

Review

Not peer-reviewed version

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Posted Date: 13 November 2024

doi: 10.20944/preprints202410.2334.v3

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Review

Magnesium and Longevity

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Abstract: Magnesium (Mg) is not prominent among the list of well known anti-aging agents. Yet the signs and symptoms of aging mimic those of Mg deficiency. Mg is required for nearly a thousand enzymatic reactions. This narrative review does not correlate Mg status with clinical data on agents linked to longevity. The approach is more novel and highlights specific Mg dependent physiologic reactions required by these longevity linked biomarkers. Many of these share common pathways to extend healthspan. Mg is a required cofactor in the synthesis of vitamin D and melatonin and activation of six of the eight B vitamins. It is a required cofactor for all CYP450 enzymes. It is directly responsible for the appropriate methylation of proteins and DNA, which control the epigenome. The MTHFR (methylenetetrahydrofolate reductase) 677T allele that compromises methylation is present in a majority of Americans. Aberrant methylation predicts the severity of Covid-19 and its persistence into long Covid. Mg is a silent benefactor that may indirectly link these longevity agents, but only if viewed in context with calcium (Ca), i.e., Ca:Mg. Both compete for the same receptor. To fully exploit these longevity agents sufficient Mg is required. The pertinent physiology is presented, although cause and effect awaits publication of supporting clinical data.

Keywords: histone deacetylase inhibitors; methylation; Ca:Mg; MTHFR 677T; gut microbiome

Introduction

Optimal longevity involves extending healthspan, not just lifespan. Its pursuit has been energized by recent breakthroughs in our understanding of its pathobiology. The contribution of the gut microbiome to our general health is at the top of this list. Many elements are associated with longevity. Some are well known, e.g., high density lipoprotein cholesterol (HDL-C), heart rate variability (HRV), vitamin D, and telomeres. Others are less well known but well documented, e.g., aryl hydrocarbon receptors (AhRs), histone deacetylase inhibitors (HDACi). There are numerous molecules associated with longevity. Popular ones include short chain fatty acids (SCFAs), polyunsaturated fatty acids, and glucagon-like peptide-1 (GLP-1). Ozempic (semaglutide) is a GLP-1 agonist. Although well known for weight loss, it also brings longevity benefits. Almost all exhibit some connection to the gut microbiome. Many involve the epigenome and raise the question - can we control our genes to some extent by what we eat? Intake of Mg is critical. It is required as a cofactor or activator for over 800 enzymatic reactions [1]. It is involved in over 80% of known metabolic functions [2]. The dominance of so many Mg dependent enzymes may in part explain why many Mg deficiency symptoms mimic those of aging [3]. Mg deficiency has long been connected to cellular senescence [4]. Mg potentiates each of the discussed longevity agents, either directly or indirectly by enhancing the precursors or metabolites of their designated biopathways. Half of Americans are deficient in Mg. This figure would be much higher if the lower limit of its acceptable range were to be slightly increased to eliminate normomagnesemia Mg deficiency, as indicated by intra-erythrocytic Mg [5], now known as chronic latent Mg deficit.

Discussion

I. Gut Microbiome

A healthy gut microbiome produces abundant longevity agents - secondary bile acids, indoles, and short chain fatty acids [6]. Each triggers secretion of GLP-1 [7]. GLP-1 agonists are also linked to longevity [8,9], primarily because they preserve insulin sensitivity. This biomarker deteriorates with

age, even in those with normal blood glucose and body weight [10]. Insulin resistance is an early hallmark of cancer, type 2 diabetes (T2DM), and dementia (T3DM)

A. Secondary Bile Acids

Primary bile acids are normally conjugated in the liver after hepatic degradation of cholesterol. This involves CYP450 enzymes, which are all Mg dependent [11]. These primary bile acids must be deconjugated before gut bacteria can dehydroxylate and dehydrogenate them to produce secondary bile acids [12]. A central pathway in the production of secondary bile acids by gut bacteria is 7-alpha dehydroxylation [13]. 7-dehydroxylated bile acids are the most potent agonists for host bile acid receptors [14]. The process of 7- α -dehydroxylation is enabled by 7-alpha dehydrogenase, a Mg dependent enzyme [15]. The contribution of Mg to production of secondary bile acids is, therefore, operating in both the liver (CYP 450 enzymes) and the intestinal lumen (7-alpha dehydrogenase).

Gilbert's syndrome, linked to longevity, is a genetic disorder characterized by an increase in unconjugated bilirubin [16]. It is characterized by less oxidative stress, less inflammaging, lower body mass index, stronger vagal tone and less risk for cardiovascular disease (CVD) or T2DM than healthy controls [17]. The longevity benefits in Gilbert's Syndrome might be due to the fast tracking of unconjugated primary bile acids to secondary bile acids. Unconjugated primary bile acids normally compose less than 1% of total biliary acids [18]. Nonetheless, production of primary bile acids is critical and Mg deficiency compromises this. Bile acid production decreases with age [19], as do Mg levels. Indeed the symptoms of Mg deficiency reflect those of aging [3].

B. Indoles

The gut microbiome also produces indole/indole derivatives, longevity agents that also trigger release of GLP-1. Gut bacteria metabolize tryptophan, creating these indole derivatives. Down regulation of tryptophan dioxygenase (TDO) and indoleamine dioxygenase (IDO) increases tryptophan and decreases kynurenine, extending lifespan [20] (see Figure 1).

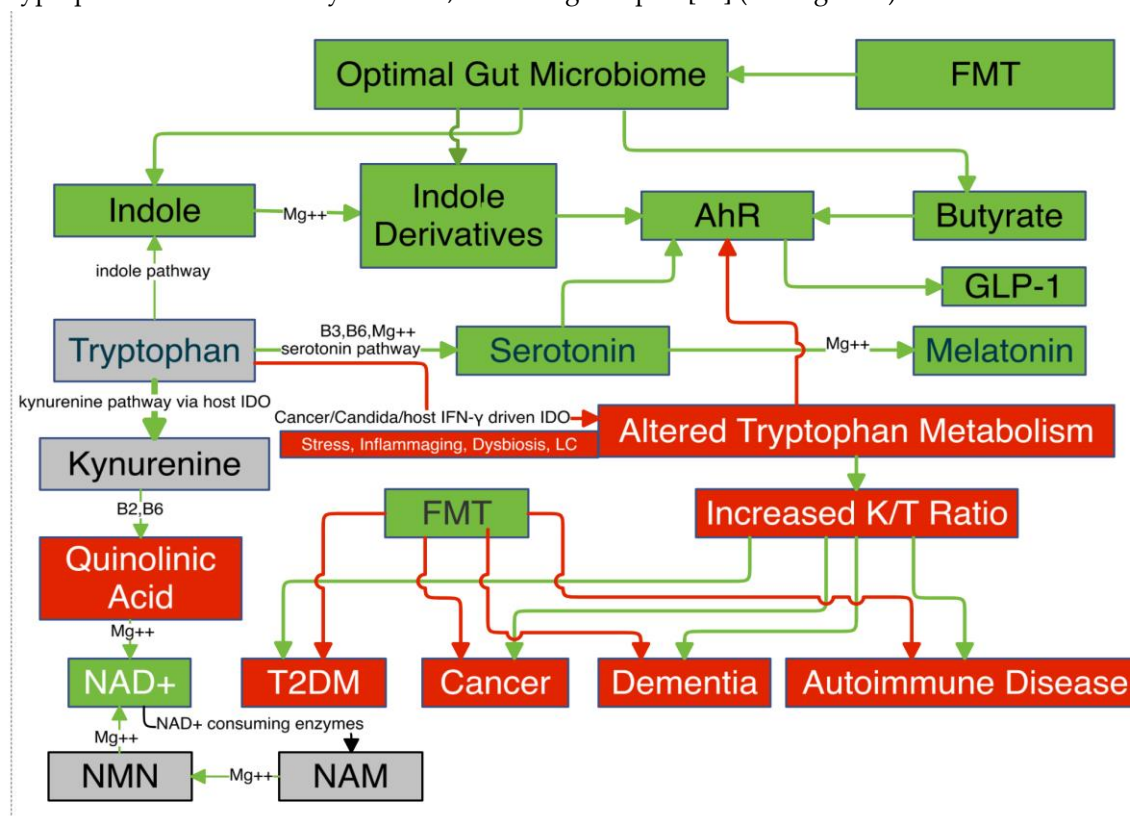


Figure 1. AhR=aryl hydrocarbon receptor, LC=long Covid, FMT=fecal microbiota transplantation, K/T=kynurenine to tryptophan, T2DM=type 2 diabetes, GLP=glucagon like peptide, NAD=nicotinamide adenine dinucleotide, red arrows, boxes => unfavorable, green arrows, boxes => favorable.

Altered tryptophan metabolism (ATM) and increased kynurenine to tryptophan ratio are hallmarks of cancer, dementia, autoimmune disease, and obesity. In each tryptophan depletion is prominent, leaving less for indole synthesis. Indole derivative production also requires CYP 450 enzymes, all of which are Mg⁺⁺ dependent [11]. Indoles also induce the release of GLP-1, known to suppress appetite, increase insulin secretion and slow gastric emptying [8]. Indoles are also ligands for aryl hydrocarbon receptors (see section IV), another longevity agent conduit.

C. Butyrate

Butyrate is another GLP-1 agonist [21] and an aryl hydrocarbon ligand. Both are longevity indicators. Probiotics, rich in butyrogenic bacteria, are associated with longevity [22] and Mg enhances probiotic efficacy [23]. Butyrate produced by gut bacteria via vagal afferents may improve HRV [24,25]. Candida and cancer cells are prominent secretagogues for HDAC [26,27]. Butyrate is an HDACi [28] and may also mediate the efficacy of calorie restriction in enhancing longevity [29]. Gut microbiota cannot produce SCFAs in the absence of Mg [30]. Omega 3 fish oils upregulate SCFA production, especially butyrate [31] and enhance biodiversity [32].

II. Vitamin D

Vitamin D is another well recognized longevity agent [33] and Mg is critical to its synthesis [34]. The active forms of vitamin B2 (FAD) and B3 (NAD), required for the synthesis of the D3 precursor, 7-dehydrocholesterol, are also Mg dependent (see Figure 2).

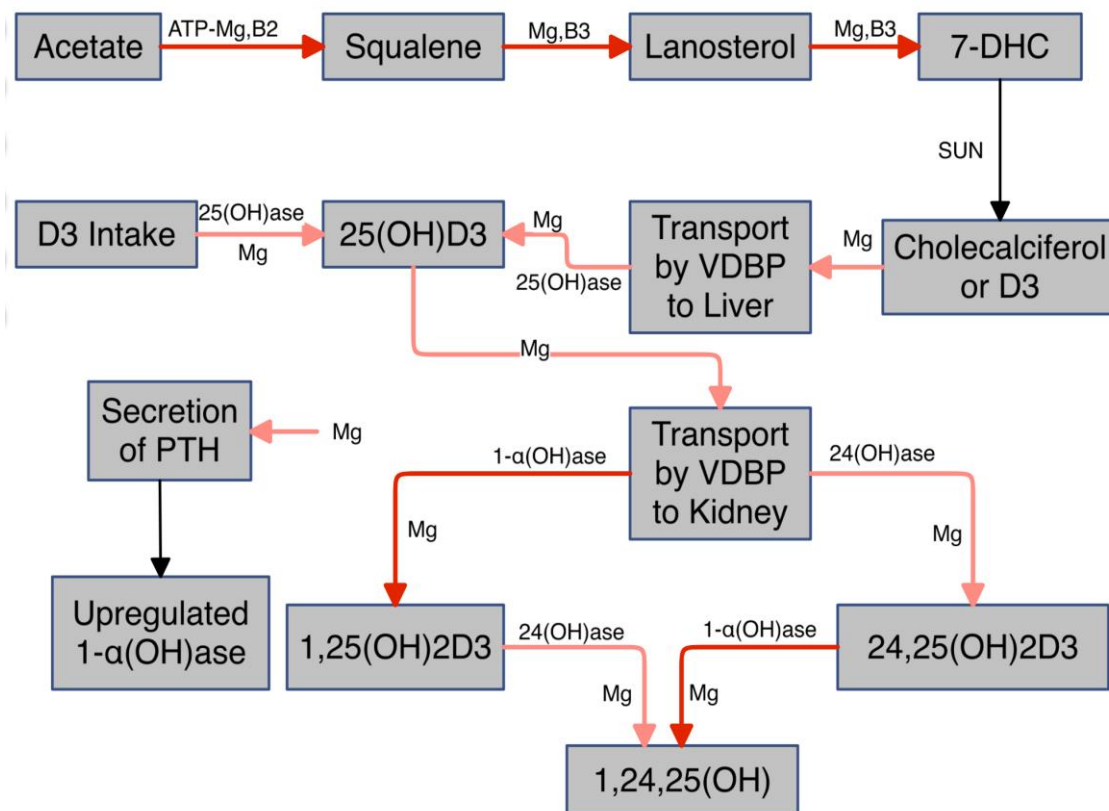


Figure 2. This sterol biosynthetic pathway for cholecalciferol decreases with age and is further challenged by Mg deficiency. Intensity of red arrows indicates the impact of Mg deficiency. DHC=dehydrocholesterol, PTH=parathormone, VDBP=vitamin D binding protein, D3=cholecalciferol.

Vitamin D efficacy in longevity is linked to its healthful effects on methylation and the epigenome [35]. Vitamin D supplementation reduces total cholesterol, low density lipoprotein (LDL) cholesterol, and triglyceride levels but not HDL-C levels [36] (see section V). Vitamin D reversibly improves the gut microbiome [37]. D3 directly inhibits Candida hyphal morphogenesis. Candida can

produce its own IDO, which depletes tryptophan, upregulates the kynurenine pathway, and alters tryptophan metabolism (ATM) [38].

III. Telomeres

The link between telomere length and mortality, like HDL-C (section V), may be U shape. Initially telomere length was reported as positively linked to longevity. However, recently this has been challenged. Long telomeres may be associated with cancers [39]. Telomeres shorten with age (attrition) and longevity is characterized by less telomere attrition, i.e., longer telomeres v those less long lived [40]. This shortening is due to loss of telomere homeostasis with cellular senescence. Mg maintains telomere homeostasis [41]. Anti-aging agents and conditions that delay telomere shortening include vitamin D [42], dietary Mg [43], calorie restriction [44], and GLP-1 [45]. Telomere attrition is influenced by oxidative stress, inflammation, insulin resistance, and hyperglycemia, well controlled by GLP-1 [46]. Gilbert's Syndrome also manifests less telomere attrition [47]. Regulation of telomerase and telomere homeostasis is subject to epigenetic control and DNA methylation [48] (see section VIII).

IV. AhR

Recently the vital role of aryl hydrocarbon receptors (AhRs) in aging [49], dementia, autoimmune disease, cancer [50], and ASCVD [51] has been recognized. AhR activity is dependent on its ligands. Kynurenines are AhR ligands that accelerate aging and neurodegeneration, while butyrates and indoles of intestinal bacterial origin are AhR ligands that oppose this [49] and promote longevity. ATM inactivates the immune response dependent function of AhR [52]. Not only are indoles and butyrate AhR ligands [53], but subsequent AhR activation induces cytochrome CYP450 enzymes that facilitate gut absorption of indoles [54]. All CYP450 enzymes are Mg dependent [11]. Indole derivatives also stimulate butyrate-producing gram-positive bacteria [54].

V. HDL-C

HDL-C has long been linked to longevity [55]. However, more recent studies report that the HDL-CVD relationship is U-shape, i.e., low and extremely high HDL-C levels can entail health risks [56]. Mechanisms underlying this non-linear relationship are presently unknown. However, one study suggests that the capacity of HDL to acquire free cholesterol during triglyceride-rich lipoprotein (TGRL) lipolysis by lipoprotein lipase underlies the non-linear relationship between HDL-C and cardiovascular risk [57]. Lipoprotein lipase (LPL) induced lipolysis removes blood triglycerides. Elevated triglycerides directly compromise the ability of HDL to clear cholesterol, as HDL-C increases above 100 mg/dL. This creates a scenario of elevated but ineffectual HDL-C in a triglyceride rich environment, hypothetically explaining the increase in CVD despite extremely high HDL-C. LPL mediated lipolysis is the rate-limiting step in the removal of triglyceride from the bloodstream [58] and also regulates HDL-C. LPL is Mg dependent [59]. Perhaps a Mg shortfall and its consequent impact on rate limiting LPL contribute to the increase in CVD, despite high HDL-C. Might Mg deficiency compromise the efficacy of elevated HDL-C just as it compromises the efficacy of vitamin D3 (see Figure 2)?

VI. HRV

Serum HDL-C levels correlate with high frequency HRV indices [60]. Low total cholesterol and LDL-C were significantly associated with low frequency HRV indices [61]. Not surprisingly HRV is another well recognized longevity agent [62].

It can predict disease well before symptoms appear [63] and directly reflects vagal tone [64]. Anti-aging butyrate suppresses food intake via vagal signals to the brain [65].

Calorie restriction also improves HRV [66]. The impact of HRV and calorie restriction on longevity suggest that the appetite suppressing properties of butyrogenic gut bacteria via vagal afferents may increase HRV. This has recently been reported [67]. Mg level is positively related to

HRV, while Ca/Mg ratio is negatively related to HRV [68]. Vitamins D and B-12 deficiencies are associated with reduced HRV [69]. The active forms of both are Mg dependent.

VII. Melatonin, Resveratrol, Vitamin C, Tryptophan, Calorie Restriction, α -Ketoglutarate, Methionine Restriction, and Lactate Dehydrogenase

Two popular decades old anti-aging supplements are melatonin and resveratrol. Melatonin can be sourced endogenously from the pineal gland or exogenously. Its synthesis from tryptophan is Mg dependent (see Figure 1). Melatonin opposes CVD and neurodegenerative disease with antioxidant and anti-inflammatory properties [70].

Many of the healthful benefits of resveratrol are mediated by Mg dependent enzymes, e.g., protein and nucleotide kinases. This enables resveratrol to function as anti cancer, antioxidant, anti obesity, anti-dementia, anti-T2DM, and anti CVD [71]. Moreover, resveratrol and quercetin, proven to extend lifespan, are compounds that can also serve as AhR ligands [72].

Mg enhances the anti cancer property of Vitamin C via SCVT (sodium coupled vitamin C transporter) [73,74]. Tryptophan has recently emerged as a longevity agent [75]. It opposes the hyphal morphogenesis of *Candida* [76], associated with decreased healthspan [77]. ATM is characterized by tryptophan depletion and increased K/T ratio and is associated with cancer, dementia, autoimmune disease, and T2DM [78].

Alpha-ketoglutarate is another recently discovered longevity agent, prominent in the Krebs cycle. Its longevity property mimics calorie restriction via dietary restriction and inhibition of ATP synthase [79]. However, Mg enhances the efficacy of calorie restriction [80] and probably α -KG as well. Both depress oxidative stress. In addition the enzymes responsible for the synthesis of α -KG and glutamine from glutamate are both Mg dependent. Any Mg deficiency may increase glutamate, an anti-aging and dementia promoting agent [81].

Methionine restriction (MR) also possesses longevity properties also via a mechanism similar to that of calorie restriction [82]. These include anti-cancer, anti-aging, anti-inflammatory, and anti-obesity [83]. The benefits of MR may be due to reduced oxidative stress and redox status changes through mechanisms not yet discovered [82]. Six of ten enzymes in the Krebs Cycle are dehydrogenases (Mg dependent). These are mitochondrial electron transfer reactions (redox reactions) that also require magnesium dependent B2 as flavin adenine dinucleotide (FAD) and B3 as niacinamide adenine dinucleotide (NAD). MR longevity benefits may be due to a reduction in free radical leakage from mitochondria [82]. B2 and B3 protect mitochondria from oxidative stress, e.g., transsulfuration pathway and glutathione synthesis [84] (see Figure 3). Consequently any Mg shortfall may curtail the longevity benefits of MR. It will curtail production of glutathione, the most powerful human antioxidant (see Figure 3).

Not surprisingly another Mg dependent dehydrogenase, lactate dehydrogenase (LDH), is a longevity biomarker, albeit an inverse one [85]. It converts lactic acid to pyruvate, its most critical function [86]. While blood lactate is bad, gut lactate is good. During exercise blood lactate can enter the gut and feed butyrogenic bacteria [87].

Lactogenic bacteria, e.g., *Bifidobacteria* and *Lactobacilli*, can also crossfeed butyrogenic bacteria, e.g., *Faecalibacterium* and *Roseburia* [88] and lower host lactate levels [89]. Elevated levels of lactate and LDH are linked to cancer (Warburg effect), CVD, dementia, and chronic inflammatory diseases, including Covid-19 [90].

VIII. Methylation

Methylation of certain CpG islands (cytosine paired with guanine) in the DNA epigenome promotes or not the expression of other genes. Aberrant DNA methylation predicts aging [91–93]. Aberrant methylation enhances risks for cancer, dementia, and autoimmune disease [94]. This promotion/suppression mechanism for the epigenome occurs through transfer of methyl groups from SAME to DNA and proteins (see Figure 3). Aberrancy arises when this transfer is compromised. Methylation is compromised by the 677T MTHFR allele, present in most Americans [95], and certain vitamin B deficiencies (see Figure 3). B9 (folate) and B12 (cobalamin), critical to both the folic acid

cycle and the methionine cycle, require methylation for activation. Heterozygous 677T reduces MTHFR activity by 35%, while the homozygous state reduces MTHFR activity by 70% [96]. B2 and B3 are FAD and NAD dependent respectively. Dinucleotides contain two phosphates, incorporation of which requires two ATP-Mg⁺⁺ molecules. To convert inactive B6 (pyridoxine) to its active form (pyridoxal phosphate) also requires phosphorylation (ATP-Mg⁺⁺). Therefore, any Mg deficiency further compromises optimal DNA methylation and accelerates aging.

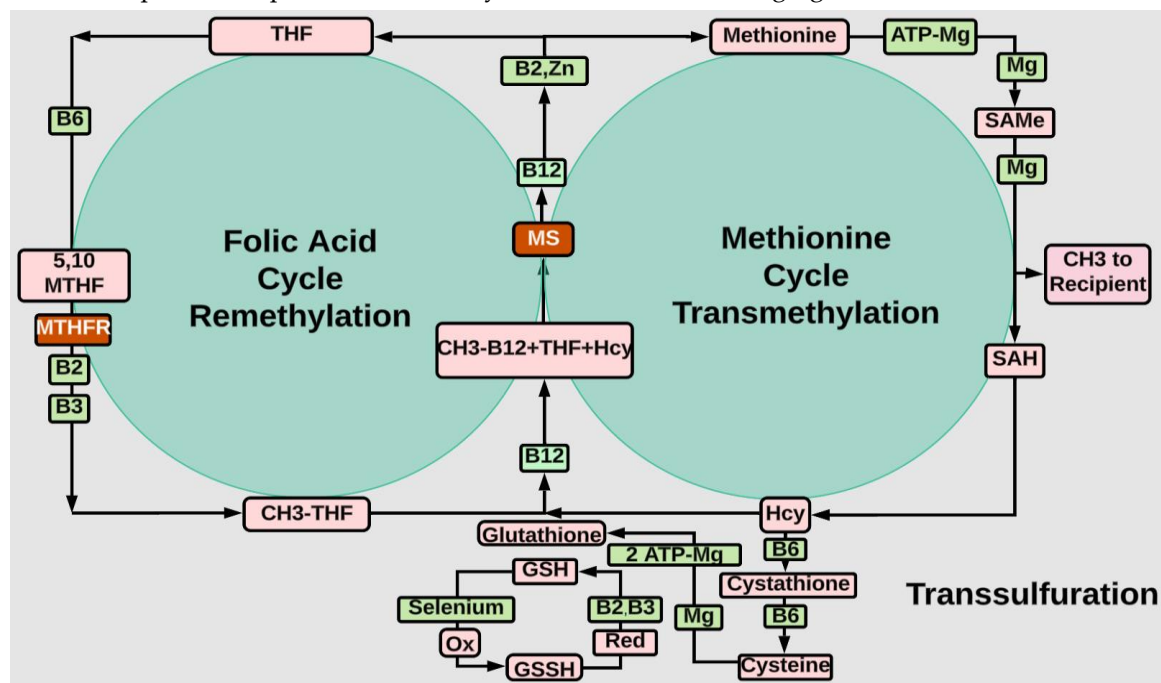


Figure 3. Methylation is the primary promoter/suppressor mechanism for the epigenome. Pink boxes are molecules, green boxes are required cofactors, and red boxes are critical enzymes. MTHFR=methylenetetrahydrofolate reductase, THF=tetrahydrofolate, SAMe=S-adenosyl methionine, SAH=S-adenosyl homocysteine, Hcy=homocysteine, GSH=reduced glutathione, GSSH=oxidized glutathione.

IX. Magnesium

Mg deficiency has been directly linked to aging [97]. It clearly potentiates directly or indirectly many recognized longevity agents. However, it also stands alone as a longevity agent itself, both with respect to biochemistry and to the gut microbiome. Seven of nine enzymes in the glycolytic pathway are Mg dependent. In the Krebs cycle seven of 10 enzymes are Mg dependent. Thus, Mg deficiency negatively impacts ATP production and increases oxidative stress. Mg deficiency is linked to insulin resistance, an early hallmark of cancer, T2DM, and T3DM. Mg is critical to the kynurenine pathway (see Figure 1) and production of NAD⁺. ATM characterizes cancer, dementia, autoimmune disease, and T2DM [78]. Mg dependent phosphoribosyl transferases and adenylyl transferases, key enzymes determining aging [98], convert quinolinic acid (neurotoxic) to NAD⁺ and nicotinamide adenine mononucleotide (NAM) to NAD⁺ respectively (see Figure 1). NAD⁺ decreases with age [99], while Mg deficiency increases with age⁴. Thus, Mg deficiency compromises the ability to recycle NAD⁺, enhancing risks due to stress, inflammaging, disease, and dysbiosis.

ATM is linked to gut dysbiosis [100], which is linked to the gut microbiome [101]. Mg status is also directly linked to gut microbiota. A Mg-deficient diet reduces the abundance of Bifidobacterium. A Mg rich diet increases both biodiversity and the abundance of Bifidobacterium [102]. The Mediterranean diet, rich in Mg, enhances biodiversity and growth of lactobacilli and bifidobacteria [103]. Lactobacillus spp. can significantly increase the bioavailability of magnesium [102]. These lactogenic bacteria (lactobacilli and bifidobacteria) then crossfeed butyrogenic bacteria, increasing butyrate, an emerging longevity agent (see section IC). The gut microbiome of centenarians exhibits

increased activity in the phosphatidyl-inositol pathway and glycosphingolipid biosynthesis [104]. The phosphatidyl-inositol pathway starts with the magnesium dependent conversion of glucose to glucose-6-phosphate. Subsequent pathway steps are also heavily dependent on ATP and cAMP, both of which are Mg dependent. Glycosphingolipid biosynthesis involves glycosyltransferases and glucosidases. Most glycosyltransferases are Mg dependent and some β -glucosidases are enhanced by Mg^{++} [105]. The gut microbiome of the younger elderly shows decreased saccharolytic capacity (aka glucose metabolism) and low levels of SCFAs, tryptophan, indole, and nicotinamide [104]. All of these are longevity agents and have been discussed in depth. Yet awareness of Mg deficiency has always been subordinate to that of Ca, e.g., routine chemistry panels offer Ca but not Mg. Few realize that they are antagonists. Ca:Mg is rarely mentioned.

A. Ca:Mg

The calcium sensing receptor (CaSR) is a Mg dependent G protein coupled receptor activated by Ca^{++} or Mg^{++} [106,107]. Most of the focus between Mg and vitamin D pertains to the criticality of Mg in the synthesis of the sunshine vitamin. But vitamin D improves the absorption of not only Ca but also Mg, although to a lesser extent [108]. The active forms of Ca and Mg are their cations (Ca^{++} , Mg^{++}). Both bind to the CaSR and excess Ca^{++} can competitively inhibit Mg^{++} . In the Western diet Ca outweighs Mg. According to NHANES (National Health and Nutrition Examination Surveys) the mean dietary intake of Ca:Mg for Americans has escalated from 2.6 in 1977 to over 3.0 since 2000. Between 1977 and 2012, US Ca intake increased at a rate 2 - 2.5 times that of Mg [109]. In 1989 Jean Durlach, founder of the International Society for Development of Research on Magnesium, reported that 2.0 was the proper target ratio (circulating cation concentrations in mM). An elevated Ca:Mg ratio is characteristic of cancer, autoimmune disease [110] and ASCVD [111] and this ratio should be maintained between 1.7 and 2.8 [109]. The Oriental diet is typically low in Ca, while the Occidental diet is typically low in Mg [112]. This Ca:Mg imbalance is often overlooked, because a) Mg is not usually included in any lab chemistry panel, b) lower limit on the "normal" range may be too low, c) serum Mg (bound and free) does not reflect Mg^{++} . The median intake of Mg is insufficient to fully exploit the healthful benefits of vitamin D, especially for CVD and colon cancer.[113]. This suggests that the lower limit of "normal" lab serum Mg^{++} values (.75-.95 mM), determined by extensive sampling from this large "healthy" population (50% are deficient), is too low. Several studies have suggested .85 mM, as a lower limit [114,115]. Yet lab range values for serum Mg^{++} in healthy controls remain unchanged, despite repeated alerts over the past two dozen years [116–118]. Another study of 91 participants found that a detailed diet questionnaire predicted suboptimal Mg status in 100%, yet lab testing confirmed this in only 76% [119]. Might this also challenge the validity of .75 mM as a lower limit? This gray zone between .75 and .85 may correspond to low intra-erythrocytic Mg when serum Mg is within normal limits. Initially termed normomagnesemia Mg deficiency [5], it is now known as chronic latent Mg deficit. This has been demonstrated for migraines and PMS [5].

Calculation of serum Mg^{++} in "healthy" individuals with normal renal function, with midrange serum albumin, and without medications can most likely be determined from serum Mg (bound and unbound). If one compares the normal ranges for serum Mg and Ca with the normal ranges for ionized Mg and Ca, they align exactly, but only if Mg^{++} and Ca^{++} represent 70% and 50% of total serum levels respectively. When the midpoints of the ranges for the ionized forms (Ca^{++} = 1.2 mM, Mg^{++} = .6 mM) is determined, the Ca:Mg is 2.0, very much in line with Durlach's recommendation.

This means that if the lower limit of normal for serum Mg were to be raised to .85 mM (2.0 mg/dL), then to maintain this recommended ratio the lower limit of normal for serum Ca should be raised to ~2.4 mM (9.5 mg/dL). This increase in the lower limit of normal Ca in addition to Mg seems appropriate. According to the NIH, data from NHANES 2009-2010 indicated that 42% of Americans did not meet their Estimated Average Requirements for Ca as recommended by the Institute of Medicine [120]. The prevalence of Ca deficiency is even greater in low and middle income countries [121].

B. Magnesium and Covid-19

Ca:Mg > 5.0 is strongly associated with Covid-19 mortality [122]. Mg levels directly correlate with Covid-19 disease for risk of hospitalization, length of stay, mortality, and long Covid [123]. Ca:Mg might even further refine this link with severity. Among individuals less than 65 y with

Ca:Mg > 2.6, reducing the ratio to around 2.3 downregulated the TMRSS2 gene. Decreasing Ca:Mg improved methylation and ameliorated or prevented Covid-19 [124]. Aberrant methylation is not only a biomarker for Covid-19 but also for long Covid [125]. This suggests that those with the 677T MTHFR variant allele (half of Americans) are at greater risk, as has been reported [126].

ACE2 receptor bearing cells are targeted and lysed by SARS CoV2. Intestinal epithelial cells are rich in ACE2 receptors. This is problematic because these receptors must complex with B⁰ATs (neutral or nonpolar amino acid transporters) to enable absorption of tryptophan. Tryptophan, a longevity agent, opposes Candida hyphal morphogenesis [76]. Candida produces its own IDO [76] that competes with host IDO and drives ATM [38] (see Figure 1).

In summary, the dozen or so longevity agents evaluated in this review appear to be linked to Mg, either directly in the synthesis of the agent or indirectly along the relevant metabolic pathway. Although the magnitude of their impact in any individual is complex and impossible to quantitate, their limited presence in those on a Western diet or lifestyle is difficult to deny. Additional longevity agents may yet be discovered, expanding options in our quest for longevity. Figure 4 illustrates their interlinkage.

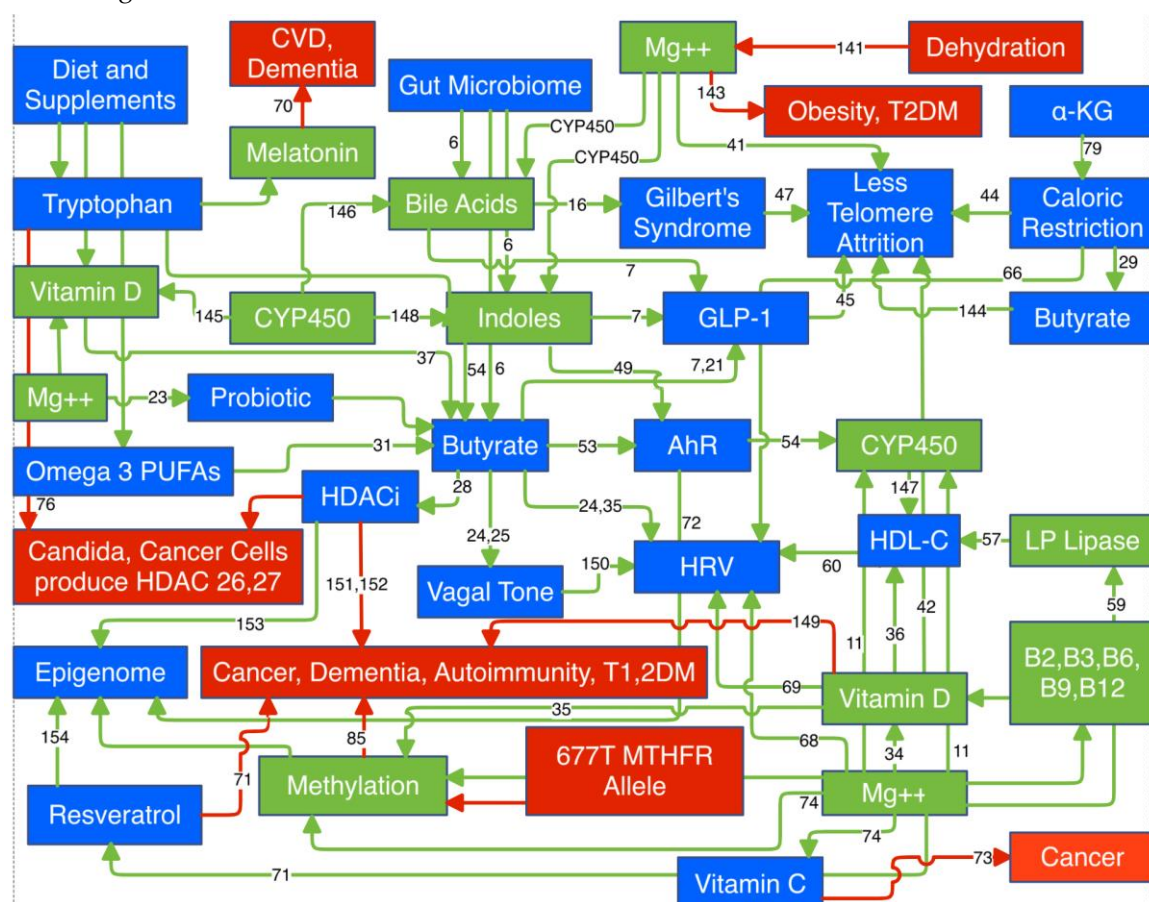


Figure 4. All blue boxes are directly associated with longevity. Green boxes are Mg⁺⁺ dependent. Red boxes are anti-longevity. Green arrows promote and red arrows inhibit. PUFAs=polyunsaturated fatty acids, HDAC=histone deacetylase, GLP=glucagon like peptide, CYP=cytochrome P, AhR=aryl hydrocarbon receptor, HRV=heart rate variability, HDL-C= high density lipoprotein cholesterol, LP=lipoprotein.

C. Therapeutic Interventions

The first step in addressing a potential Mg shortage is to assess Ca:Mg. If greater than 2.6, then efforts must be directed to lowering oral intake of Ca. Otherwise, increasing oral Mg will lower PTH and suppress Mg absorption. Administering a variety of Mg chelates, e.g., glycinate, maleate, taurate, threonate, also enhances absorption. Bowel tolerance should be the limiting factor and should be

approached slowly. Mg citrate is especially noted for its laxative side effect. Combining oral intake of Mg with vitamin D is also helpful.

Mg bioavailability is increased by concomitant intake of the active form of vitamin B, pyridoxal phosphate (PLP) [127]. PLP, but not pyridoxine, appears to form a complex with Mg and hence may enhance the transport or accumulation of Mg in cells [128]. However, several old and recent articles have challenged this beneficial effect of B6 on Mg absorption [129,130], but both employed Magne, which is 300 mg Mg and 30 mg pyridoxine. Another article claimed that B6 enhances erythrocytic Mg but only at high doses and that high doses risk peripheral neuropathy. This study also used Magne [131].

Even the NIH in its Aug 2023 update on B6 failed to acknowledge the efficacy differential between pyridoxine and PLP. Furthermore, taking P5P concomitantly with Mg can potentially double [127] or triple [128] the absorption of Mg. Not only does PLP enhance cellular uptake of Mg but Mg enhances that of PLP [132]. B6 as pyridoxine, the inactive form and the most common form in B supplements, competitively inhibits P5P, the active form, and can cause peripheral neuropathy [133]. B2 as FAD is a Mg dependent and required cofactor for the synthesis of PLP. This means that if B2 is deficient without PLP supplementation, then B6 supplementation as pyridoxine can cause symptoms of B6 deficiency. Synthesis of PLP is also Mg dependent.

Not surprisingly B vitamins are linked to longevity [134]. Of the eight, six require Mg to attain activated status. B1 as thiamine pyrophosphate, B2 as FAD, B3 as NAD, and B6 as pyridoxal phosphate require phosphorylation. B9 and B12 require methylation. All phosphorylation and methylation reactions require Mg. All five of these B vitamins are critical to methylation (see Figure 3). The value of a prebiotic, e.g., sauerkraut, kimchi, D-mannose, probiotic, e.g., yogurt, and postbiotic, e.g., butyrate, in the quest for a better gut microbiome and healthful longevity cannot be underestimated. Fecal microbiota transplantation has shown significant efficacy in treating cancer [135], autoimmune disease [136], and dementia [137]. This suggests that it is never too late to upgrade your gut microbiome in any therapeutic approach to disease, much less any preventative one (see Figure 4).

Conclusions

Bile acids and HDL-C are longevity agents that necessitate hepatic metabolism by magnesium dependent CYP450 enzymes. Production of indoles by gut bacteria also require magnesium dependent CYP450 enzymes. Syntheses of the active forms of vitamins D,B1,B2,B3,B6,B9, and B12 are magnesium dependent. These activated B vitamins and Mg⁺⁺ are all required cofactors in the remethylation (folate) and transmethylation (methionine) cycles, critical to the epigenome. Any shortfall in Mg status will weaken methylation and exacerbate the significant health problems associated with the MTHFR 677T variant allele, present in the majority of Americans (see Figure 3). Aberrant methylation compromises the immune response to SARS CoV2 and increases risk for long Covid. Mg actively suppresses obesity and T2DM. The longevity properties of Mg are highly dependent on Ca:Mg, rarely mentioned in contrarian reviews on the benefits of vitamin D or Mg supplementation. Compromised recycling of NAD⁺ due to Mg deficiency (see Figure 1) and upregulation of IDO by host IFN-gamma, cancer cells, and Candida drive ATM, linked to cancer, dementia, autoimmune disease, T2DM, oxidative stress, inflammaging, and dysbiosis are all opposed by a healthy gut microbiome. Health problems related to normomagnesemia Mg deficiency, e.g., migraines and premenstrual syndrome, challenge the validity of the accepted lower limit for serum Mg. Multiple interlinked biomarkers indicative of healthful aging are Mg dependent. Mg potentiates the healthful benefits of the gut microbiome and vice versa. Unfortunately Mg status has steadily declined primarily due in part to

- 1) the deteriorating quality of our food
- 2) the popularity of refined carbohydrates and alcohol
- 3) the prevalence of antibiotics and other medications, e.g., proton pump inhibitors
- 4) the high Ca:Mg in supplements (mean ratio of 2.9 in those containing both) [138], even higher in women
- 5) the lack of Mg awareness (not on routine chemistry panels)

- 6) the absence of exercise (reduces aldosterone) [139]
- 7) the increasing tendency toward obesity (increases aldosterone) [140]
- 8) the presence of widespread, unrecognized, mild, chronic dehydration (aldosterone) [141]
- 9) Stress (cortisol also activates mineralocorticoid receptors) [142].

Although the discussed biochemistry and physiology are generally accepted, convincing clinical data, adjusted for D3 and Ca status, supporting the underappreciated role of Mg in longevity awaits.

“Every known illness is associated with a magnesium deficiency,”

Norman Shealy, Father of Holistic Medicine

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