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 the West ingests too much calcium and the East 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 (mammalian target of rapamycin) and energy sensitive AMPK 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 as a longevity agent. Any inhibition of mTOR by rapamycin can upregulate kinases that activate mTOR via alternate pathways. Whether this occurs with low-dose, intermittent rapamycin is unknown. But Mg is perfectly placed to block this.

Rapamycin 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 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 rapamycin 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. The term vitamin D (VD) includes solar/supplemental D3, its storage form 25(OH)D, and its active form $1,25(OH)_2D$, unless otherwise specified. mTOR means mTORC1 (mammalian or mechanistic target of rapamycin complex 1).

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), 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)

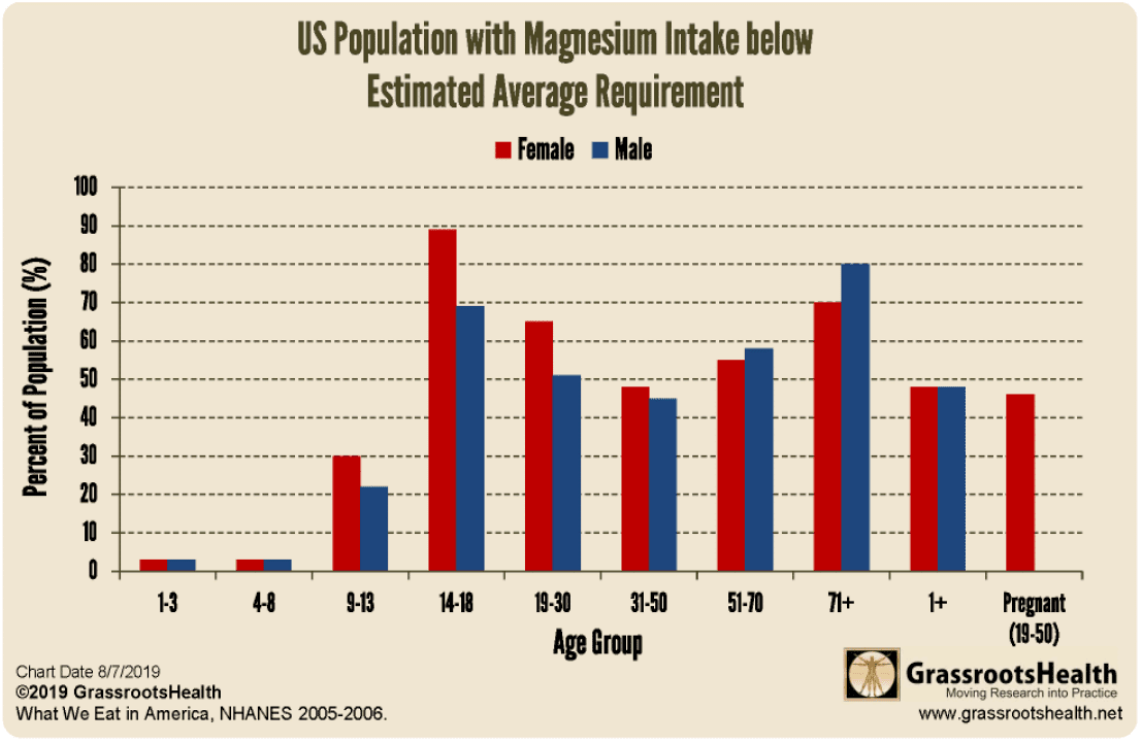


Figure 1. This figure from NHANES data demonstrates the low intake for Mg in females 9 to 50 years of age.

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 B0AT1, their designated amino acid transporter [29][30]. B0AT1 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

Rapamycin induces healthy aging via inhibition of mTOR [33].

Intermittent chronic feeding of low-dose rapamycin 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 rapamycin allosterically inhibits mTORC1, but many of the subsequently generated interactions and pathways are unknown or incompletely understood. Although rapamycin 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 rapamycin 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 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]. Mg^{2+} 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 transport; 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$(OH)_2$D) require Mg (see figure 2).

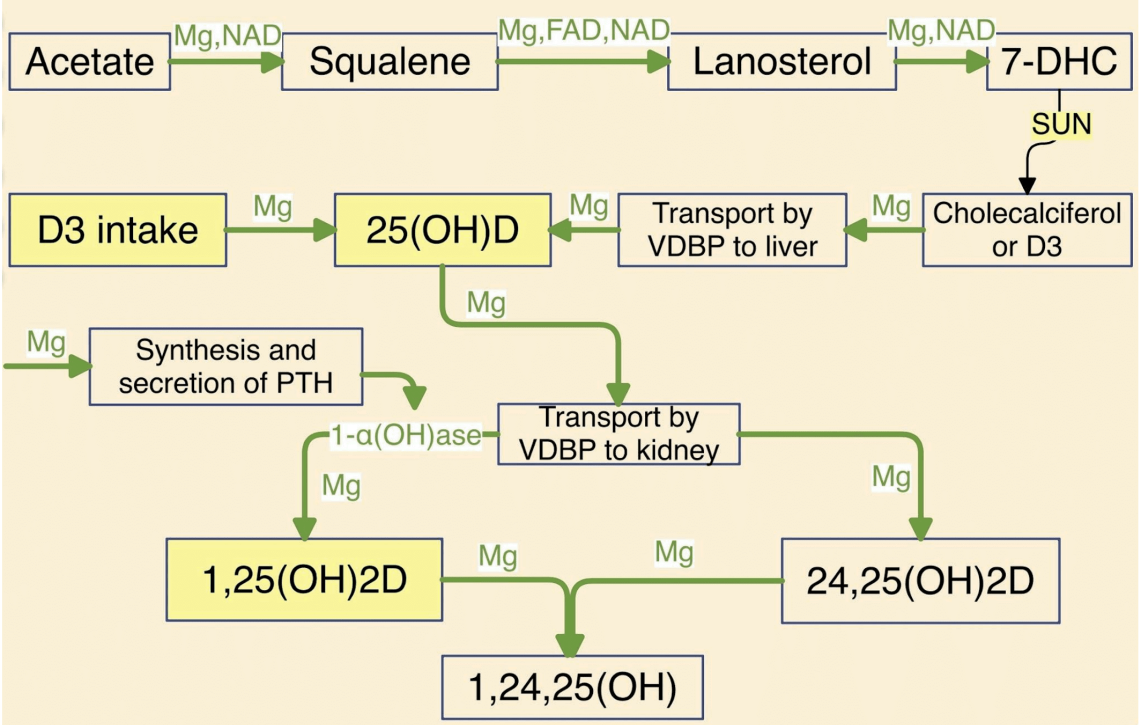


Figure 2. The intake, storage, and active forms of vitamin D are yellow. DHC is dehydrocholesterol, VDBP is vitamin D binding protein, FAD is flavin adenine dinucleotide, and NAD is nicotinamide adenine dinucleotide. Mg dependent B2 and B3 are crucial to synthesis of FAD and NAD and redox reactions to 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(OH)D<30 ng/mL and Mg<1.8 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-proprionate and butyrate are other longevity linked molecules produced by gut flora. SIRT1, PGC-1α, 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).

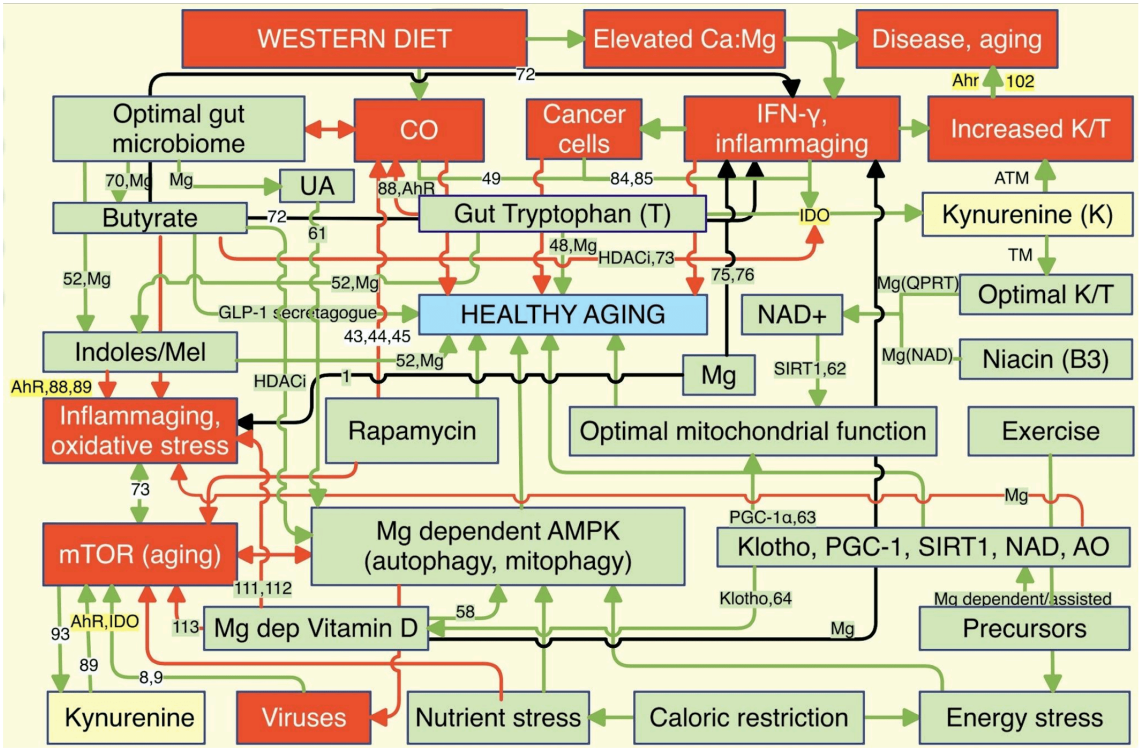


Figure 3. Healthy aging sits at the center of the discordance between the Western lifestyle (inflammaging, oxidative stress, and elevated Ca:Mg) and Mg enabling a balanced mTOR/AMPK. Despite their differences they are synergistic collaborators. RAP is top down (mTOR/AMPK) and Mg is bottom up via Ca/Mg balance and immunomodulation (black arrows) of IDO, K/T, and AhR in yellow). CO is Candida overgrowth, ATM is altered tryptophan metabolism, IFN is interferon, NAD is nicotinamide adenine dinucleotide, AhR is aryl hydrocarbon receptor, IDO is indoleamine dioxygenase, GLP is glucagon-like peptide, HDACi is histone deacetylase inhibitor, Mel is melatonin, AO is antioxidant, Klotho, PGC-1, and SIRT1 are longevity linked molecules. Those in green are Mg linked. Numbers are supporting references.

SIRT1 enhances ATP dependent mitochondrial biogenesis in adipocytes [62]. PGC-1α, called the master regulator of energy metabolism, also drives ATP dependent mitochondrial biogenesis [63]. Synthesis of Klotho requires redox reactions and its intracellular signaling is dependent on Mg dependent cAMP [64]. Secondary bile acids from gut microbiota also enhance longevity [65], but microbiota rely on Mg dependent 7-alpha dehydrogenase for their production of secondary bile acids [49]. 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 [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. 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).

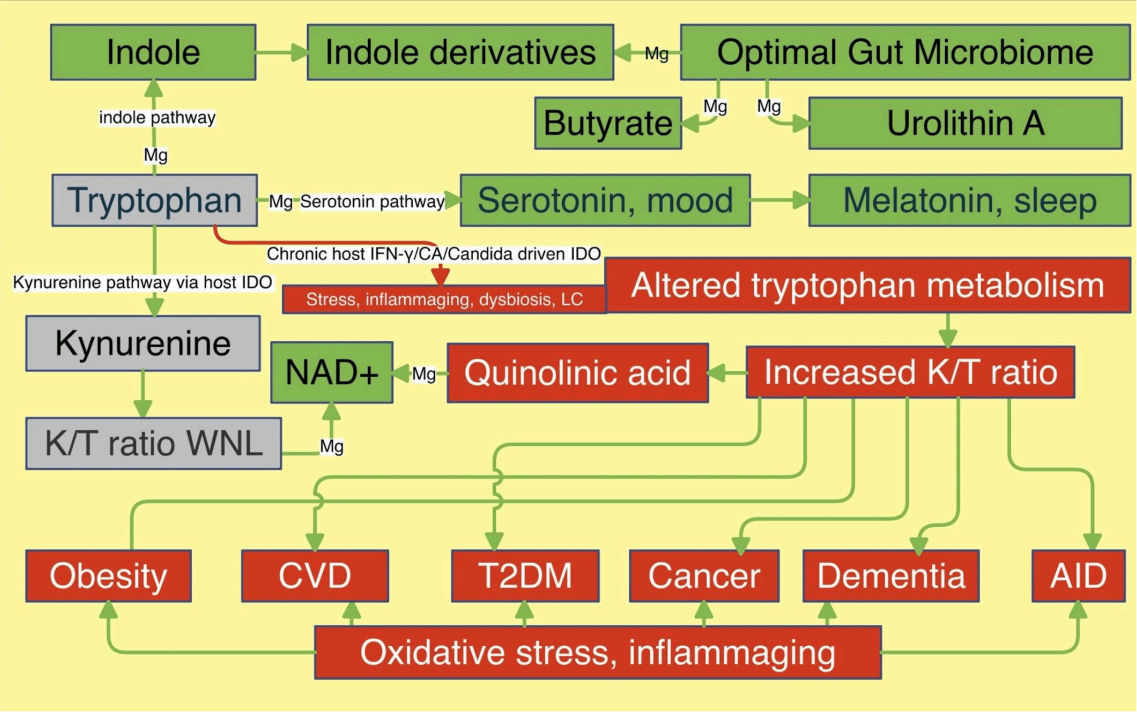


Figure 4. This figure demonstrates the three pathways (other than protein synthesis) that tryptophan can follow and how an ATM can steal this essential amino acid with dire consequences for longevity. Green boxes promote longevity and red boxes suppress it. AID is autoimmune disease and T2DM is type 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 and 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 activating AhR 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 rapamycin. 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)D3, and $25(OH)_2D3$ 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 ↔ more IFN-γ, IFN-γ → more IDO, more IDO → more kynurenine pathway activity → more AhR signaling [93].

V. Therapeutic Approaches for LC and Longevity

1. Determine BMI
2. Determine 25(OH)D level
3. Determine iCa:iMg (see figure 6)
4. Consider Mg supplementation and monitoring
5. Consider D3 supplementation and monitoring

6. Consider prebiotics and probiotics
7. Consider butyrate (postbiotic)
8. Consider other supplements, if appropriate
9. Consider low dose, intermittent RAP, if 25(OH)D is at least 40 ng/mL and serum iCa:iMg (mM:mM) is optimal.

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%+½ of normal reference range).

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].

2001-2002	3.2
2003-2004	3.5
2005-2006	3.48
2007-2008	3.5
2009-2010	3.6
2011-2012	3.27
2013-2014	3.29
2015-2016	3.23
2017-2018	3.28
2017-3/20	3.25
2021-2023	3.17

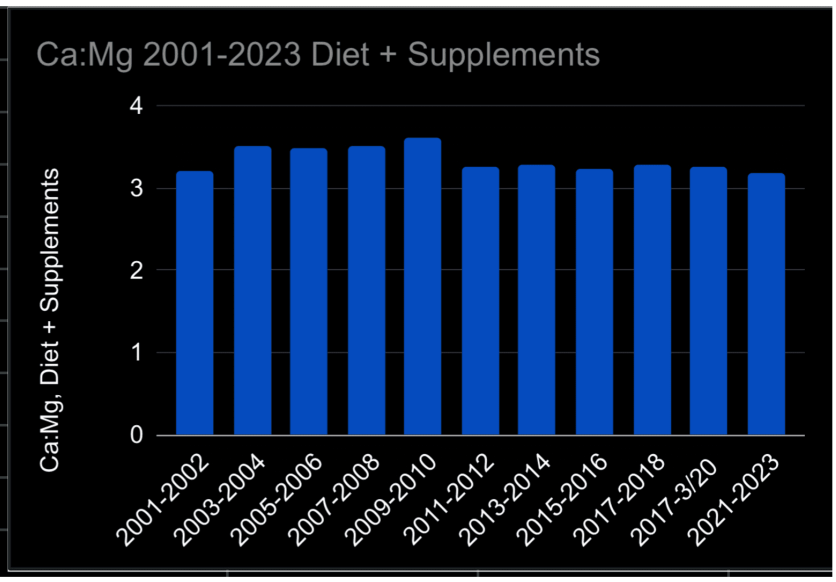


Figure 5. This figure, based on NHANES data, demonstrates the past 23 year history of the Ca:Mg intake ratio in American males and females over 10 years of age.

Figure 6 depicts the normal reference range limits for Ca and Mg. The derived range for Ca:Mg is 1.7-2.5. This conforms well to that derived clinically from intake - 1.7 (China) to 2.6 (US) [100]. If the upper limit of serum Mg is raised to 2.28 (0.95 mmoles/L), the conformity is even closer (1.7-2.6).

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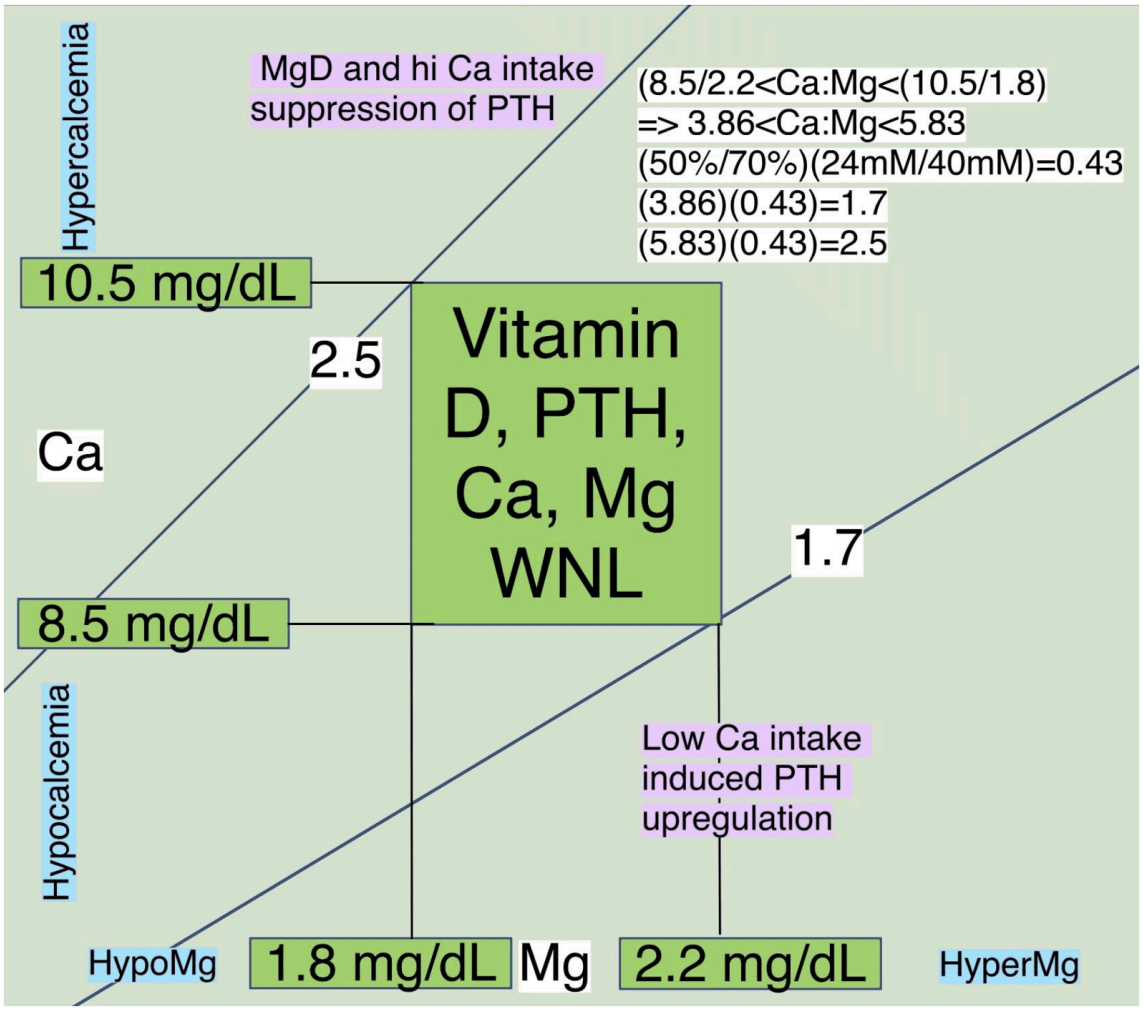


Figure 6. Normal reference range limits may vary. Comparing the upper and lower normal limits for each cation, a maximum normal range for Ca:Mg can be determined. In non-hospitalized, otherwise healthy individuals by comparing the lower limit of unbound cation with its lower serum limit and the same for the upper limits, the percentages of iCa at both limits is about the same at about 50% and that for iMg is about 70% [101]. Adjusting the units mg/dL to mmoles/L and adjusting for ionization to more accurately reflect physiologic interactions, yields a conversion factor of 0.43 (see upper right of figure 6).

RBC Mg is generally recommended 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. Consequently RBC Mg is much more dynamic (4.2-6.8 mg/dL) than serum Mg (1.8-2.2 mg/dL). Knowing both enables determination of total blood Mg. Assuming steady state and homeostatic equilibrium over time, amount ingested should equal amount excreted and total circulating Mg should approximate absorbed intake of Mg and vice versa, assuming steady state distribution from blood.

	RDA Ca 1000-1100, Mg 320-420								
	Calculated intake	Absorption			**Serum Mg**	**Serum Ca**			
	based on mean or	**assuming**	Amount	mg in 3L	**(1.8-2.2)**	**(8.5-10.5)**	**mg in**	**RBC Mg**	Amount
	rec'd serum values	**adequate D**	absorbed	plasma	**mg/dL**	**mg/dL**	**2L RBCs**	(4.2-6.8 mg/dL)	in blood
Ca	814 mg/day	35%	285 mg	285 mg		**9.5 (mean)**			285 mg
Mg	486 mg/day	35%	170 mg	60 mg	**2 (mean)**		110 mg	**5.5 (mean)**	170 mg
Ca:Mg	**1.67**								
iCa:iMg	**2.04**								
Ca	814 mg/day	35%	285 mg	285 mg		**9.5 (mean)**			285 mg
Mg	520 mg/day	35%	182 mg	62.1 mg	**2.07 (min)**		120 mg	**6.0 (rec'd)**	182.1 mg
Ca:Mg	**1.57**			**Rosanoff et al.**			**Razzaque et al.**		
iCa:iMg	**1.97**								
	2:1 (Durlach)								
Ca	1120 mg/day	35%	392 mg	392		13.1			
Mg	560mg (8x70)	35%	196 mg	**>65.5**	**>2.18**		<130.5	**<6.5**	196
6-10 mg/kg (Seelig)									
Ca	814		285	285		**9.5 (mean)**			285
Mg	560 (520)		196	**>65.5**	**>2.18**		130.5	**<6.5**	196
Ca:Mg	3:2								
iCa:iMg	1.45 (1.57)								

Figure 7. This figure presents data for non-hospitalized, otherwise healthy individuals, and assumes hematocrit 40%, blood volume 5 liters, Ca ref range 8.5-10.5 mg/dL, Mg ref range 1.8-2.2 mg/dL, adequate vitamin D, Ca absorption around 35% [102][103], Mg absorption 30-40% (NIH Mg fact sheet), and recommended RBC Mg of 6 mg/dL [104]. Comparing the minimum recommended serum Mg of 2.07 mg/dL [100] and the recommended RBC Mg of 6.0 mg/dL [104], suggest that in a healthy population the latter should average just under three times the former.

Given the ongoing increase in global obesity, vitamin D deficiency, and growing popularity of western processed fast foods over the intervening four decades, perhaps Durlach's 1989 recommendation of 2:1 Ca:Mg intake ratio should be revisited, especially in view of Seelig's mean recommendation of over 560 mg of daily Mg for one weighing 70 kg [105]. Processed foods impact Mg absorption and Durlach's recommendation did not include RBC Mg.

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 [100] and vitamin D deficiency is even more prevalent in the third world [60]. Furthermore, a leaner body weight might lower Seelig's mean Mg intake recommendation. Other modifying factors not addressed include dark skin, Muslim women's attire, genes, e.g., lactose intolerance, and long office hours.

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 represents only about 10% of the total. The laxative effect can be minimized by intermittent dosing, varying the forms, and combining absorption facilitators, like 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 [106][107]. Several recent articles have challenged this beneficial effect of B6 on Mg absorption [108][109], but both employed Magne, which is 300 mg Mg and 30 mg pyridoxine. Mg chelated with an amino acid like glycine or lysine are absorbed better than are inorganic Mg salts like Mg oxide.

Many are resistant to the notion that MgD is linked to obesity and vice versa. Obese individuals tend to have lower Mg intake [110] and more Mg consuming chronic inflammation [77]. MgD is also associated with inflammaging [1].

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, 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 inflammagents. 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 serum iCa:iMg 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 [104], 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. The resulting easily

determined optimal serum iCa:iMg in mM (see figure 6) should duplicate the optimal intake ratio, because the optimal serum iMg reflects the optimal recommended RBC Mg, a proxy for the status of intracellular Mg in general.

Seelig's 1991 recommendation of 6-10 mg Mg/kg was based on physiologic needs. On the other hand, the 1989 recommendation of Durlach, a French physiologist, for the optimal intake at Ca:Mg of 2:1 weight to weight may be outdated. BMI has steadily grown, vitamin D deficiency has increased globally [60], and the popularity and convenience of the Western 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.

Adjusting for BMI, Ca:Mg, and vitamin D status might drive optimal Ca:Mg lower, perhaps from 2:1 to 3:2 (see figure 7) in those on a Western diet of fast food. Transitioning to a more healthy diet and slowly increasing Mg intake might gradually improve iCa:iMg. 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: [111][112][113]

References

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