

Review

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Magnesium and Longevity

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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 a required cofactor for over 800 enzymatic reactions (as of 2022). This review does not correlate Mg status with clinical data on agents linked to longevity. The approach is physiologic and highlights specific Mg dependent 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 five 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.

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 a requirement for over 800 enzymatic reactions¹, not just the frequently quoted 300 enzymatic reactions. It is involved in over 80% of known metabolic functions². The dominance of so many Mg dependent enzymes may in part explain why many Mg deficiency symptoms mimic those of aging³. Mg deficiency has long been connected to cellular senescence⁴. 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 Mg⁵, 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 acids⁶. Each triggers secretion of GLP-1⁷. 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 weight¹⁰. 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 dependent¹¹. These primary bile acids must be deconjugated before gut bacteria can dehydroxylate and dehydrogenate them to produce secondary bile acids¹². A central pathway in the production of secondary bile acids by gut bacteria is 7-alpha dehydroxylation¹³. 7-dehydroxylated bile acids are the most potent agonists for host bile acid receptors¹⁴. This makes the subsequent 7-alpha dehydrogenation equally significant. This latter reaction is significantly enhanced by Mg¹⁵. 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 bilirubin¹⁶. 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 controls¹⁷. 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 acids¹⁸. Nonetheless, production of primary bile acids is critical and Mg deficiency compromises this. Bile acid production decreases with age¹⁹, as do Mg levels. Indeed the symptoms of Mg deficiency reflect those of aging³.

A. 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 lifespan²⁰ (see figure 1).

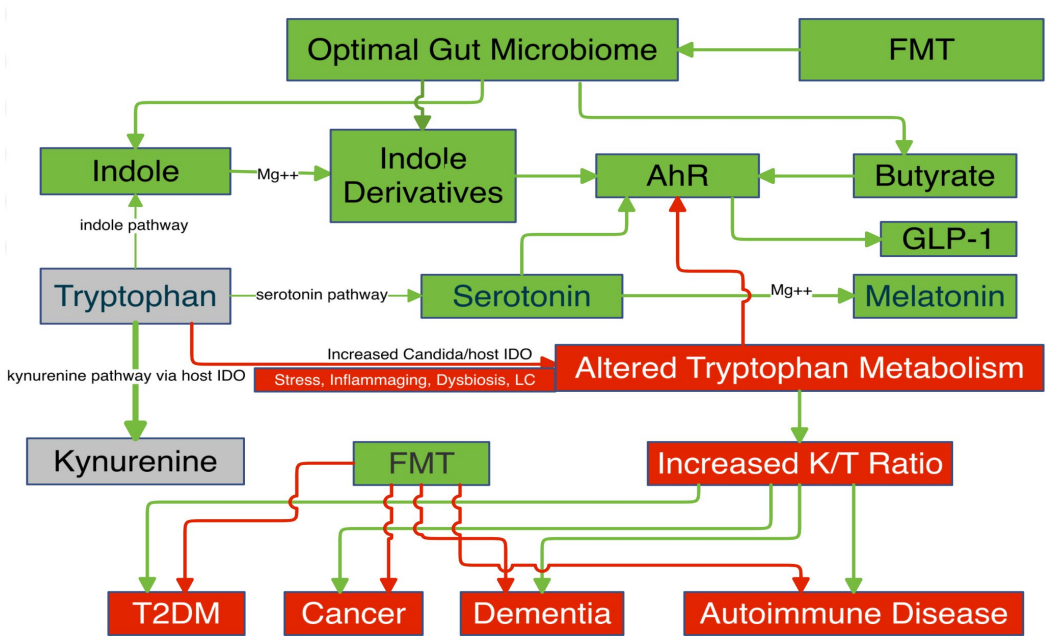


Figure 1. AhR=aryl hydrocarbon receptor, LC=long Covid, FMT=fecal microbiota transplantation, K/T=kynurenine to tryptophan, T2DM=type 2 diabetes, GLP=glucagon like peptide, red arrows, boxes => unfavorable, green arrows, boxes => favorable.

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++ dependent¹¹. Indoles also induce the release of GLP-1, known to suppress appetite, increase insulin secretion and slow gastric emptying⁸. Indoles are also ligands for aryl hydrocarbon receptors (see section IV), another longevity agent conduit.

A. Butyrate

Butyrate is another GLP-1 agonist²¹ and an aryl hydrocarbon ligand. Both are longevity indicators. Probiotics, rich in butyrogenic bacteria, are associated with longevity²² and Mg enhances probiotic efficacy²³. 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 HDACi²⁸ and may also mediate the efficacy of calorie restriction in enhancing longevity²⁹. Gut microbiota cannot produce SCFAs in the absence of Mg³⁰. Omega 3 fish oils upregulate SCFA production, especially butyrate³¹ and enhance biodiversity³².

I. Vitamin D

Vitamin D is another well recognized longevity agent³³ and Mg is critical to its synthesis³⁴. 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).

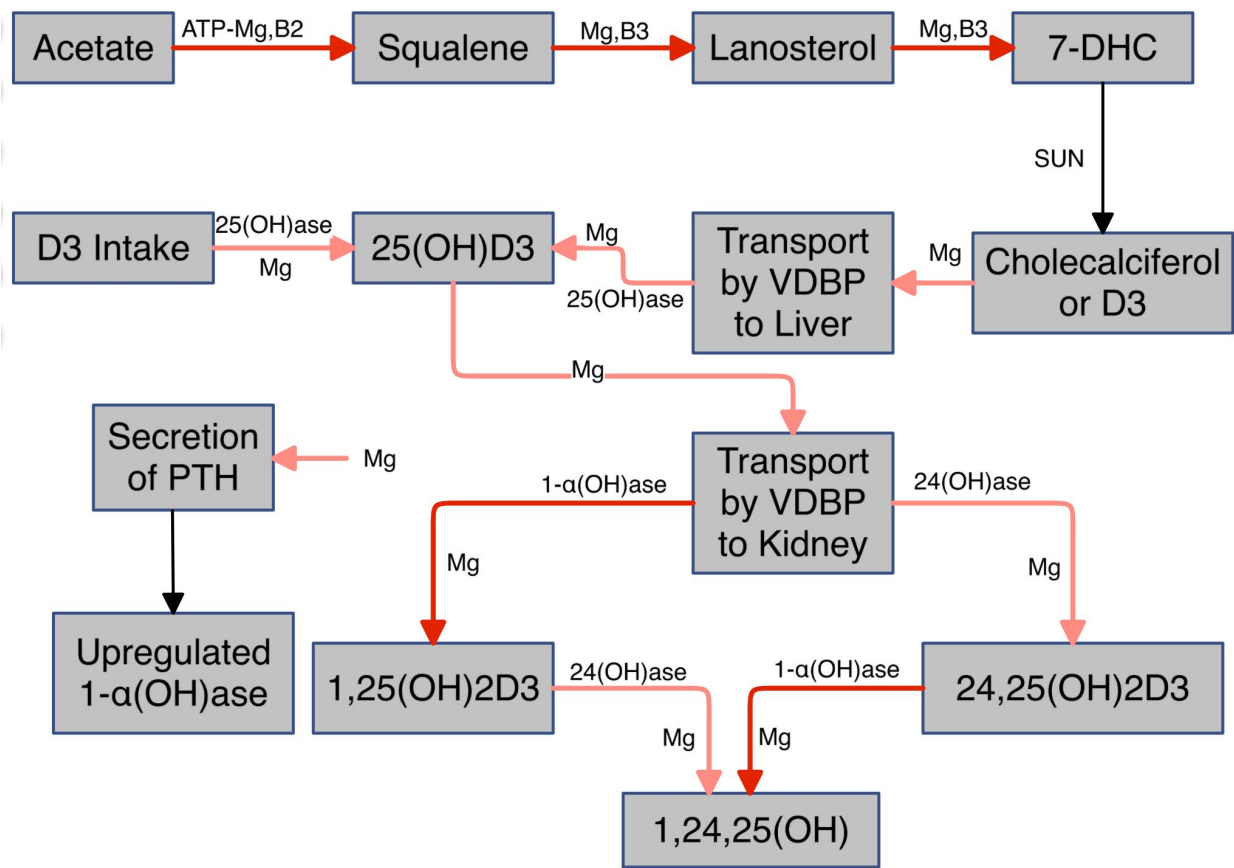


Figure 2. This sterol biosynthetic pathway for cholecalciferol decreases with age and is further challenged by Mg deficiency. Intensity of red arrows indicates the impact of Mg deficiency. DHC=dehydrocholesterol, PTH=parathormone, VDBP=vitamin D binding protein, D3=cholecalciferol.

Vitamin D efficacy in longevity is linked to its healthful effects on methylation and the epigenome³⁵. Vitamin D supplementation reduces total cholesterol, low density lipoprotein (LDL) cholesterol, and triglyceride levels but not HDL-C levels³⁶ (see section V). Vitamin D reversibly

improves the gut microbiome³⁷. D3 directly inhibits *Candida* hyphal morphogenesis. *Candida* can produce its own IDO, which redirects and alters tryptophan metabolism (ATM)³⁸.

I. Telomeres

The link between telomere length and mortality, like HDL-C (section VI), 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 cancers³⁹. Telomeres shorten with age (attrition) and longevity is characterized by less telomere attrition, i.e., longer telomeres v those less long lived⁴⁰. This shortening is due to loss of telomere homeostasis with cellular senescence. Mg maintains telomere homeostasis⁴¹. Anti-aging agents and conditions that delay telomere shortening include vitamin D⁴², dietary Mg⁴³, calorie restriction⁴⁴, and GLP-1⁴⁵. Telomere attrition is influenced by oxidative stress, inflammation, insulin resistance, and hyperglycemia, well controlled by GLP-1⁴⁶. Gilbert's Syndrome also manifests less telomere attrition⁴⁷. Regulation of telomerase and telomere homeostasis is subject to epigenetic control and DNA methylation⁴⁸ (see section VIII).

I. AhR

Recently the vital role of aryl hydrocarbon receptors (AhRs) in aging⁴⁹, dementia, autoimmune disease, cancer⁵⁰, and ASCVD⁵¹ 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 this⁴⁹ and promote longevity. ATM inactivates the immune response dependent function of AhR⁵². Not only are indoles and butyrate AhR ligands⁵³, but subsequent AhR activation induces cytochrome CYP450 enzymes that facilitate gut absorption of indoles⁵⁴. All CYP450 enzymes are Mg dependent¹¹. Indole derivatives also stimulate butyrate-producing gram-positive bacteria⁵⁴.

I. HDL-C

HDL-C has long been linked to longevity⁵⁵. 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 risks⁵⁶. 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 risk⁵⁷. 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 bloodstream⁵⁸ and also regulates HDL-C. LPL is Mg dependent⁵⁹. 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 just as it compromises the efficacy of vitamin D3?

I. HRV

Serum HDL-C levels correlate with high frequency HRV indices⁶⁰. Low total cholesterol and LDL-C were significantly associated with low frequency HRV indices⁶¹. Not surprisingly HRV is another well recognized longevity agent⁶².

It can predict disease well before symptoms appear⁶³ and directly reflects vagal tone⁶⁴. Anti-aging butyrate suppresses food intake via vagal signals to the brain⁶⁵.

Calorie restriction also improves HRV⁶⁶. 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 reported⁶⁷. Mg level is positively related to HRV, while Ca/Mg ratio is negatively related to HRV⁶⁸. Vitamins D and B-12 deficiencies are associated with reduced HRV⁶⁹. The active forms of both are Mg dependent.

Melatonin, Resveratrol, Vitamin C, Tryptophan, and α -Ketoglutarate

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 properties⁷⁰. 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 CVD⁷¹. Moreover, resveratrol and quercetin, proven to extend lifespan, are compounds that can also serve as AhR ligands⁷². 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 agent⁷⁵. It opposes the hyphal morphogenesis of *Candida*⁷⁶, associated with decreased healthspan. ATM is characterized by tryptophan depletion and increased K/T ratio and is associated with cancer, dementia, autoimmune disease, and T2DM⁷⁸. Alpha-ketoglutarate is another recently discovered longevity agent, prominent in the Krebs cycle. Its longevity property mimics calorie restriction via inhibition of ATP synthase⁷⁹. However, Mg enhances the efficacy of calorie restriction⁸⁰ and probably α -KG as well. 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 agent⁸¹.

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^{82,83,84}. Aberrant methylation enhances risks for cancer, dementia, and autoimmune disease⁸⁵. 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 Americans⁸⁶, 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%⁸⁷. B2 and B3 are FAD (flavin adenine dinucleotide) and NAD (niacinamide adenine dinucleotide) dependent respectively. Dinucleotides contain two phosphates, incorporation of which requires two ATP-Mg⁺⁺ molecules. The active form of B6 also requires phosphorylation (ATP-Mg⁺⁺). Therefore, any Mg deficiency further compromises optimal DNA methylation and accelerates aging.

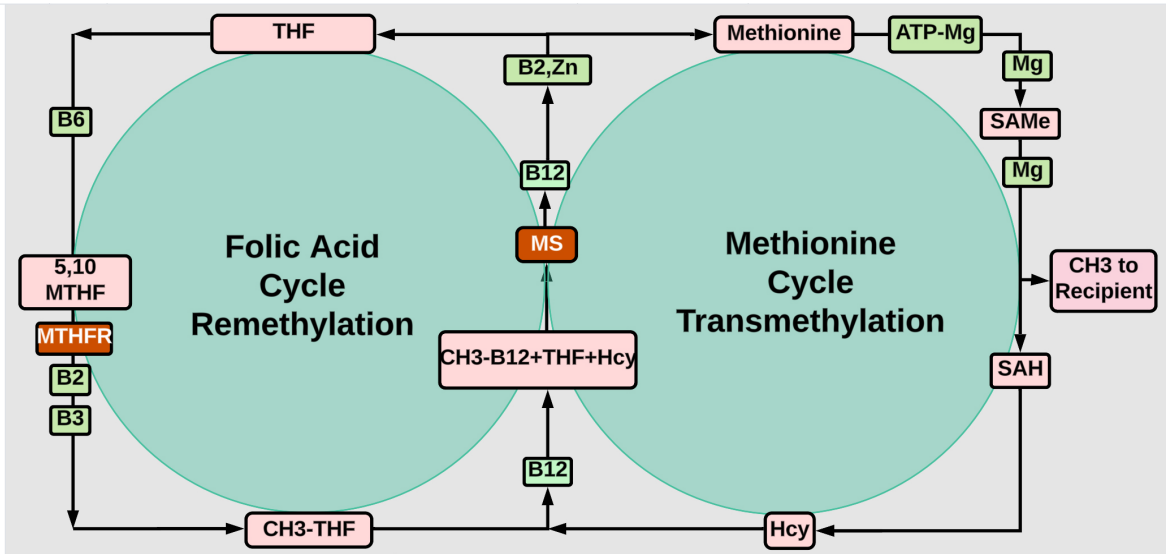


Figure 3. Methylation is the primary promoter/suppressor mechanism for the epigenome. Pink boxes are molecules, green boxes are required cofactors, and red boxes are critical enzymes.

MTHFR=methylenetetrahydrofolate reductase, THF=tetrahydrofolate, SAMe=S-adenosyl methionine, SAH=S-adenosyl homocysteine, Hcy=homocysteine.

I. Magnesium

Mg deficiency has been directly linked to aging⁸⁸. However, the general consensus seems to be that Mg deficiency triggers altered Ca homeostasis. 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^{++} ^{89,90}. 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 extent⁹¹. 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 Mg⁹². 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 disease⁹³ and ASCVD⁹⁴ and this ratio should be maintained between 1.7 and 2.8⁹². The Oriental diet is typically low in Ca, while the Occidental diet is typically low in Mg⁹⁵. 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 cancer⁹⁶. 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^{97,98}. Yet lab range values for serum Mg^{++} in healthy controls remain unchanged, despite repeated alerts over the past two dozen years^{99,100,101}. 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%¹⁰². 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 deficiency⁵, it is now known as chronic latent Mg deficit. This has been demonstrated for migraines and PMS⁵.

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 Medicine¹⁰³. The prevalence of Ca deficiency is even greater in low and middle income countries¹⁰⁴.

A. Magnesium and Covid-19

Ca:Mg > 5.0 is strongly associated with Covid-19 mortality¹⁰⁵. Mg levels directly correlate with Covid-19 disease for risk of hospitalization, length of stay, mortality, and long Covid¹⁰⁶. 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 TMPRSS2 gene. Decreasing Ca:Mg improved methylation and ameliorated or prevented Covid-19¹⁰⁷. Aberrant methylation is not only a biomarker

for Covid-19 but also for long Covid¹⁰⁸. This suggests that those with the 677T MTHFR variant allele (half of Americans) are at greater risk, as has been reported¹⁰⁹.

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.

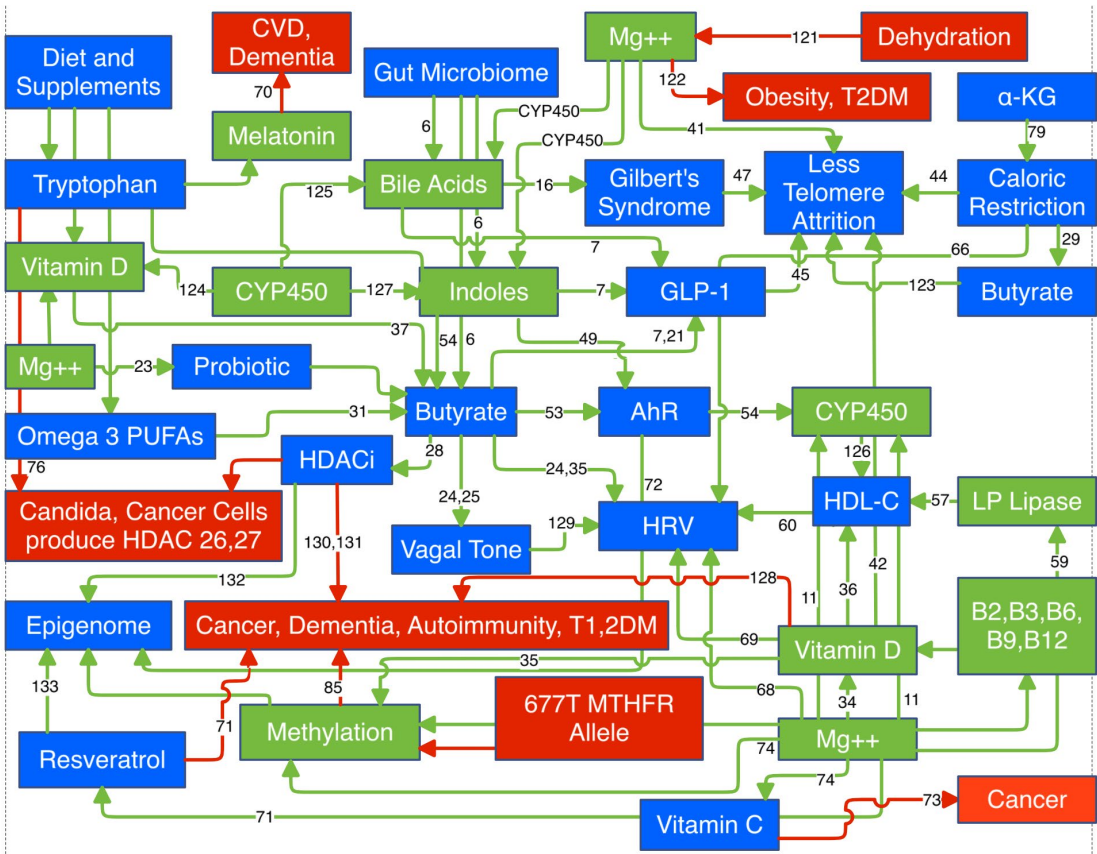


Figure 4. All blue boxes are directly associated with longevity. Green boxes are Mg++ dependent. Red boxes are anti-longevity. Green arrows promote and red arrows inhibit. PUFAs=polyunsaturated fatty acids, HDAC=histone deacetylase, GLP=glucagon like peptide, CYP=cytochrome P, AhR=aryl hydrocarbon receptor,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

A. 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)¹¹⁰. PLP, but not pyridoxine, appears to form a complex with Mg and hence may enhance the transport or accumulation of Mg in cells¹¹¹. However, several old and recent articles have challenged this beneficial effect of B6 on Mg absorption^{112,113}, 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 Magne¹¹⁴.

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 double¹¹⁰ or triple¹¹¹ the absorption of Mg. Not only does PLP enhance cellular uptake of Mg but Mg enhances that of PLP¹¹⁵. B6 as pyridoxine, the inactive form and the most common form in B supplements, competitively inhibits P5P, the active form, and can cause peripheral neuropathy¹¹⁶. 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 longevity¹¹⁷. Of the eight, five require Mg to attain activated status. 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 cancer¹¹⁸, autoimmune disease¹¹⁹, and dementia¹²⁰. 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, 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. Magnesium potentiates the healthful benefits of the gut microbiome. It 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. Health problems related to normomagnesemia Mg deficiency, e.g., migraines and premenstrual syndrome, challenge the validity of the accepted lower limit for serum Mg. Although the discussed biochemistry and physiology are generally accepted, convincing clinical data supporting the underappreciated role of Mg in longevity awaits.

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