial activation of AhR. GLP-1 agonists are also linked to longevity ^{[105][106]}, primarily because they preserve insulin sensitivity. This biomarker deteriorates with age, even in those with normal blood glucose and body weight ^[107]. Insulin resistance is an early hallmark of cancer, type 2 diabetes (T2DM), and dementia (T3DM)

Indole derivatives also modulate inflammaging and oxidative stress. But production of indoles and their derivatives by intestinal microbiota requires Mg and tryptophan (see figure 5).

If kynurenine production remains high, negative AhR signaling may persist, even if mTOR is partially suppressed by RAP. However, Mg sits upstream of many pathways relevant to long COVID, e.g., ATP production and mitochondrial function, vitamin D activation, NAD⁺ production, and inflammatory signaling. The impact of MgD on the synthesis of D3, 25(OH)D, and 1,25(OH)₂D cannot be overlooked (see figure 2).

In summary, chronic inflammatory systems often become partially “decoupled.” In this environment tryptophan insufficiency due to increased IFN- γ , IDO, kynurenine, and AhR signaling can upregulate mTOR, overriding its downregulation normally triggered by nutrient stress. In long Covid the nutrient stress induced by loss of ACE2 receptors on enterocytes is subservient to the increase in mTOR activity induced by the loss of ACE2 receptors and increase in angiotensin II that promotes hypertension and

chronic inflammation ^[108]. Elevated IFN- γ and mTOR/AMPK ratios are hallmarks of aging. Both are intimately linked and reinforce each other.

mTOR activation $\leftrightarrow$ more IFN- γ , more IFN- γ $\rightarrow$ more IDO, more IDO $\rightarrow$ more kynurenine pathway activity $\rightarrow$ more AhR signaling ^[109](see figure 4). Signaling pathways are complex, but the IFN- γ /IDO/K/AhR axis may be a primary determinant of longevity.

Conclusion

Mg and RAP are both recognized longevity agents. Both have demonstrated efficacy in the treatment of long Covid. Although they appear to have little in common, there may be some overlap. RAP operates in a topdown manner, influencing and influenced by hormones, while Mg is an element, working in a bottom up manner.

The long-term efficacy of RAP may fall short of expectations. Its allosteric inhibition of mTOR may trigger an increase in MAPK/ERK that upregulates mTOR via an alternate pathway. It is unknown whether low dose, intermittent RAP can trigger this. MAPK/ERK activates cytokine inflammagens. Mg may divert this via its suppressive action at the IFN- γ -IDO-kynurenine-AhR interface (see figure 4 and section IV).

Long Covid and many other diseases associated with intracellular pathogens, primarily viral, are linked to elevation of mTOR/AMPK ^[8]. Inadequate levels of Mg and Mg dependent vitamin D reveal a threefold increased risk for long Covid. The combination of Mg supplementation with intermittent low-dose RAP seems attractive.

Although human clinical trials are ongoing, the efficacy of RAP, like the efficacy of vitamin D, may never be fully realized in the absence of adjustment for the Ca:Mg ratio, tightly linked to health. Although dosage is very low and once a week, fear of the extent of its immunosuppressive effects has dampened interest and any such use of this prescriptive medication for longevity is off label.

Meanwhile the global epidemic of obesity, diabetes, chronic fatigue diseases, and those age related remains unaddressed. Interestingly RAP is also an antifungal and is theoretically capable of suppressing Candida overgrowth, linked to long Covid ^[46]. What has been proposed is theoretical and dependent on several reasonable physiologic assumptions. Nonetheless, the general approach is hypothetical and must be validated clinically.

PART B: Proposed Therapeuticss

Introduction

Mg has long been recognized as critical to human health. Signs and symptoms of Mg deficiency (MgD) reflect those of aging ^[1]. RAP likewise has extended the lifespan in flies, worms, yeasts, and rodents. Trials involving humans are underway. Because viral pathogens, including SARS CoV2, upregulate mTOR ^[8], RAP should decrease risks for diseases of chronic fatigue. Because vitamin D and Mg deficiency increase LC risk threefold ^[10], Mg should do likewise. Furthermore, adequate Mg may offer health benefits that complement those of rapamycin (RAP) via many disparate pathways outside those directly involving mTOR (mechanistic or mammalian target of rapamycin). Mg is bottom up, while RAP is top down.

Unfortunately, serum Mg is not considered representative of intracellular Mg and is not even offered on a routine chem panel. Although RBC Mg is intracellular, the test has not been embraced as representative of Mg within mesenchymal cells (bone and muscle), despite their shared TRPM7 channels and its role 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. This assumes adequate vitamin D, which implies approximately equivalent absorption rates for both Ca and Mg. When Ca:Mg is determined after converting mg/dL into mmol/L for iMg at the reference range limits, the ratio range closely reflects recommended intake weight to weight for general health. Ionization rates for both Ca and Mg can be determined by comparing reference range upper and lower limits for iCa and iMg with their counterparts for serum Ca (tCa) and Mg (tMg). iCa:iMg value at the upper limit duplicates that at the lower limit for both cations. These points are discussed in detail and the implications for intake are explored.

Although this review is supported by the relevant human physiology, it is nonetheless a hypothetical approach. While time consuming randomized controlled trials are underway, the global epidemic of obesity, diabetes, chronic fatigue diseases, and those age related remains unaddressed.

I. Ca:Mg Balance

The Ca:Mg ratio is critical, as both divalent cations compete for the same transcellular receptor (CaSR) and transient receptor potential melastatin (TRPM6,7) channels in intestinal absorption and renal

resorption. CaSRs are Mg dependent G protein coupled receptors (GPCRs) and TRPMs are Mg dependent kinases and transcellular channels (chanzymes). CaSRs are present on parathyroid, kidney, bone, intestine, stomach, pancreas, brain, blood vessel and immune cells.

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, which reflects parathyroid activity. 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 6).

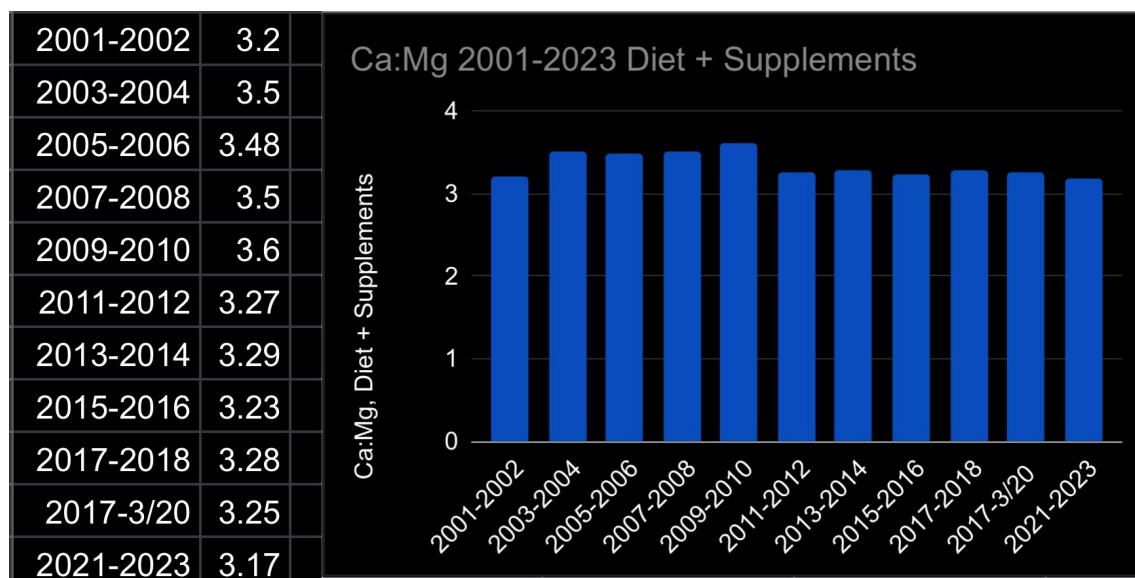
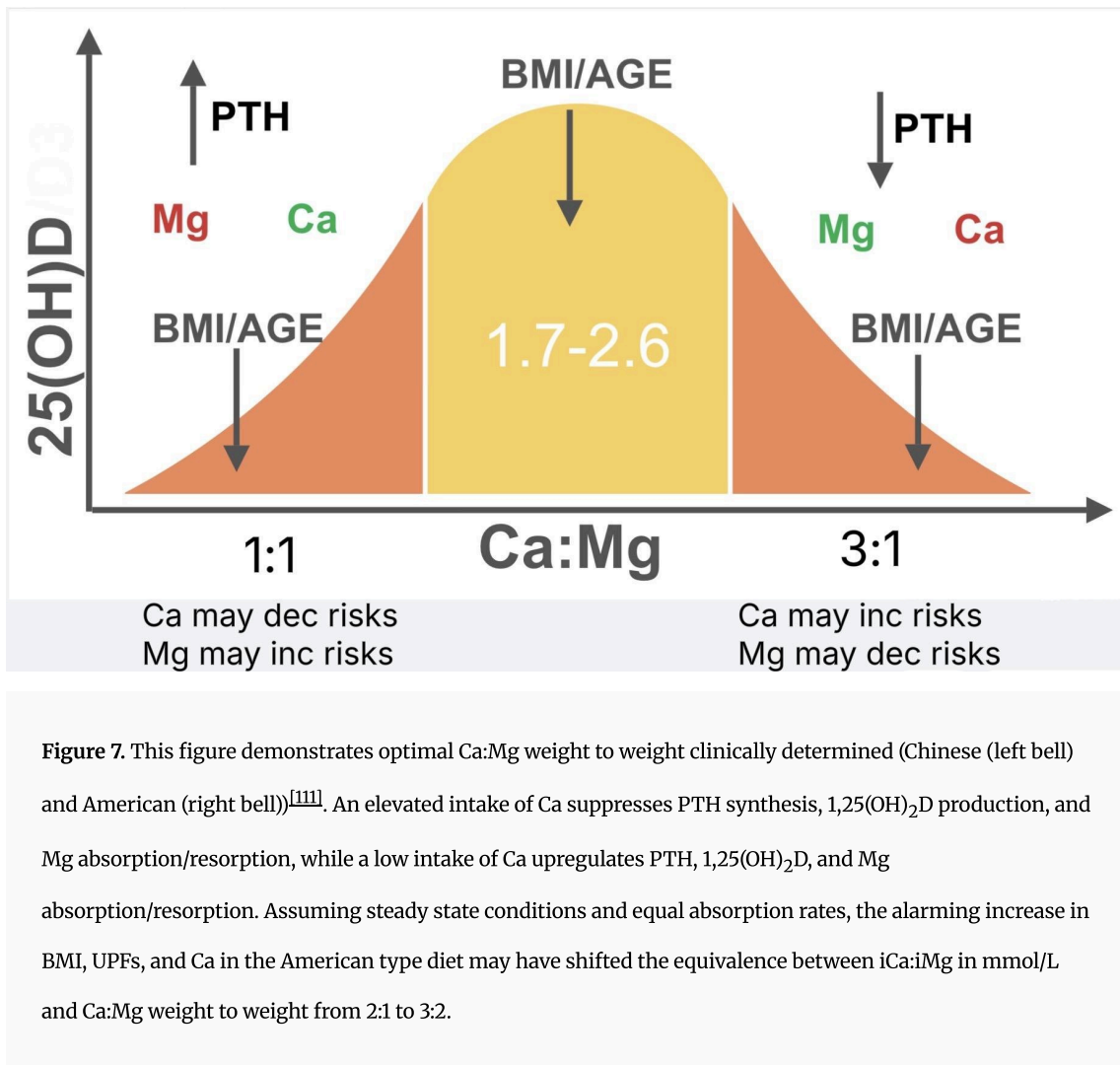


Figure 6. This figure, based on NHANES data, demonstrates the past 23 year history of the Ca:Mg intake ratio weight to weight in American males and females over 10 years of age.

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 7). 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.



The Ca:Mg weight to weight intake range of 1.7-2.6 linked to better health ^[111], depicted in figure 6, conforms well to the iCa:iMg range derived from the reference ranges for serum Ca and Mg, depicted in figure 8.

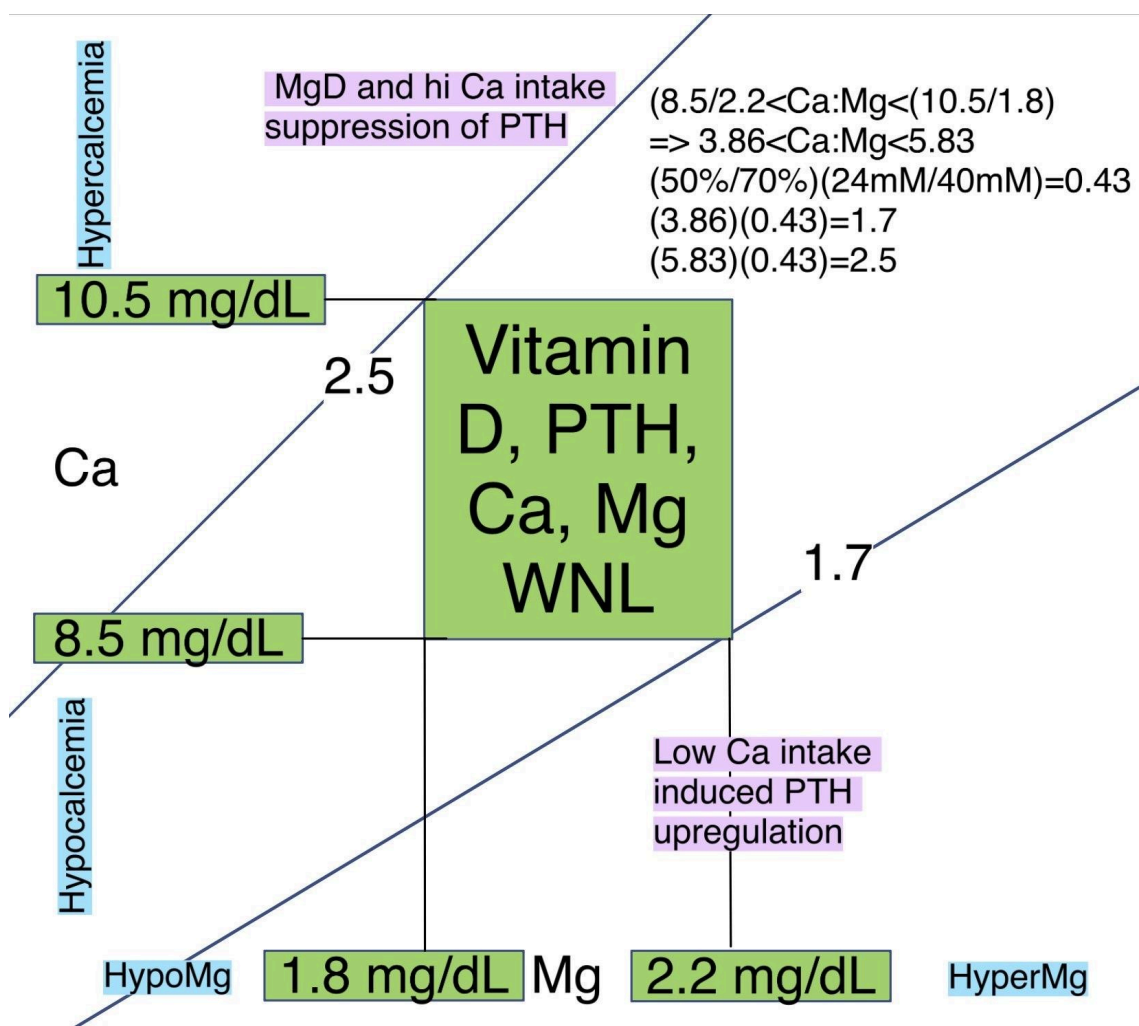


Figure 8. This figure demonstrates that the largest range for a healthy Ca:Mg is defined by minimum Ca:Mg (min Ca/max Mg) to maximum Ca:Mg (max Ca/min Mg). Converting this range from mg/dL to mmol/L and then to unbound or ionized forms yields $1.7 < \text{Ca:Mg} < 2.5$ (see upper right). Ionization rate for serum Mg in 1994 (70%) is used. If the ionization rate in 2023 (62%) is used, the range becomes 1.87-2.82, much worse.

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 ^[112]. 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 ^[113]. Using the present tMg range of 0.75-0.95 mmol/L, mean iMg:tMg has fallen from 72% in 1994 ^[112] to 62% in

2025 ^[113]. The continuing Ca driven secondary hypoparathyroidism might explain this drop in iMg over the past three decades.

The risk of long Covid is three times more likely if vitamin D and Mg deficiencies are present ^[110]. The majority of healthy adults worldwide are vitamin D deficient. This is especially true in females (57% v 44%) ^[114].

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 ^{[115][116]} and Chinese ^[117] studies have demonstrated this. Another study by Mansmann revealed the lower range of normal to be linked to pre-menstrual syndrome and migraines (normal tMg but low RBC Mg) ^[53]. Therefore, the true incidence of MgD in Americans is probably at least 50%.

Vitamin D immunomodulates the immune response primarily via Th1 lymphocytes. 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 Th1 cells ^[118]. 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 section IV). 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) ^[119].

II. Intracellular Mg Versus Intravascular Mg

Although Ca and Mg compete for the same CaSRs and dictate 80% of human metabolism ^[52], defining the relationship between intake, intravascular concentration, and intracellular distribution has been difficult, especially for Mg. CaSRs are not involved in intestinal absorption or renal resorption. In fact 80–90% of the absorption/resorption for epithelial and endothelial cells is passive and paracellular via tight junctions. This enables easy absorption and dissemination of Mg to and from the intravascular space and into the extracellular space. RBC membranes, like those of skeletal muscle cells and almost all mesenchymal cells (no tight junctions), contain TRPM7. TRPM7 is the only Mg transporter for cellular influx that possesses an extracellular domain (extracellular pore vestibule) to sense extracellular Mg concentration ^{[120][121][122]}. TRPM7 channels control influx of Mg and influx is inhibited by intracellular

free Mg^{2+} and MgATP. Because erythrocytes and skeletal myocytes 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) ^[123] should reflect optimal skeletal myocyte Mg, despite a larger intracellular Mg gradient in the latter.

However, RBC Mg also functions as a reservoir to maintain serum Mg within a tight range. RBC Mg sits at the nexus between intake/serum 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 9). 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 9 suggests that the optimal weight to weight intake ratio of Ca:Mg should approach 3:2. This figure demonstrates that:

1. If serum Mg = ~2.04 mg/dL (Rosanoff minimum)^[111] 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) ^[123] 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 3:2 ratio

is difficult. Vitamin D is critical to absorption of Ca and Mg, and Mg is critical to production of vitamin D. Assuming at least 32 ng/mL of 25(OH)D, Ca and Mg absorptions should range between 30 and 40% ^[124] ^[125]^[126]. These assumptions suggest that with adequate vitamin D:

1. A daily Ca intake of 285 mg/35% = ~814 mg Ca is needed per day, well below the 1000–1100 mg Ca RDA for males and females.

2. A daily Mg intake of $182 \text{ mg}/35 = \sim 520 \text{ mg Mg}$ is needed per day (Ca:Mg, $812/520=1.57$), well above the 320 mg Mg RDA for females or 410 mg Mg RDA for males

In 1964 Seelig recommended an intake of 6 mg Mg/kg [127]. In 1971 Seelig [128] updated her recommendation to 6-10 mg Mg/kg. Durlach repeated the 6 mg Mg/kg recommendation in 1989 [129]. Mean weight for Americans in 1964 was $\sim 70 \text{ kg}$ (75 for males and 65 for females). Presently mean weights in the US are 80 kg for females and 90 kg for males. Using Seelig's and Durlach's minimum 6 mg Mg/kg yields

3. A minimum daily Mg intake of $(6 \text{ mg} \times 85) = 510 \text{ mg Mg}$ is needed per day; absorption of 35% [126] $\Rightarrow 179 \text{ mg}$ intake for the average American, which conforms well to the 182 mg serum Mg derived from the Rosanoff and Razzaque recommended minima (see figure 9) (Ca:Mg = $814/510 = 1.6$ Seelig and Durlach (intake derived) versus 1.57 Rosanoff and Razzaque (lab derived))

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 9). Durlach's 2:1 weight to weight intake recommendation was from 1989, when Mg ionization was $\sim 72\%$ [112] (BMI/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
		Absorp'n	D=E+H	E=30xF	Serum Mg	Serum Ca	H=20xI	RBC Mg	
		25(OH)D	absorbed	plasma	mg/dL	mg/dL	RBCs	mg/dL	Total
		>32 ng/mL	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									
Ca	814 mg/day	x 35% <=	285 mg	285 mg	<= 9.5 (mean)				285 mg
Mg	520 mg/day	x 35% <=	182 mg	62.1 mg	<=2.04(min)		120 mg <= 6.0 (min)	182 mg	
Ca:Mg	1.57 (~3:2)(max)			Rosanoff et al.			Razzaque et al.		
6 mg/kg Seelig (1964), 6 mg Mg/kg (Durlach 1989), 6-10 mg Mg/kg (Seelig 1991)									
Ca	814	x 35% <=	285	285	<= 9.5 (mean)				285 mg
Mg	510 (min 6x85 (US mean))	x 35% =>	179	61	2.04 (min)		120	<= 6.0 (min)	181 mg
Ca:Mg	1.6 (~3:2)(max)								

Figure 9. This figure approximates and interprets laboratory reference data determined by “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 greater than 32 ng/mL => Ca absorption ^{[124][125]}, and Mg absorption ^[126] to be ~35%. 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. This is based on a minimum serum Mg of 2.04 mg/dL or 0.85 mmol/L ^[1] and a minimum RBC Mg of 6 mg/dL ^[123]. Seelig’s 1964 ^[127], Seelig’s 1971 ^[128] and Durlach’s 1989 ^[129] recommendations are included and support the 3:2 ratio.

Under steady state conditions absorption should approximate excretion. When the recommended serum minimum of 2.04 mg Mg/dL ^[111] and the recommended serum minimum of 6.0 mg RBC Mg/dL ^[123] 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 9). 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 ^[108] 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% ^[130]. 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 ^[131] and vitamin D deficiency is even more prevalent in the Third World ^[114]. 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 ^[129] 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 6).

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 ^[132], 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 ^{[133][134]}. Several recent articles have challenged this beneficial effect of B6 on Mg absorption ^{[135][136]}, 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 ^[137] and more Mg consuming chronic inflammation ^[89]. 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^[138].

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 ^[139]. 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 (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 to mmol/L ($\times 24/40$) and then to that ionized ($\times 50\%/62\%$) or
 $\text{Ca:Mg} \times 0.484 = \text{iCa:iMg}$ (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)
7. Consider D3 supplementation and monitoring
8. Consider prebiotics and probiotics (synbiotics)
9. Consider butyrate (postbiotic)
10. Consider other supplements, if appropriate
11. Consider low dose, intermittent RAP, if 25(OH)D is at least 32 ng/mL, RBC Mg is at least 6.0 mg/dL, and Ca:Mg is no more than 2:1

Conclusion

RBC Mg sits at the nexus between intracellular Mg and serum Mg and is representative of both. RBCs, immune cells, and myocytes, 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 transcellular passage against a 20:1 gradient. RBC Mg gradient is only 3:1 (6.0/2.04). When its value is optimal at 6.0 mg/dL (minimum) ^[123], intracellular concentrations of Mg elsewhere should also be optimal. RBC Mg should be the first to register any Mg intake shortfall ^[53]. An optimal RBC Mg is linked to an optimal serum Mg, because RBC Mg also functions as a reservoir for serum Mg ^[123].

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 ^[111].

Seelig's 1964 ^[127] and Durlach's 1989 minimum recommendation of 6 mg Mg/kg ^[129] and Seelig's 1971 updated recommendation of 6-10 mg Mg/kg ^[128] 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 9), 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 ^[114], and the popularity and convenience of the American type UPF laden diet has assaulted Mg intake. Unfortunately $\frac{1}{2}$ 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 (1964) and Durlach (1989). The RDA for Mg dependent D3 is also too low, despite the revelation of a near 10 fold statistical error in 2014 ^[139].

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 by 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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Declarations

Funding: No specific funding was received for this work.

Potential competing interests: No potential competing interests to declare.