

Review Article

Magnesium and Rapamycin in Long Covid and Longevity: A Mechanistic and Therapeutic Approach

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A global shortfall in magnesium (Mg) is linked to long Covid and a shortened lifespan. Calcium (Ca) competes with Mg for the same receptor and developed countries (and cities) ingest too much Ca and the Third World 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 a Western diet 3:2 might be a better target. RBC Mg sits at the nexus of intracellular Mg and serum Mg. This enables easy determination of serum Ca:Mg that reflects the intake ratio and general health status.

Nutrient sensitive mTOR (mechanistic or mammalian target of rapamycin) and energy sensitive AMPK (AMP-activated protein kinase) are inversely related. A balanced mTOR:AMPK ratio, is linked to healthy aging. Multiple studies in yeast, worms, flies, and rodents support the efficacy of rapamycin (RAP) as a longevity agent. Any inhibition of mTOR by RAP can 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. RAP is a top down longevity agent, while Mg empowers longevity from the bottom up. They collaborate without competing. Efficacies may merge at the IFN- γ , indoleamine dioxygenase (IDO), kynurenine, aryl hydrocarbon receptor (AhR) interface. Persistence of any intracellular pathogen, e.g., SARS CoV2, can prolong IFN- γ activation of IDO. IDO metabolizes tryptophan (T) and upregulates the kynurenine (K) pathway, leaving less T for the indole (longevity biomarker) and serotonin pathways. An elevated K/T is linked to cancer, autoimmune disease, cardiovascular disease, dementia, diabetes, obesity, and chronic inflammation in general. Furthermore, Mg-dependent vitamin D immunomodulates IFN- γ .

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Introduction

Mg has long been recognized as critical to human health, but has not yet been embraced as a longevity agent. Signs and symptoms of Mg deficiency (MgD) reflect those of aging ^[1]. Furthermore, Mg may offer health benefits that complement those of rapamycin (RAP) via many disparate pathways outside those directly involving mTOR. 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 studies on humans demonstrate limited evidence of tangible clinical benefit, many 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 this review is supported by the relevant human physiology, it is nonetheless a hypothetical approach. While time consuming randomized controlled trials are undergoing, 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 beneficial functions many other conditions can overactivate mTOR with deleterious consequences. These include manipulation of host-cell mTOR pathways by viruses to support 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. 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, 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)

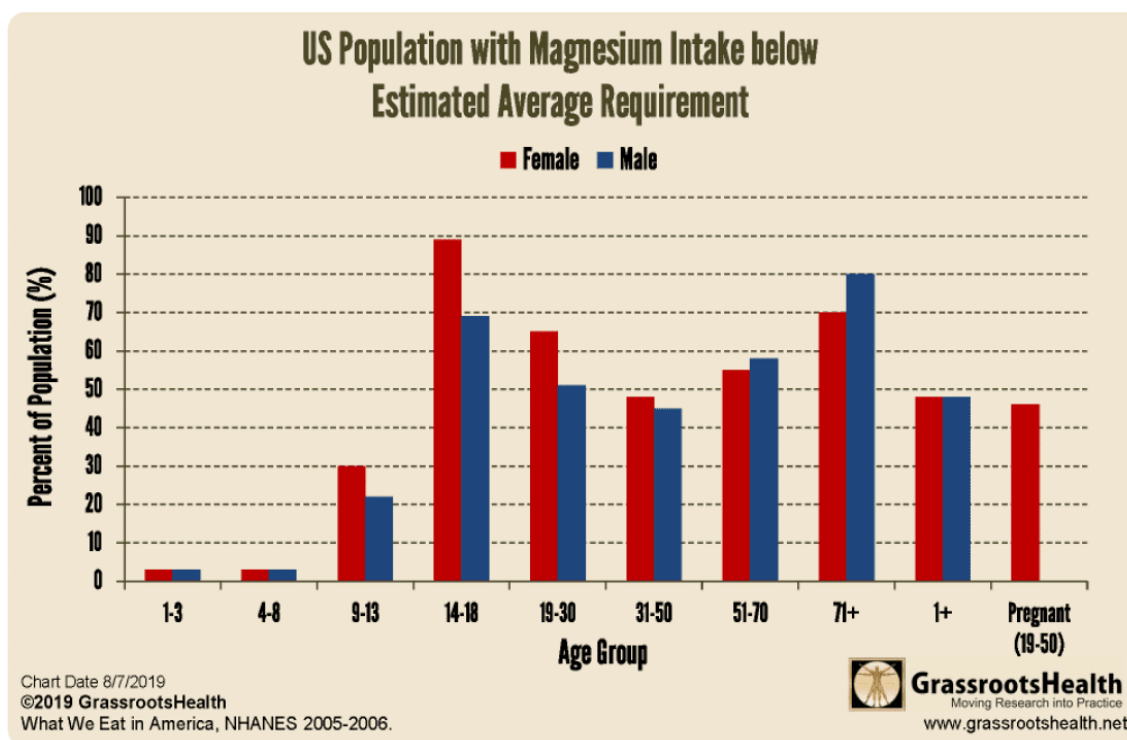


Figure 1. This figure from NHANES data demonstrates the low intake for Mg in females 9 to 50 years of age.

They are also particularly prone to long Covid and autoimmune disease, characterized by elevated mTOR [28]. Long haulers have difficulty absorbing seven of the nine essential amino acids. This is due to

the dysfunction of ACE2 on enterocytes due to persistent SARS CoV2. These seven neutral amino acids primarily depend on BOAT1, their designated amino acid transporter ^{[29][30]}. BOAT1 requires ACE2, as a chaperone for tryptophan, methionine, and branched chain amino acid absorption ^{[31][32]}. 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 to be the worst. 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 ^[33].

Intermittent chronic feeding of low-dose RAP increases autophagy ^[34]. Such doses do not compromise muscle mitochondrial content or endurance ^[35]. RAP has been touted for Covid-19 ^[36] and anecdotally for long Covid. Efficacy for chronic fatigue diseases has already been reported ^[37].

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 ^[38]. MAPK may activate mTORC1 via other pathways and bypass RAP inhibition of mTORC1 ^{[39][40][41]}. Dysfunctional MAPK/ERK signaling is tumorigenic and its suppression is touted in cancer therapy ^[42]. 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-kB 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.

In addition to its down regulation of mTOR and upregulation of AMPK, RAP has antifungal properties ^[43] and is toxic to *Candida albicans* ^[44]. *Candida* overgrowth is linked to LC ^[45]. 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 ^[46]. So, RAP can directly suppress *Candida albicans*, linked to long Covid ^[47], and with it production of an IDO like enzyme produced by *Candida* ^[46], preserving tryptophan, a known biomarker for longevity ^[48].

III. Mg, Vitamin D, and Mg 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 ^[49], increased oxidative stress and mTOR activity, and inflammaging - all hallmarks of MgD. MgD even adversely impacts the gut microbiome ^[50].

Mg is required for more than 80% of all human metabolic functions ^[51]. These include all reactions that require ATP/GTP, ADP/GDP, cAMP/cGTP, all CYP450 enzymes ^[52] and all GPCRs (require a second messenger - cAMP). Of all FDA approved drugs 34% involve GPCR ligands ^[53]. Mg²⁺ itself can also function as a second messenger ^[54]. 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 both beta-cell-dysfunction-induced insulin resistance and post receptor insulin resistance ^[55].

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 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 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 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 ^[56], and up regulates AMPK ^[57] and autophagy ^[58]. All forms of vitamin D (D3, 25(OH)D, and 1,25(OH)₂D) require Mg (see figure 2).

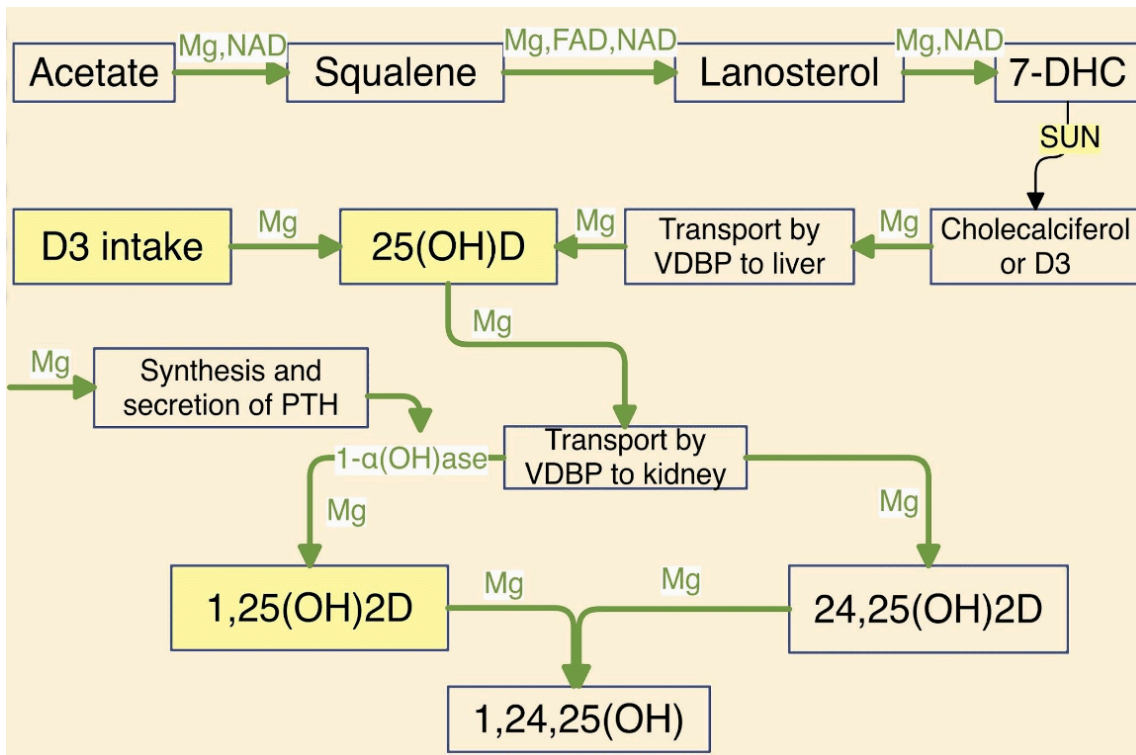
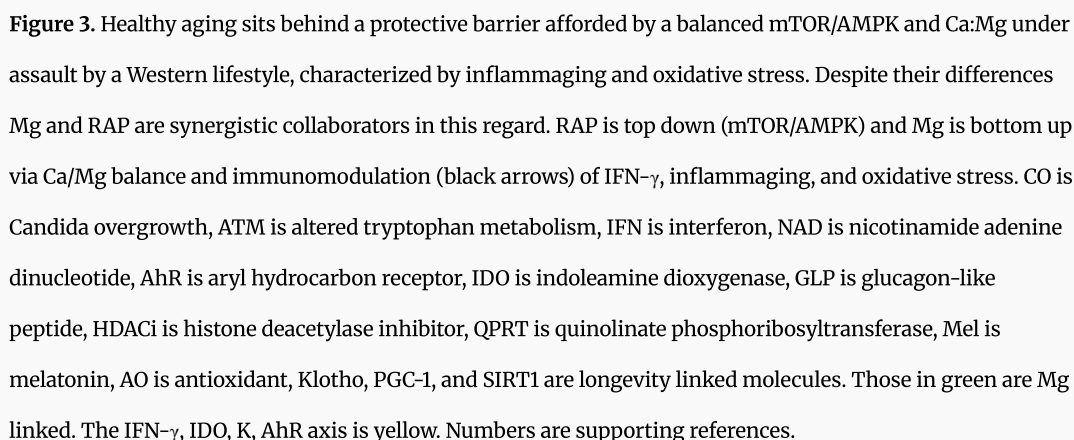


Figure 2. The intake, storage, and active forms of vitamin D are yellow. DHC is dehydrocholesterol, VDBP is vitamin D binding protein, FAD is flavin adenine dinucleotide, and NAD is nicotinamide adenine dinucleotide. Mg dependent B2 and B3 are crucial to synthesis of FAD and NAD and redox reactions to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

In a study of 125 long haulers versus controls the risk of long Covid increased more than three times if $25(\text{OH})\text{D} < 30 \text{ ng/mL}$ and $\text{Mg} < 1.8 \text{ mg/dL}$ [59]. This underscores the tight link between vitamin D and Mg. 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].

Urolithin A is an antioxidant and ATP dependent mitophagy catalyst [61]. Its synthesis by gut microbiota involves redox reactions. Mg-dependent indole-3-propionate and butyrate are other longevity linked molecules produced by gut flora. SIRT1, PGC-1 α , and Klotho are host derived longevity agents. SIRT1 signaling is NAD⁺ dependent and NAD⁺ synthesis from neurotoxic quinolinate by quinolinate phosphoribosyl transferase (QPRT) is Mg dependent (see figure 3).



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Vitamin C also increases lactose producing Bifidobacteria [66]. Lactogenic bacteria feed butyrogenic bacteria [67]. Deficiency in gut butyrogenic bacteria is linked to CFS [68] and LC [69]. Mg increases production of butyrate by gut microbiota [70]. Butyrate activates AMPK [71], immunomodulates IFN- γ [72], and downregulates IDO [73]. It also challenges obesity [74], which can raise estradiol and increase IFN- γ .

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

This cytokine, enzyme, metabolite, and receptor are significant determinants of aging. When they are chronically activated, lifespan is shortened. They operate primarily upstream of mTOR but downstream from Mg (see figure 3).

A. IFN γ

Viral invasion initiates an innate immune response. Natural killer (NK) cells and CD8+ T cells produce the predominance of IFN γ [75].

Mg immunomodulates these cells [76] and attenuates any over response, i.e., prevents inflammaging [77]. 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 [78] and glioblastoma [79], 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 4).

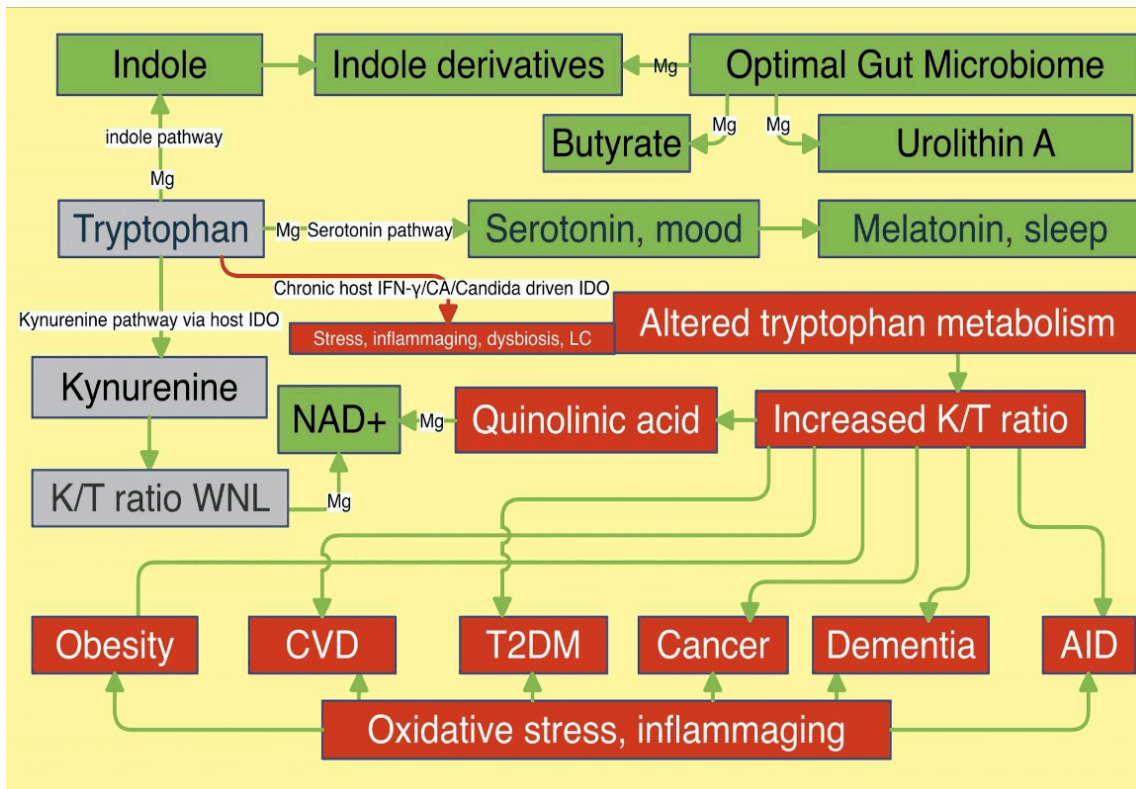


Figure 4. This figure demonstrates the three pathways (other than protein synthesis) that tryptophan can follow and how ATM (altered tryptophan metabolism) can steal this essential amino acid with dire consequences for longevity. Green boxes promote longevity and red boxes suppress it. AID is autoimmune disease and T2DM is type 2 diabetes mellitus

B. IDO

IDO activity driven by inflammaging^[80] or persistent virus may represent states where inflammatory or immune-growth signaling overrides the normal nutrient-stress driven suppression of mTOR/upregulation of AMPK^[81]. Candida can produce an IDO like enzyme^[49], as do many cancer cells, including carcinomas of kidney, lung, endometrium, urinary bladder, colorectum, cervix, ovary, and melanoma^[82]. In the tumor microenvironment this IDO can suppress NK cells and CD8+ T cells and their production of IFN- γ , facilitating immunoevasion^{[83][84][85]}.

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 ^[48]. 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 ^[86]. Impact of this on the efficacy of RAP is unknown. Kynurenine pathway metabolites are the most prominent endogenous AhR activating ligands ^[87].

D. AhR

Indole derivatives, on the other hand, are AhR ligands that oppose kynurenine and exogenous toxins ^[88]. Indole derivatives modulate inflammaging and oxidative stress ^[89] and their down regulation of AhR may enhance longevity ^{[90][91]}. But production of indoles and their derivatives by intestinal microbiota requires Mg and tryptophan.

If kynurenine production remains high, 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 the 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 ^[92]. Elevated IFN- γ and mTOR/AMPK ratios are hallmarks of aging. Both ratios 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 ^[93]. Signaling pathways are complex, but the IFN- γ /IDO/K/AhR axis may be a primary determinant of longevity.

V. Therapeutic Approaches for LC and Longevity

These recommendations are for those otherwise healthy on an American type diet (relative secondary hypoparathyroidism due to high intake of Ca and high BMI)

1. Determine 25(OH)D level (should be over 40 ng/mL)
2. Determine RBC Mg (minimum should at least 6.0 mg/dL)

3. Determine serum Mg (should be $\sim\frac{1}{3}$ of RBC Mg)
4. Determine serum Ca and iCa (iCa:Ca should be about 50%)
5. Calculate serum Ca:Mg (mM to mM)
6. Consider Mg supplementation and monitoring
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

The high dietary Ca elevates iCa and suppresses PTH. Ionized Ca dictates PTH secretion, regulating not only serum Ca but also the per cent ionized. Comparing the upper and lower laboratory reference limits for serum iCa with their serum Ca counterparts yields about 50% ionization. Secondary hypoparathyroidism will lower this figure and hyperparathyroidism will increase it.

The risk of long Covid is three times more likely if vitamin D and Mg deficiencies are present ^[59]. The majority of healthy adults worldwide are vitamin D deficient. This is especially true in females (57% v 44%) ^[60]. According to the 2013-16 NHANES, 48% of Americans of all ages ingest less than the estimated average requirement (EAR) for Mg. This suggests that the serum levels for these 48% are all likely below the lower limit of the normal range, which is close to 1.8 mg/dL or about 0.75 mM in most Western hospitals. However, serum values between Mg .75-.85 mmoles/L are associated with increased insulin resistance - 20% increase between 0.80 and 0.85 and 50% increase between 0.75 and 0.80. Both American ^{[94][95]} and Chinese ^[96] studies have demonstrated this. Another study by Mansmann revealed the lower range of normal to be linked to PMS and migraines ^[52]. Therefore, the true incidence of symptomatic MgD in Americans is probably around 75% (48%+ $\frac{1}{2}$ of normal reference range, which is 0.75-0.95 mmol/L).

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 mg/mL, otherwise sufficient for skeletal needs (endocrine). Th1 cells produce IFN- γ ^[97]. 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) ^[98].

Evaluating serum or RBC Mg alone is insufficient. The Ca:Mg ratio is far more significant, as both divalent cations compete for the same transcellular receptor (CaSR) and paracellular channel (TRPM7) in intestinal absorption and renal resorption. CaSR is a Mg dependent GPCR and TRPM7 requires the ATP-Mg complex. The American ratio has exceeded 3:1 for the past quarter century (see figure 5). In 1989 the recommended intake of Ca:Mg was 2:1 for developed countries ^[99].

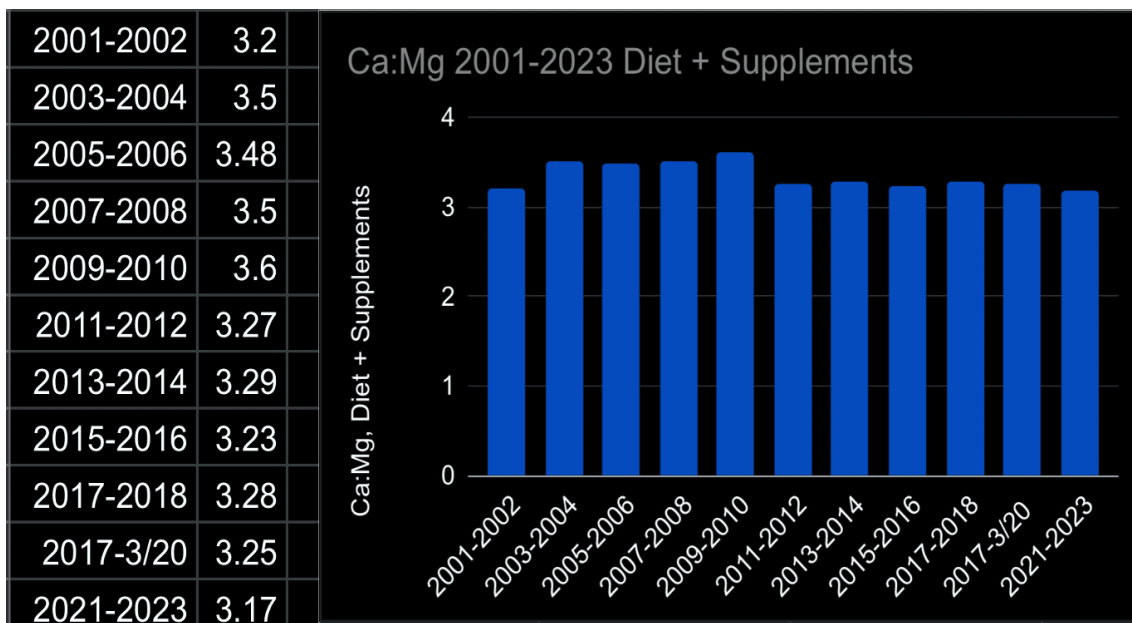


Figure 5. This figure, based on NHANES data, demonstrates the past 23 year history of the Ca:Mg intake ratio in American males and females over 10 years of age.

RBC Mg is generally recognized as a better measure of Mg status than serum Mg, as it reflects intracellular levels. However, RBC Mg also functions as a reservoir to maintain serum Mg within a tight range. 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. Assuming steady state and homeostatic equilibrium over time, total circulating Mg should approximate absorbed intake of Mg and vice versa with steady state distribution from blood. Specific intake and blood minimums must reflect optimal intracellular efficiency.

Figure 6 suggests that the optimal weight to weight intake ratio of Ca:Mg for anyone on a typical American diet from laboratory data approaches 3:2. Figure 6 demonstrates that:

1. If serum Mg = ~ 2.07 mg/dL (Rosanoff minimum)^[100] 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)^[101] 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 is (95 mg/L)(3 liters) = 285 mg Ca in circulation.
4. 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 is critical to production of vitamin D. Assuming at least 32 ng/mL of 25(OH)D, Ca and Mg absorptions range between 30 and 40% ^{[102][103]}. These assumptions suggest that

1. a daily Ca intake of $285 \text{ mg} / .35 = \sim 814$ mg Ca is needed per day.
2. a minimum daily Mg intake of $182 \text{ mg} / .35 = \sim 520$ 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 1991 Seelig ^[104] recommended 6-10 mg Mg/kg. Mean weights in the US are 80 kg for females and 90 kg for males.

3. a minimum daily Mg intake of $179 \text{ mg} (6 \text{ mg} \times 85) / .35 = 510$ mg Mg is needed per day (Ca:Mg 1.6) by the average American.

So, from both an intake weight for weight basis and from a lab reference range mM to mM basis Ca:Mg should be about 3:2. (see figure 6).

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, Ca:Mg 2.84								mg/dL)	blood
Minimum Mg blood limits									
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	<=2.07(min)			120 mg <= 6.0 (min)	182 mg
Ca:Mg	1.57 (~3:2)				Rosanoff et al.			Razzaque et al.	
6-10 mg Mg/kg (Seelig 1991), 6 mg Mg/kg and 2:1 max for developed country (Durlach 1989)									
Ca	814	x 35% <=	285	285	<= 9.5 (mean)				285 mg
Mg	510 (min 6x85 (US mean)	x 35% =>	179	60	2		120	6	179 mg
Ca:Mg	1.6 (~3:2)								

Figure 6. This figure approximates and interprets laboratory reference data for “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 mM), vitamin D greater than 32 ng/mL, Ca absorption ^{[102][103]}, and Mg absorption ^[105] around 35%. It suggests that a blood Ca:Mg (mM to mM) 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 2.07 mg/dL or 0.85 mmol/L ^[100] and a minimum RBC Mg of 6 mg/dL ^[101]. Durlach's 1989 ^[99] and Seelig' 1991 ^[104] recommendations are included and support the 3:2 ratio.

Under steady state conditions absorption should approximate excretion. When the recommended serum minimum of 2.1 mg Mg/dL ^[100] and the recommended serum minimum of 6.0 mg RBC Mg/dL ^[101] are met or exceeded, this homeostatic equilibrium suggests that either analyte might accurately reveal Mg status, all else being equal.

Ultra processed food 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 absorption and ultraprocessed foods (UPFs) make dietary Mg intake less available. Unlike Seelig's and Durlach's recommendations, the RDA's do not adjust for weight. Individual iCa:iMg should be much more easily determined ^[92] 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% ^[106]. 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 to Mg poor substitutes. Soil depletion and ultra processing continue to challenge the effort 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 ^[107] and vitamin D deficiency is even more prevalent in the Third World ^[60]. 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 ^[99] was framed as a maximum for developed countries. Given the increase in BMI and dietary Ca since 1989, perhaps 3:2 should be the new target.

Under steady state conditions the iCa:iMg ratio is elevated (American type diet) and suppresses PTH (secondary hypoparathyroidism). The typical Asian diet lowers iCa:iMg and promotes secondary hyperparathyroidism (left side of bell in figure 7).

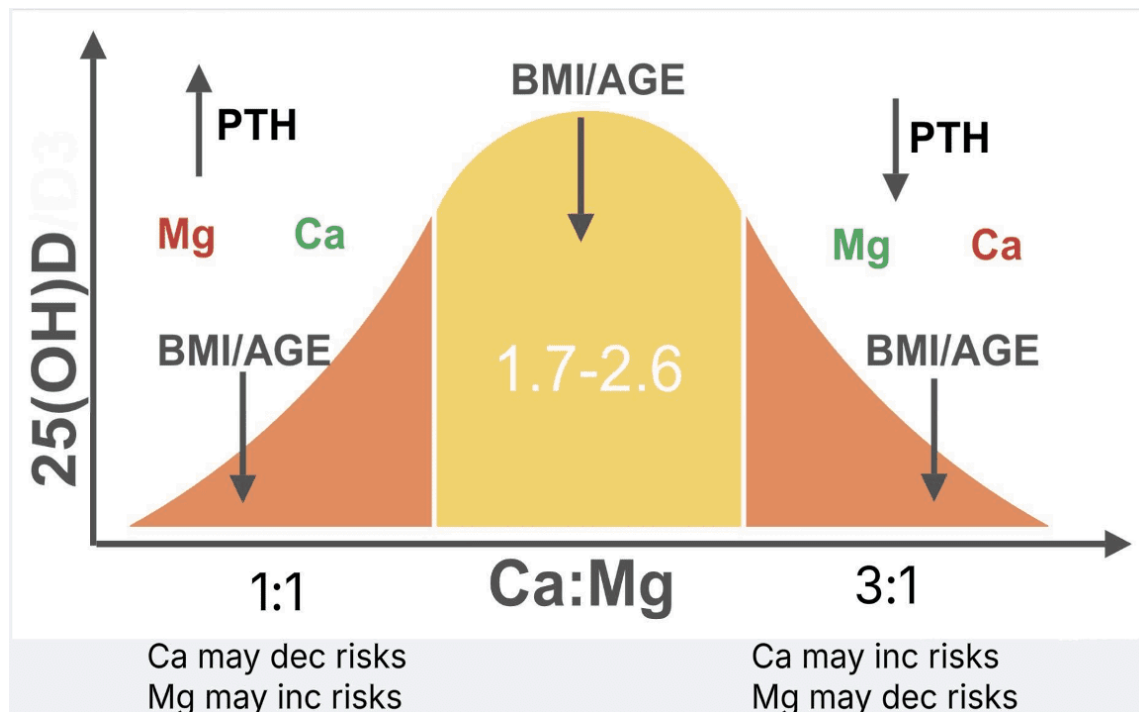


Figure 7. This figure demonstrates optimal Ca:Mg weight to weight clinically determined (American and Chinese)^[107]. Increased PTH increases the ratio and decreased PTH depresses it. Assuming steady state conditions and equal absorption rates, the alarming increase in BMI, ultraprocessed foods, and Ca in the American type diet may have shifted or is shifting the equivalence between iCa:iMg in mM and Ca:Mg weight to weight from 2:1 to 3:2.

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, a prebiotic, and pyridoxal-5-phosphate, the active form of vitamin B6. Mg bioavailability is increased by the concomitant intake of vitamin P5P. Pyridoxal phosphate but not pyridoxine, appears to form a complex with Mg and may enhance absorption ^{[108][109]}. Several recent articles have challenged this beneficial effect of B6 on Mg absorption ^{[110][111]}, 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 paracellular channel absorption (TRPM7).

Many are resistant to the notion that MgD is linked to obesity and vice versa. Obese individuals tend to have lower Mg intake ^[112] and more Mg consuming chronic inflammation ^[77]. MgD is associated with inflammaging ^[1] and a higher Ca:Mg.

Conclusion

Mg and RAP are both recognized longevity agents. Both have demonstrated efficacy in the treatment of long Covid. Yet they appear to have little in common. While there is some overlap, RAP operates in a topdown manner influencing hormones 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 may upregulate 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 section IV and figure 3). Accordingly, determining Mg status is pivotal. However, this can be difficult, especially since RBC Mg may be more informative. Serum values for Mg contain both bound and unbound forms. Fortunately RBC Mg sits at the nexus between intracellular Mg and plasma Mg and is representative of both. When its value is at its optimal 6.0 mg/dL ^[101], intracellular concentrations of Mg elsewhere should also be optimal. At this level of RBC Mg, serum Mg should be about 2.1 mg/dL ^[100].

Under steady state conditions and homeostatic equilibrium the recommended optimal intake of Ca:Mg weight to weight should meet the physiologic needs for intracellular Ca:Mg. This should duplicate the optimal intake ratio, because the optimal serum Mg reflects the optimal recommended RBC Mg. RBC Mg is a reservoir reflecting the status of serum Mg and a proxy for the status of intracellular Mg in general.

Seelig's 1991 recommendation of 6-10 mg Mg/kg ^[104] was based on physiologic needs. If Seelig's mean and the American mean weight were used (8x85=680), even the average RDA for Ca of 1050 mg would yield 3:2 or specifically 1.54. The 1989 Durlach's recommendation Ca:Mg of 2:1 weight to weight, a minimum for developed countries ^[99], may be outdated.

BMI has steadily grown, vitamin D deficiency has increased globally ^[60], and the popularity and convenience of the American type ultra processed food diet has assaulted Mg intake. Unfortunately ¾ 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 supplementary content of elemental Mg in their supplements.

Lowering BMI and improving iCa:iMg and vitamin D status might be a worthy goal for those on an American type diet of ultra processed food. Transitioning to a healthier diet, 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. These conclusions are theoretical and dependent on several reasonable physiologic assumptions. Nonetheless, the general approach is hypothetical and must be validated clinically.

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 ^[45].

Notes

Figure 3 displays the following references: ^{[113][114][115]}

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Declarations

Funding: No specific funding was received for this work.

Potential competing interests: No potential competing interests to declare.