Review Article

Magnesium Deficiency Accelerates Aging and Shortens Healthspan

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The global population is undergoing an expanding epidemic of T2DM. Insulin resistance (IR) is at its center. IR is linked to many age-accelerating hormones and magnesium deficiency (MgD) is tightly linked to IR. Deficiencies of multiple vitamins, including A, B1-3,5,6,9,13, D, and E are tied to MgD, as Mg is linked to their activation. Optimal signaling of Mg dependent G-protein coupled receptors (GPCRs), the largest family of membrane proteins, extends healthspan. Indeed Mg is critical to most human metabolic functions. MgD increases the kynurenine to tryptophan (K/T) and the Ca:Mg ratios, both biomarkers for inflammaging, and has a strong connection to many cancers, cardiovascular disease (CVD), dementia, autoimmune/infectious disease, and obesity. Mg is directly linked to an optimal gut microbiome and potentiates the benefits of butyrate. Yet despite these associations between accelerated aging/healthspan and MgD, laboratory reference ranges continue to accept clinical MgD as within normal limits. Mg depleted soil and Western diets further exacerbate the epidemic, as does decreased absorption with age. The physiologic capacity of Mg is extensive and complex. Accordingly, this limited but focused narrative review attempts to link some of the deleterious effects of a long-term Mg shortfall with the premature symptoms of aging and a shortened healthspan.

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I. Introduction

Healthspan measures not the number of years a person lives (lifespan) but the number in good health. Similarly healthcare accentuates prevention and lifestyle modifications, while medical care is more reactive, accentuating treatment. MgD may represent the great divide. For example, Mg dependent GPCRs are the largest family of membrane proteins (800) encoded in the human genome. GPCRs are an important drug target, as over ⅓ of all Food and Drug Administration (FDA) approved drugs target GPCRs [1]. Aging is

the result of a complex combination of many pathophysiological processes. Mg deficiency can accelerate many symptoms of aging, frequently called the dwindles, from diminishing recall [2] to sight, taste, smell, behavior, mood, immune system regulation, fatigue, depression, loss of appetite [3], and sarcopenia [4] to a shorter lifespan. Mg is a required cofactor for over 600 different enzymes, It is required for the activation of perhaps another 200. A small subset of these enzymes involve ATP and energy metabolism. Mg is also required for the vast majority of functions involving GTP, which drives GPCR signaling.

Several prominent hormones have been implicated as accelerants. IR due to Mg deficiency may represent the primary, consolidating feature. Appreciation for the vital role of Mg in health and disease is becoming mainstream. Initially this was limited to its function as a required cofactor for many enzymes. That list has continued to grow. Its criticality to reactions involving ATP/GTP and their cousins ADP, cAMP, GDP, and cGMP is less widely appreciated. ATP driven reactions and GPCR driven transmembrane/intracellular signaling deteriorate with age.

Optimal signaling plays a vital role in maintaining glucose homeostasis and preventing IR [5], thereby extending healthspan [6]. Accordingly interest in Mg status as a determinant of and prognosticator for aging and healthspan is rapidly expanding [7].

The linkage between aging and magnesium deficiency has only recently been exposed [8]. The present perspective is much more reliant on a biochemical and physiologic approach. Although accepted and well established, many of the interlinking details presented in this review are not well known and have only recently been revealed. Research on this topic was limited to a search of peer reviewed medical journal articles for relevant terms.

II. MgD and inflammaging/oxidative stress/insulin resistance

MgD plays a multifactorial role in promoting IR. It is not only associated with β-cell-dysfunction-induced IR [9], but also post receptor IR. Chronic inflammaging is at the heart of this. The intimacy of Mg and the glycolytic pathway is underscored by Mg dependency of over half the enzymes. MgD is tightly linked to mitochondrial dysfunction and an electron transport system that relies on Mg dependent NAD and FAD with consequent increase in ROS and oxidative stress [10].

Mg suppresses NF-kB, an inflammatory transcription factor, via blockade of Ca channels [11]. MgD induces a pro-inflammatory state with elevations of pleiotropic cytokines, e.g., IL-1, IL-6, TNF-α [12]. Hypothetically these changes may work in concert with an elevated K/T to up-regulate pleiotropism - TGF-β transits

from anti-tumor to tumorigenic and desmoplastic in the TME [13][14], while IFN-γ transits from anti-inflammatory to pro-inflammatory, driving autoimmune disease [15] and dementia [16]. Butyrate, a short chain fatty acid that characterizes a healthy gut microbiome, immuno-modulates IFN-γ [17] and TGF-β (transforming growth factor), which are reciprocals and counterbalance each other [18][19].

The direct link between MgD and IR is well documented. The growing global incidence of IR plays a key role in the development of T2DM, cardiovascular diseases, and obesity-related conditions [20][21]. It is also directly linked to many age accelerating hormones.

III. IR and Age Accelerating Hormones

MgD enhances the ill effects of ACTH, GH, TSH, angiotensin II, aldosterone, and obesity, well known age accelerating hormones. GPCRs are well known cell membrane receptors, but recently intracellular receptors on endoplasmic reticulum (ER), mitochondria, and other organelles [22] have been described, further expanding the impact of MgD.

ACTH directly induces IR [23] and IR elevates ACTH, GH, TSH, RAAS, obesity, and IR [24]. Cortisol, induced by stress, may be the primary culprit [25][26][27][28]. Furthermore, 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2), that converts active cortisol to its inactive form, cortisone, is Mg-dependent [29]

The relationship between MgD and growth hormone releasing hormone receptor (GHRHR) versus Insulin-like Growth Factor-1 Receptor (IGF-1R) is complex. GH and IGF-1 have a reciprocal (negative feedback) relationship. GH is considered a longevity agent, and the offspring of centenarians generally have lower IGF-1 levels [30]. GHRHR is a Mg dependent GPCR, while IGF-1R is a Mg dependent receptor tyrosine kinase (RTK). MgD may down-regulate RTK and IGF-1 more than GHRHR (GPCR) and GH. This may disrupt the feedback loop to the point of GH resistance [31]. GH resistance may be likened to IR, which involves GPCRs that modulate glucose-induced insulin secretion and insulin receptors that are RTKs.

IR is linked to hyperthyroidism [32]. Thyroid hormones T3 and T4 maintain a fine balance of glucose homeostasis by acting as insulin agonist and antagonist [33]. Both hypothyroidism and hyperthyroidism can increase IR, not only in overt thyroid dysfunction but also in subclinical disorders or even alterations of hormone levels in the reference range (like Mg) [34]. Hyperthyroidism may also increase magnesuria [35].

RAAS activity and IR have a positive bidirectional relationship [36][37]. Secretion of angiotensin II and aldosterone are Ca dependent processes. Mg is a Ca channel blocker [38]. Aldosterone may not only increase blood pressure but also increase magnesuria [39]. This is why hydration is so vital. Thus, the relationship between RAAS and MgD is also bidirectional. Increased RAAS activity, MgD, and IR all conspire to accelerate aging [40][41]

Obesity can cause IR [42]. One study on long-term obesity demonstrated accelerated aging that exceeded chronological age by 15% to 48% [43]. IR can lead to obesity, i.e., the relationship is bidirectional [44]. Obesity is independently linked to MgD [45] and irrespective of obesity, hyperglycemia is associated with hypomagnesemia [46]. Direct correlation of obesity with MgD is dependent on fat distribution - higher correlation in central obesity and lower in peripheral obesity [47]

IV. MgD and ATP/GTP, GPCRs

GPCR signaling directly impacts aging [48] and impacts vision, taste, smell, memory, mood, sleep, hormones, neurotransmission, and many other functions [49]. There are two types of GPCR's - GTP dependent and GTP independent. The vast majority of GPCRs are GTP dependent, while most GTP independent GPCRs are kinase dependent. All GTP dependent GPCRs require Mg, and the vast majority of kinases are Mg dependent. Although GPCRs are primarily cell membrane localized, some have intracellular capabilities, affecting learning and memory [50], pain (ER) [51] and energy (mitochondria) [52]

Although MgD should theoretically reduce the intracellular GPCR activity, it appears that MgD has a greater impact downstream. As a calcium channel blocker, the absence of sufficient intracellular Mg enables overexpression of some Ca-mediated, age accelerating hormones, e.g., angiotensin II, catecholamines [53][54]. The primary mechanism is the chronic inflammation, oxidative stress, and cellular senescence that they induce.

V. MgD and K/T, Ca:Mg, Gut Microbiome

A. K/T

In a 2023 poll of over 1000+ Americans aged 18 or older, ⅔ suffer some degree of gut dysbiosis or imbalanced gut microbiota. An elevated K/T is tightly linked to gut dysbiosis [55]

Given the indiscriminate use of antibiotics, Candida overgrowth may be a leading culprit in causing gut dysbiosis. Candida albicans can produce its own indoleamine dioxygenase (IDO) that governs the rate limiting step in conversion of tryptophan to kynurenine (see figure 1). IFN-γ upregulates IDO and plays a prominent role in the "tryptophan steal" that drives the kynurenine pathway. This reduces indole pathway activity, compromising production of multiple longevity agents produced by intestinal microbiota. Tryptophan hydroxylase is the rate-limiting enzyme for the serotonin pathway and involves the conversion of tryptophan to 5-hydroxytryptophan. This enzyme can be inhibited by stress, IR, MgD, vitamin B6 deficiency, or increasing age. The result is often some degree of depression and insomnia [56].

Mg is required for conversion of neurotoxic quinolinic acid to NAD by quinolinate phosphoribosyl transferase [57] (see figure 1). Other kynurenine pathway metabolites are also neurotoxic and can trigger N-methyl-D-aspartate (NMDA) receptors. Mg inhibits these glutamatergic excitatory receptors by blocking calcium channels [58]

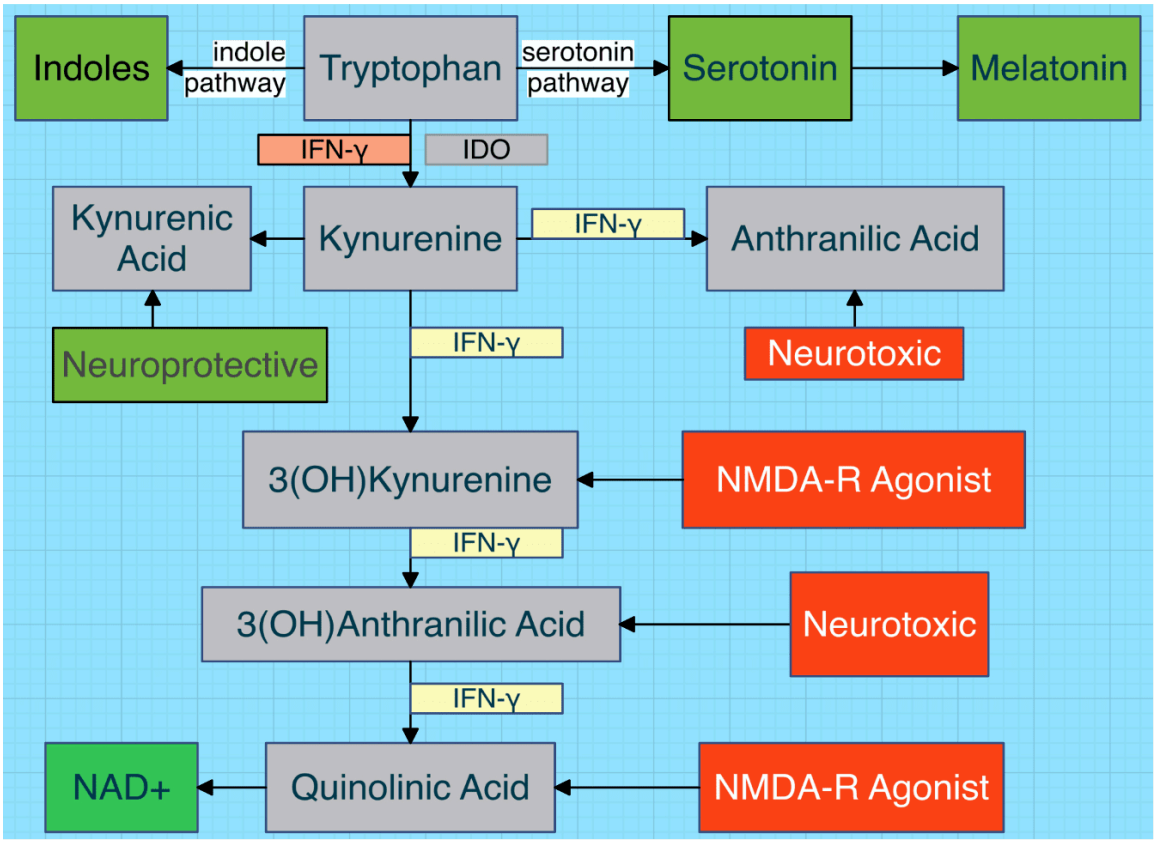

Figure 1. Altered tryptophan metabolism (ATM) is demonstrated. NMDA-R is an excitatory glutamate receptor. Note the upregulating presence of the proinflammatory cytokine IFN-γ driving ATM.

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ATM is tightly correlated with cancer, dementia, CVD, obesity, autoimmune/infectious disease (including COVID-19 complications), and post-COVID syndrome [59]

B. Ca:Mg

Ca and Mg compete for the same receptor, the calcium sensing receptor (CaSR), which is also a GPCR. An elevated Ca:Mg plagues those partial to processed foods and carbonated colas. According to NHANES, this ratio has continuously exceeded 3.0 since 2000. Jean Durlach founded the International Society for Magnesium Research in 1970. In 1989 he established 2.0 weight to weight intake as the target ratio based on physiologic considerations. Authorities in Mg research have repeatedly reinforced this figure based on clinical grounds [60].

Ca:Mg > 5.0 was strongly linked with death from COVID-19 [61]. Given the fact that hypocalcemia is a biomarker for Covid-19 hospitalization, MgD must be extremely low to induce such elevated Ca:Mg ratios in those with severe COVID-19 [62]. This may reflect dysfunctional Mg dependent CaSRs and deficient Mg dependent vitamin D. Odds ratios for cancer, dementia, CVD, obesity, autoimmune/infectious disease (including COVID-19 complications), and post-COVID syndrome increase when imbalanced and outside the recommended 1.7<Ca:Mg<2.6 range [60][63]

Evaluating Mg status is complicated due to the competition between iCa and iMg for the same receptor (CaSR). The Ca:Mg ratio is the only biomarker that accurately reflects this. This ratio, calculated by comparing serum Ca with serum Mg after converting from mg/dL to mmoles/L and adjusting for ionization rates, should range from 1.7 to 2.5 in healthy individuals. By comparing the reference range for serum iCa by ion sensitive probe with the reference range for serum Ca yields about 50% ionization. The rate is about 70% for Mg. Alternatively, one can determine intra-erythrocytic Mg, a more accurate representation of intracellular magnesium. RBC Mg concentration is usually three times higher than that in serum [64]. Optimal RBC Mg should be about 6.0 mg/dL [65]. Therefore, optimal serum Mg should be about 2.0 mg/dL or .83 mM Mg or about 0.58 mM iMg. In one NHANES study of almost 10,000 followed for over 18 years the hazard ratio for T2DM was 1.20 when serum Mg was between 0.80 and 0.84 mmol/L and 1.51 when it was <0.80 mmol/L [66]. Serum Mg level below 0.80 mmol/L increased COVID-19 mortality by 29% and the risk of developing post-COVID syndrome by 114% [67].

Normo-magnesemic magnesium deficiency, first described by Mansmann in 1993, but now called chronic latent magnesium deficiency, i.e., serum Mg .75-.85 mmoles/L, is linked to migraines and premenstrual

syndrome [68]. Other studies have underscored this same association between IR and marginal MgD via magnesium depletion score [69]

Yet serum Mg is not available on any routine laboratory chemistry panel. This is partially due to the lack of a reliable indicator for the hospitalized patient and its tight linkage to serum calcium, which alters its efficacy. However, in the general public the ratio of serum calcium to serum Mg in mM offers a widely underappreciated biomarker of general health. An imbalanced Ca:Mg ratio is interlinked with the gut microbiome and many diseases, including cancer, dementia, CVD, autoimmune disease, and infectious disease. It is even linked to obesity. Western culture facilitates the intake of too much Ca and too little Mg.

C. Gut Microbiome

Gut dysbiosis compromises absorption and increases permeability, K/T, and Ca:Mg. An increasing K/T may limit tryptophan, which otherwise inhibits hyphal morphogenesis and may suppress gut dysbiosis due to Candida overgrowth [70]. Gut dysbiosis is also tied to IR [71] and inflammaging [72]

Commensal bacteria produce butyrate, which can down-regulate the expression of IDO in intestinal epithelial cells. Butyrate immuno-modulates IFN-γ [17] and TGF-β (transforming growth factor), which are reciprocals and counterbalance each other. The former is loosely linked to autoimmune disease and dementia, while the latter favors cancer and fibrosis. Estrogen up regulates IFN-γ [18]. IDO is more than an enzyme. It can also function as an intracellular signal transducer [73][74][75], upregulated by TGF-β. Although some bacteria can produce IDO, only mammalian IDO and fungal IDOs show high efficiency for tryptophan degradation [76][77]. IDO exerts immunosuppressive effects in the microenvironment [78]. Many different tumors can produce their own IDO [79].

Butyrate, as a ligand for three different GPCRs, strengthens the intestinal barrier and prevents translocation of harmful pathogens [80]. Butyrate downregulates the kynurenine pathway (host), thereby indirectly upregulating the indole pathway (gut microbiota) (see figure 1).

Tryptophan metabolites from the kynurenine pathway are ligands for the aryl hydrocarbon receptor that are implicated in pathophysiological processes, such as tumor immunotolerance [81], while those from the indole pathway are ligands for the AhR that improve T cell function, inhibiting tumor growth [82]

Mg dependent vitamin A and D are critical to the health of the gut microbiome [83]. Conversion of β carotene to its active form of vitamin A requires Mg dependent NAD dependent alcohol dehydrogenase and Mg dependent aldehyde dehydrogenase. B vitamins are also vital to the health of the gut microbiome [84].

B1,2,3,5,6,9,12, and A all require Mg for activation. Some intestinal bacteria can produce all eight B vitamins [85], and up to 65% of human gut microorganisms can synthesize at least one type of B vitamin [86]. Some can also produce retinoic acid (vitamin A) [87], but Mg is still needed for activation. All forms of vitamin D (solar substrate, storage form, and active form) (see figure 2) require Mg.

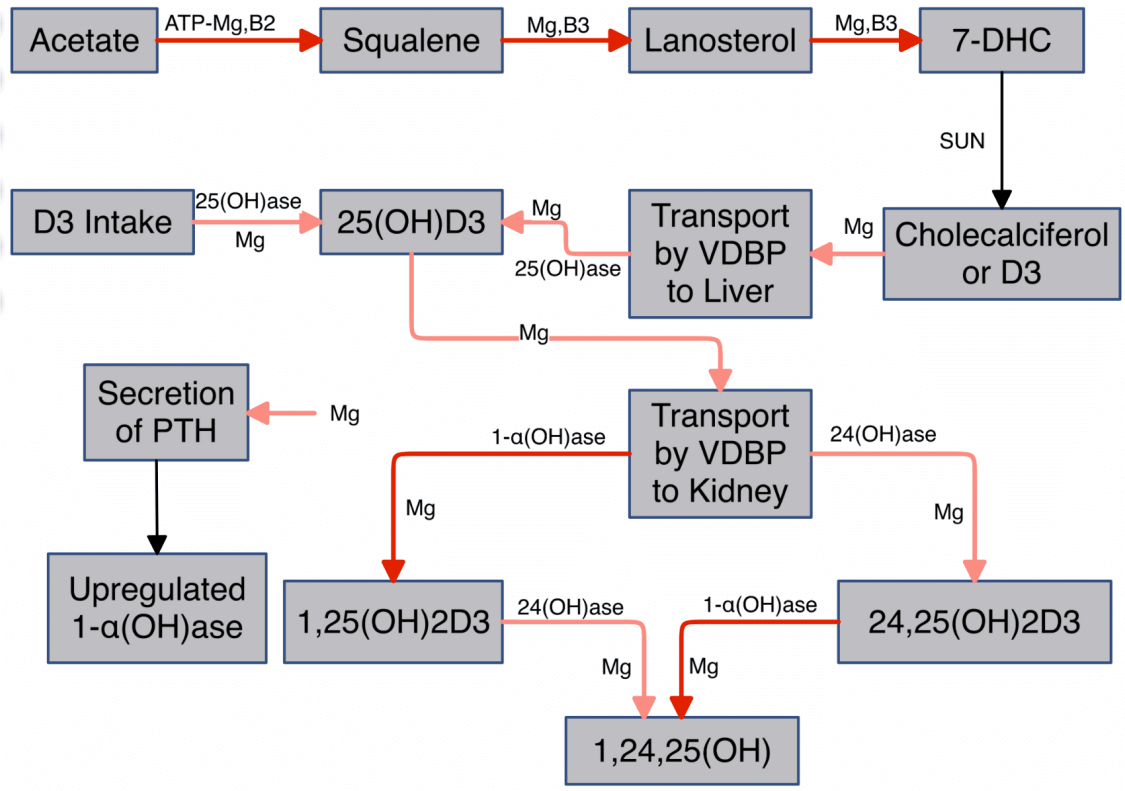

Figure 2. This sterol biosynthetic pathway for cholecalciferol decreases with age and is further challenged by Mg deficiency. Intensity of red arrows indicates the impact of Mg deficiency. DHC=dehydrocholesterol, PTH=parathormone, VDBP=vitamin D binding protein, D3=cholecalciferol

Vitamin D deficiency has been linked to gut dysbiosis and inflammation. Supplementation has a favorable impact on the composition of the gut microbiome and the gut microbiome favorably impacts vitamin D [88]. Vitamin E also favorably impacts the gut microbiome [89]. Gut bacteria can fulfill much of the body's need for vitamin E. But to produce it they utilize Mg dependent S-adenosylmethionine (SAMe). Virtually all of the body's methylation needs, e.g., DNA/RNA repair, protein synthesis, epigenome regulation, also require Mg dependent SAMe.

VI. Therapeutic Interventions

The soil content of Mg has decreased significantly over the last 100 years.

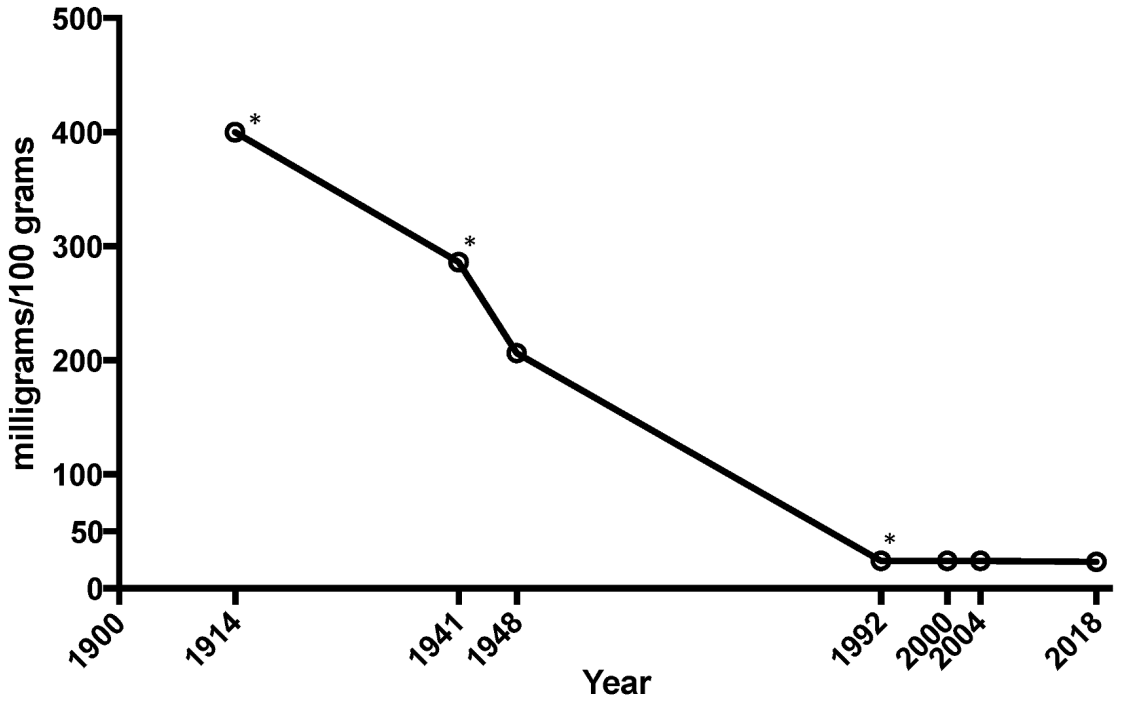

Figure 3. The average mineral content of calcium, magnesium, and iron in cabbage, lettuce, tomatoes, and spinach has dropped 80-90% between 1914 and 2018 [90]

The popularity and availability of processed foods and carbonated drinks have conspired to further compromise dietary Mg. Accordingly, supplementation is necessary.

The first step in addressing possible disease risk is to determine K/T and/or Ca:Mg. Unfortunately laboratory tests for determining K/T ratio are limited to research and are not otherwise commercially available. However, although Mg is presently not routinely offered on laboratory testing panels, the Ca:Mg can be easily determined from serum Ca and Mg. Convert their units from mg/dL to mmoles/L, i.e., multiply their ratio by 2.4/4.0 or 0.3. To obtain iCa:iMg, multiply by 5/7 (ionization rates). For the reference range limits for total serum Ca and Mg to align with the reference range limits for iCa and iMg, iCa must make up about 50% of total serum calcium, and iMg must make up about 70% of total serum magnesium. These limits are drawn from a sampling of the healthy population. The CLINICALLY determined reference range for Ca:Mg weight to weight is 1.7-2.6 [60]. The LAB TESTING determined reference range for iCa and

iMg is 1.7-2.5 [63]. Presently laboratory reference range for serum Mg is about 1.8-2.0 mg/dL or 0.75-0.95 mmol/L (mM). Many investigators familiar with the symptoms of MgD have repeatedly encouraged increasing the lower limit from 0.75 mM to 0.85 mM [60][65][91][92][93].

If the lower limit of serum Mg were to be raised to 0.85 mmol/L, the recommended Ca:Mg range would shrink to 1.7-2.3. Fear of a possible Mg induced laxative effect (especially with Mg citrate) may drive resistance to raising this lower limit. However, slowly increasing supplemental intake, using multiple different forms of Mg, especially those chelated to an amino acid, in divided doses, can lessen this risk. Concomitant intake of lysine and pyridoxal phosphate (active form of vitamin B6) enhances absorption [94] [95]. Never exceed bowel tolerance and always hydrate.

Other studies demonstrate no benefit when Mg intake is combined with pyridoxine, an inactive form of B6 [96][97]. The recommended daily allowance (RDA) for Mg is 310 mg/d for females and 420 mg/d for males. Unfortunately this is woefully inadequate in the present environment. Given a minimum target of 2.0 mg/dL for serum Mg, intake of elemental Mg must exceed 500 mg/day for females and 750 mg/day for males. This assumes homeostasis with absorption of 30-40%, mean blood volume 65 mL/kg for females and 75 mL/kg for males, mean weight 78 kg for females and 91 kg for males (2018), and 40% hematocrit. The target weight is for elemental Mg not that for the chelated molecule, where Mg usually constitutes only about 10% of the total.

Given the importance of a healthy gut microbiome to healthspan, adding a prebiotic and a probiotic (synbiotics) to the regimen should help address the symptoms of gut dysbiosis. However, gut dysbiosis will eventually reassert, if pursuit of a diet partial to simple carbohydrates and alcohol persists. Candida feeds on both. Tryptophan may help suppress transition of Candida from commensal to pathogen, as it suppresses hyphal morphogenesis. But increasing dietary intake of Mg rich foods, e.g., nuts, seeds, greens, should not be overlooked.

VII. Conclusion

There′s a growing epidemic of IR in both developed and developing countries. T2DM is rapidly increasing, as are T1DM and Alzheimer′s disease (T3DM). Imbalanced K/T and Ca:Mg increase risks for cancer, CVD, dementia, autoimmune disease, and obesity. MgD is linked to imbalances in both ratios, as well as to a suboptimal gut microbiome with vitamin A and E deficiencies. A partial litany of direct and indirect Mg dependent inputs include

1. half the enzymes in the glycolytic pathway and Krebs cycle
2. synthesis of all forms of vitamin D, including the solar substrate
3. activation of all the B vitamins, except B7 (biotin)
4. all enzymes that require ATP
5. the vast majority of GTP dependent and independent GPCRs
6. all reactions (methylation) that utilize SAMe
7. about 80% of known metabolic functions [89]

All of these are tied to accelerated aging and diminished healthspan. The linkages in this narrative review are largely associative. Cause and effect is not rigorously demonstrated.

Recognition of the connection between IR and hormones that accelerate aging and compromise healthspan is slowly emerging. Awareness of the MgD-aging connection is slowly increasing [8].

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