Review Article

Vitamin D, Calcium to Magnesium, and the Gut Microbiome

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The gut microbiome has been the subject of increasing interest as integral to our health. Few realize that the enormous benefits of vitamin D (VD) and magnesium (Mg) are highly dependent on a healthy gut microbiome. Short chain fatty acids, especially butyrate, reflect not only a healthy gut microbiome but also VD status. Suboptimal VD, Mg, or butyrate translates to some degree of gut dysbiosis and vice versa. Mg dependent secondary bile acids, indoles, and tryptophan, all microbial metabolites and longevity agents, are also discussed. Mg is indispensable to not only the synthesis of the active form of VD but also that of 7-dehydrocholesterol (7-DHC) from acetate. 7-DHC is the substrate for solar conversion to D3. The steadily increasing Ca:Mg in the Western diet and its troubling impact on parathormone (PTH) is discussed. Gut dysbiosis further complicates this. A model addressing the seemingly contradictory reports regarding calcium, magnesium, and VD efficacy among disparate groups is presented. Biochemical and physiologic interlinkages are legion and most remain hidden. This limited mini review exposes insight into the tight linkage between 25(OH) D3 and Ca:Mg, facilitated by the gut microbiome. A model incorporating the physiologically discordant but reinforcing effects on this linkage based on genes, culture, socioeconomic status, and diet is proposed.

Introduction

The term VD (VD) is often used indiscriminately. VD in this mini review will be used collectively to include its three forms D3 (cholecalciferol), 25(OH) D3 (storage form), and $1,25(OH)_2D$ (active form). VD[1], Mg[2], and a healthy gut microbiome that produces plenty of short chain fatty acids (SCFAs)[3], secondary bile acids[4], and indoles[2], are all longevity agents. They are also intertwined both directly and indirectly. VD regulates magnesium status as well as that of calcium and phosphate. Many are

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familiar with the total dependence of VD efficacy, whether of solar or supplemental origin, on adequate Mg. But the vital role of the gut microbiome in potentiating both has only recently been revealed. Gut dysbiosis disrupts the balance of beneficial bacteria and impedes the production of butyrate, secondary bile acids, indoles and many other vital nutrients[5].

Discussion

I. Vitamin D and Magnesium

VD and Mg are inextricably linked in a bidirectional manner. Through PTH VD can regulate the absorption of calcium (Ca) and Mg[6] and the urinary excretion of Ca and Mg. However, Mg is indispensable to the synthesis of VD. It is generally known that Mg is a required cofactor for every enzymatic step in the conversion of D3 aka cholecalciferol to its active form $1,25(OH)_2D3$, including the binding of D3 or 25(OH) D3 to VDBP (vitamin D binding protein). However, Mg is also required for the synthesis[7] and cAMP mediated secretion[8] of parathormone (PTH) from chief cells in the parathyroid gland. Low plasma Ca driven PTH stimulates VD synthesis and VD driven high plasma Ca inhibits PTH synthesis. Even more importantly the synthesis of 7-dehydrocholesterol (7-DHC), the immediate precursor of cholecalciferol, from acetate is dependent on Mg (see figure 1). Acetate is provided by either gut microbes or by acetyl CoA, which requires Mg dependent B5 (pantothenate). Vitamins B2 and B3 must be phosphorylated to FAD and NAD respectively to attain active status for the synthesis of 7-DHC. This phosphorylation requires ATP and Mg. Without sufficient 7-DHC the sun is powerless to create D3. This drawback elevates the value of D3 supplementation. Therefore, VD deficiency/insufficiency is a greater risk in the magnesium deficient, and sun exposure may not suffice efforts to address the VD shortfall (see figure 1).

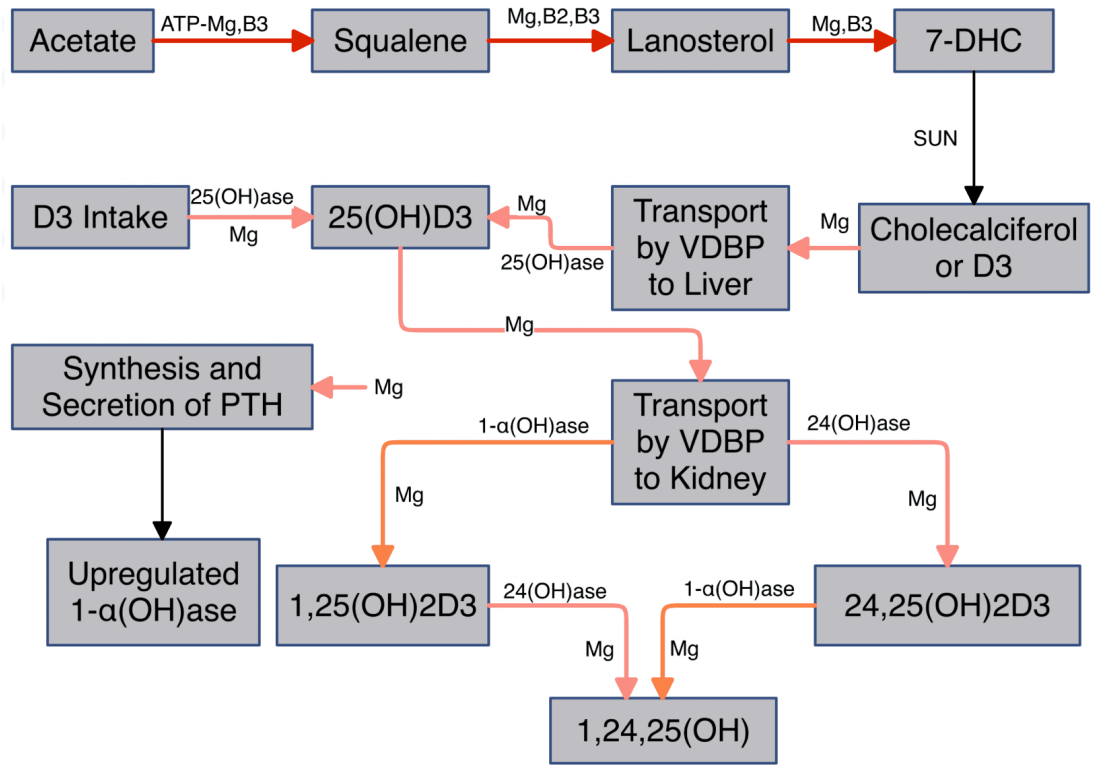

Figure 1. All enzymes that produce the active form of VD ($1,25(OH)_2D3$) from D3, including binding to the transport protein, synthesis of PTH, and secretion of PTH, are Mg dependent. Many enzymes and cofactors involved in the synthesis of 7-dehydrocholesterol from acetate are also Mg dependent. 7-DHC=7-dehydrocholesterol

Optimal 25(OH) D3 is at least 50 ng/mL (120 nmol/L), based on clinical data (see figure 2). The 20 and 30 ng/mL 25(OH) D3 targets generally recommended are suitable only for rickets and skeletal health, but optimal immune function involves intracrine, autocrine, and paracrine pathways and storage form levels that exceed those adequate for endocrine (hormonal) needs. 25(OH) D3 levels lower than 20ng/mL are considered deficient and those less than 30 ng/mL are considered insufficient.

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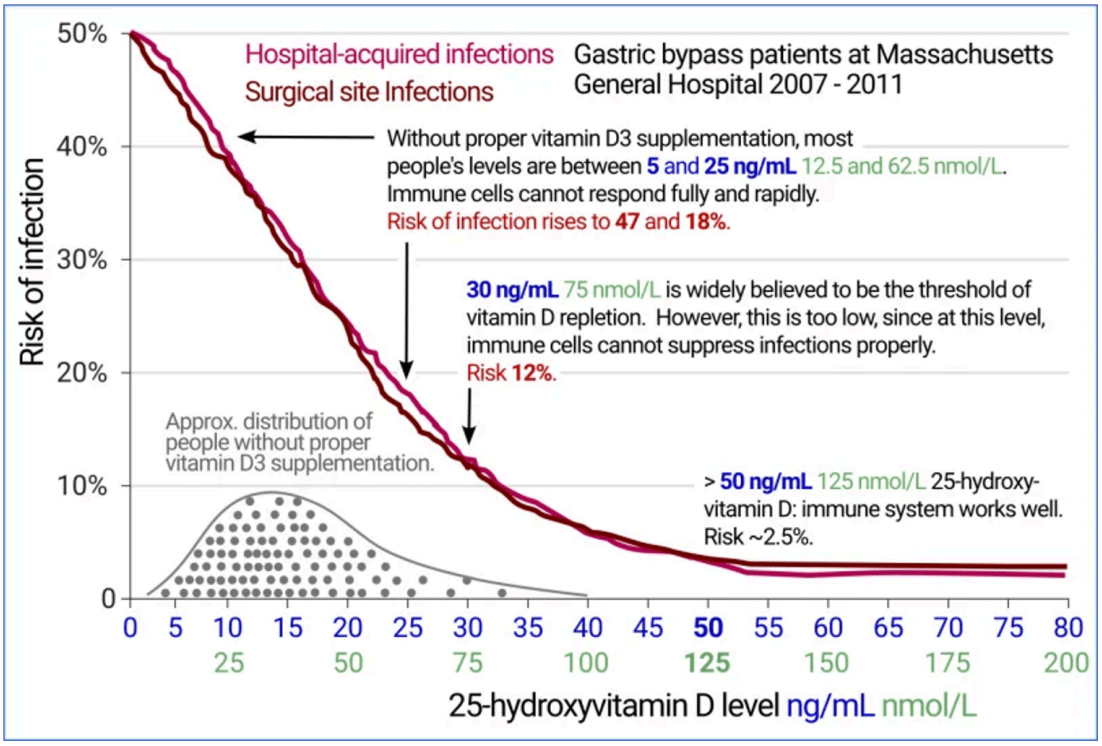

Figure 2. Adapted by Robin Whittle May 2022[9] from two studies[10][11]. The two colored curves represent VD associated risks for surgical site infection and hospital acquired infection (immune functions of VD) from the gastric bypass study[10]. The inadequate D3 supplementation distribution figure is from a Covid-19/VD study[11].

The RDA (Recommended Daily Allowance) of 600-800 IUs D3 per day recommended by the National Academy of Sciences Institute of Medicine (IOM) was proven to be off by an order of magnitude in 2014[12]. This huge error was confirmed by several Canadian and American university research teams. The IOM's RDA for VD still stands at 600 IUs to 800 IUs (for adults over 70), but their Estimated Average Requirement (EAR) was subsequently raised from 20 ng/mL to 30 ng/mL. EAR + 2SDs = RDA. An increased intake of an order of magnitude, e.g., 8000 IUs of D3 (cholecalciferol), would correlate with a serum level of at least 50 ng/mL[13]. NHANES (National Health and Nutrition Examination Surveys) data between 1988 and 2006 revealed little change in mean serum 25(OH) D3 at about 25 ng/mL[14]. From 2011 to 2018[15] median 25(OH) D3 went from 27 to 27.5ng/mL.

Regarding the cations Ca^{++} and Mg^{++}, in the relatively healthy with normal renal function without GI issues and no impacting medications Ca^{++} is usually about 50% of serum values and Mg^{++} is usually

about 70% of serum values. When midrange values of lab reference limits are compared using these percentages, the resulting ratio for Ca:Mg is very close to 2.0 (mmol comparison), further supporting Durlach's 2.0 dietary target for Ca:Mg (mg comparison)[16]. Serum Mg is not even offered on a routine chemistry panel. Furthermore, in order to avoid normomagnesemic Mg deficiency aka chronic latent Mg deficit, the lower limit of its normal range for Mg should be raised from 0.75 to 0.85 mM[2][17][18][19][20][21]. In one study trial participants completed a dietary questionnaire that predicted suboptimal magnesium status in 100% of participants. Yet 25% were found to have optimal serum status[22].

Suboptimal Mg status was defined as serum Mg<2.0 mg/dL (0.83 mM). Even increasing the lower limit of normal from 0.75 mM to 0.83 mM does not appear to exclude the 25% with optimal serum Mg predicted to be suboptimal by the questionnaire.

II. Calcium to Magnesium Ratio

Any VD and Mg discussion must include Ca. VD via Ca^{++} mediated feedback with PTH directly impacts VD mediated Ca and Mg intestinal absorption and renal resorption. Ca and Mg compete for the calcium sensing receptor (CaSR)[23] and PTH responds to both cations in the same direction but not to the same degree. Yet Mg^{++} often opposes Ca^{++}, e.g., as a Ca channel blocker. Because Ca is more dependent on VD and PTH than Mg, this can create a dilemma. For example, an elevated serum Ca:Mg can inappropriately suppress PTH, depressing Mg absorption and increasing magnesuria. Mg dependent PTH synthesis and secretion further compromise the magnesium shortfall. The Occidental diet is often short Mg and the Oriental is often short calcium. Many are lactose intolerant and eliminate dietary dairy. Durlach in 1989 suggested 2.0 as the optimal Ca:Mg intake ratio[16]. This ratio may parallel the inverse of PTH and reflect VD status. Figures 3 and 4 represent a hypothetical view of this based on

1. Increasing Ca intake when Ca:Mg is less than 1.7 decreases risk for some cancers[24][25].
2. Increasing Mg intake when Ca:Mg is less than 1.7 increases risk for some cancers[24].
3. An elevated calcium to magnesium ratio increases risks for some cancers, including lung cancer[26] and CVD[27].
4. A depressed calcium to magnesium ratio increases risks for some cancers, including lung cancer[28] and CVD[27].

5. Low Mg in the setting of elevated Ca:Mg translates to low VD[29]. This can be explained physiologically, as Mg is required for the synthesis and secretion of PTH and upregulation of VD. Elevated Ca also displaces Mg from CaSRs.
6. Low Ca in the setting of depressed Ca:Mg is physiologically contradictory to a concomitant low VD. However, this may be explained based on discrepant but mutually reinforcing genetic, cultural, socioeconomic, and dietary considerations. These may complicate and compromise clinical correlations.
7. Skin pigmentation is directly linked to VD deficiency[30].
8. Socioeconomic status is directly linked to VD deficiency[31][32]. D3 is not in the budget.
9. Cultural customs can drive VD deficiency. Most in the Middle East dress modestly[33] and many Asians are averse to solar exposure.
10. Diet is largely dependent on culture. The South Asian diet is low in VD rich foods[34] and many Asians are lactose intolerant and avoid dairy products[35], excellent sources of Ca and VD.

VD deficiency may be at the root of many health issues exacerbated by a Ca:Mg ratio outside the 1.7-2.3 range[15]. The failure to normalize for Ca:Mg in any study on the efficacy of VD may compromise any conclusions and may sell short this extraordinary micronutrient (see figure 3).

Regarding the upper limit of the optimal range, one study favored an upper limit of 2.8[36] and another favored 2.6[37]. Cancer and CVD together may be bookends for both range limits.

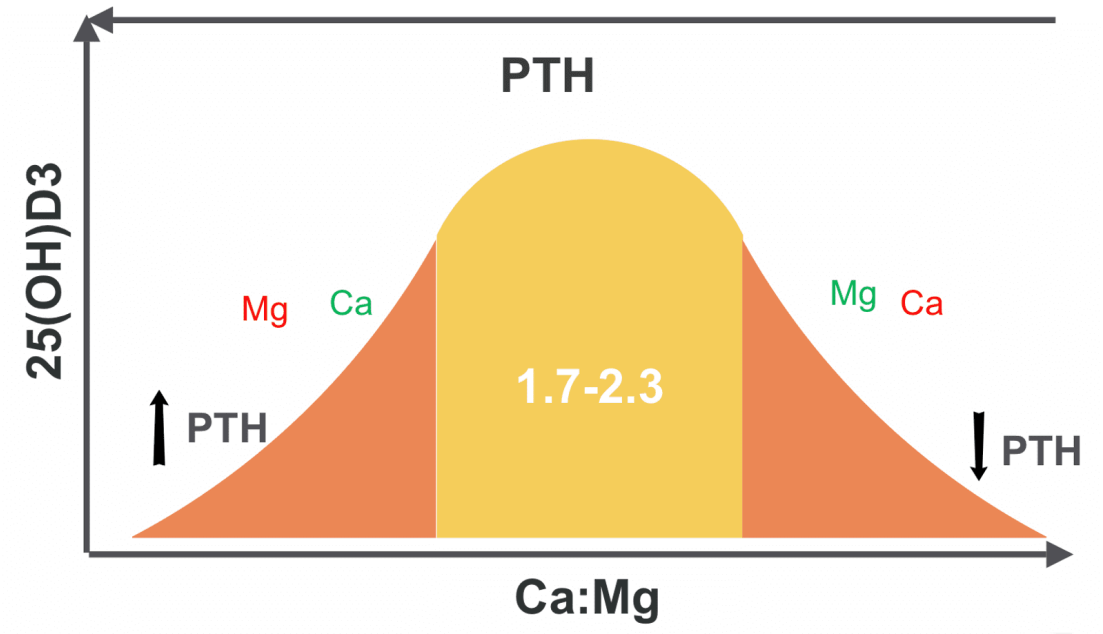

Figure 3. This bell shaped curve delineates the proposed relationships between VD, Ca:Mg, and PTH. Yellow represents the target range and orange the health risk ranges for Ca:Mg, when physiologic considerations and genetic, cultural, socioeconomic, and dietary considerations are separated.

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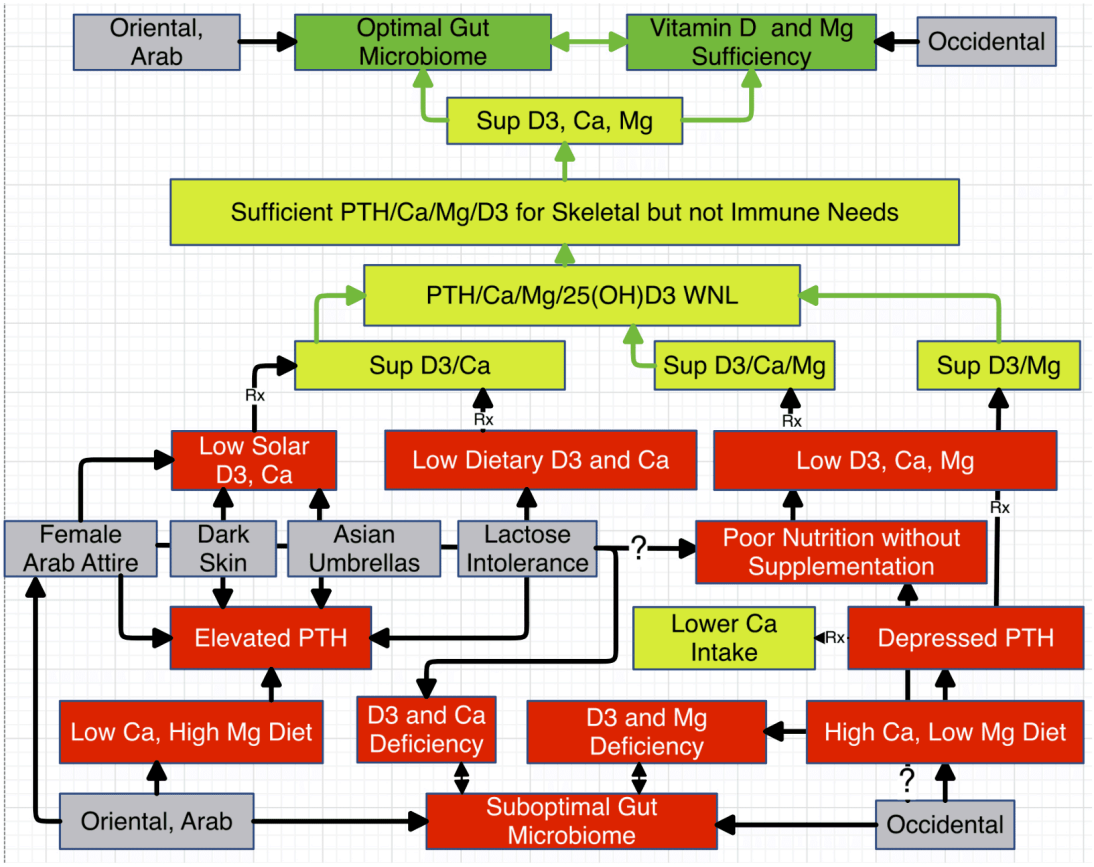

Figure 4. This illustrates a proposed flowchart for proposed deficiencies of vitamin D, Ca, and Mg in various racial, ethnic, cultural, and economic sub groups, many of which overlap.

One curious study[38] reported suppression of 25(OH) D3 with Mg supplementation, when baseline 25(OH) D3 exceeded 30ng/mL. However, the Ca:Mg ratios for the placebo and target groups were 3.9 and 3.7 respectively. This suggests that Mg supplementation when Ca:Mg is elevated may inappropriately suppress PTH and with it VD synthesis (and Ca absorption/resorption). Any Mg supplementation when 25(OH) D3 levels exceed that sufficient for skeletal health (30ng/mL) appears to be counterproductive and may compromise immune health. Perhaps in addressing an elevated Ca:Mg lowering Ca intake should precede Mg supplementation. Other studies support the figure 3 conjecture (see figure 5). VD loses efficacy for colorectal neoplasms as Ca:Mg exceeds 2.6[37] and for CVD as Ca:Mg exceeds 2.8[36].

Recent data from NHANES on Ca:Mg based on combined dietary and supplemental intake is sparse. Figure 5 was derived from 2001-23 NHANES data for both genders over age 20, diet only[39]. NHANES

data from 2001-2006[29] yielded a mean daily Ca supplement of 251mg and a mean daily Mg supplementation of 65mg. Total Ca and Mg intake was then derived.

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

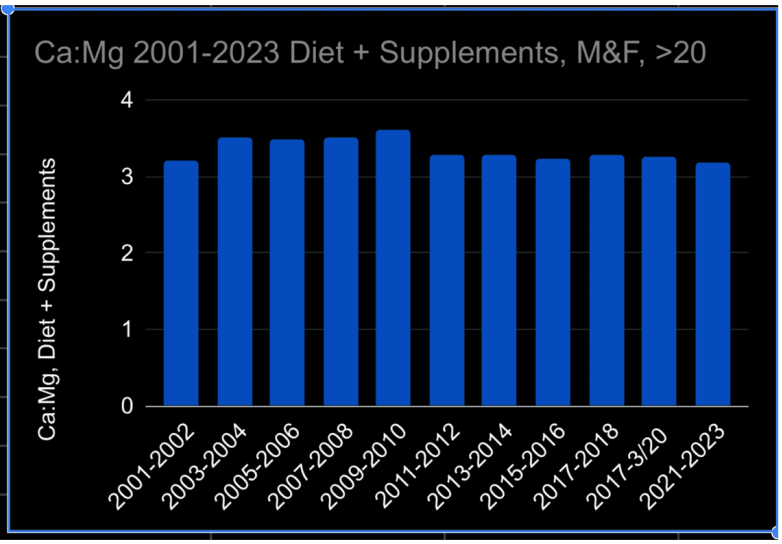

Figure 5. This step graph represents a derived approximation of Ca:Mg, using Ca and Mg dietary intake only data from 2001-2023, both genders, age greater than 20. To this was added the mean Ca and Mg supplementation only data (Ca 251 mg/d and Mg 65 mg/d) from 2001-2006 both genders, all ages. These ratios were much worse in those ages 6-19 years, usually exceeding 4.0.

The Covid-19 epidemic demonstrated the importance of this ratio, as one greater than 5.0 was tightly linked to death in Caucasians[40] and one greater than 4.0 was tightly linked to hospitalization[41].

III. Vitamin D and the Gut Microbiome

Although the active form of VD mediates its endocrine, intracrine, autocrine, and paracrine effects, D3 contributes additional benefits. D3 inhibits Candida hyphal morphogenesis[42][43]. The emerging role of the gut microbiome in health and disease and the impact of Candida overgrowth in gut dysbiosis highlights the value of D3. Candida overgrowth can be both cause and effect of gut dysbiosis[44]. In addition the active form $1,25(OH)_2D3$, but not its storage form 25(OH) D3, most frequently requested lab analyte, is linked to an abundance of butyrate producing bacteria[45], frequently linked to gut health. In fact the active form of VD correlated even more tightly with microbiome diversity. These reported results were adjusted for solar exposure. The active form of VD increases the Bacteroidetes/Firmicutes ratio, especially Akkermansia and Faecalibacterium of the Bacteroidetes

phylum, both prominent butyrate producers[46], and increases microbial diversity[47]. VD deficiency and suboptimal gut microbiome are associated with cancer[48], autoimmune disease[49], inflammatory bowel disease,[50], cystic fibrosis[51], multiple sclerosis[52], diabetes[53][54], and depression[55]. Butyrate has an ameliorative effect on dementia[56], cancer prevention/treatment[57], especially colorectal cancer[58], and obesity[59]. The SCFAs acetate, propionate and butyrate are produced from the microbial fermentation of indigestible carbohydrates and are the biomarkers of a healthy gut microbiome[60]. Acetate and propionate producing bacteria can cross feed butyrate-producing bacteria[61].

But improvements in the gut microbiome via increasing D3 supplementation in those already deficient/insufficient are not limited to the symptomatic. Increased serum 25(OH) D was associated with increased beneficial bacteria and decreased pathogenic bacteria[62]. D3 is both therapeutic and prophylactic and appears to possess prebiotic properties[54]. The well known skeletal benefits of VD are in part mediated by butyrate. Butyrate stimulates osteoblastic activity and down-regulates osteoporosis[63], possibly by stimulating the release of PTH[64]. The opposite is also true. Gut dysbiosis is linked with suboptimal VD status[65]. The gut microbiome regulates not only bone homeostasis and bone health[66] but also many extraskeletal functions of VD, e.g., anti cancer, anti diabetes, anti hypertension, anti obesity, anti dementia, anti autoimmunity. Dysbiosis compromises the absorption of D3, Ca, and Mg. The gut Firmicutes/Bacteroidetes ratio is negatively linked to a healthy gut microbiome[67] with suppression of Firmicutes phylum bacteria upon supplementation with 25(OH) D or D3[68]. VD deficiency also negatively impacts the gut microbiome, compromising B vitamin production. While Mg is required for activation of B2,3,6,9,12, the gut microbiome may fill in for any shortfall[69]. Some intestinal bacteria can produce all eight B vitamins[70] and up to 65% of human gut microorganisms can synthesize at least one type of B vitamin[71].

The few discrepant reports on the efficacy of D3 with respect to the gut microbiome may be due to:

1. Lack of baseline data indicating insufficiency/deficiency
2. Failure to property separate placebo and target groups by baseline
3. Less than 2-3 months between start of D3 supplementation and measurement of results
4. Insufficient D3 dosage
5. Failure to normalize for Ca:Mg as a confounding factor
6. Target group too small

IV. Magnesium and the Gut Microbiome

Primary bile acids are metabolized by Mg dependent CYP450 (Cytochrome P450) enzymes[72] and impact the gut microbiome[73]. Primary bile acids are metabolized to secondary bile acids by intestinal bacteria. Secondary bile acids, associated with longevity, are also Mg dependent[74] and require a healthy gut microbiome. Both SCFAs and secondary bile acids independently exert a myriad of beneficial effects on host health[75].

Recently the vital role of aryl hydrocarbon receptors (AhRs) in aging[76], dementia, autoimmune disease, cancer[77], and ASCVD[78] 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[76] and promote longevity. Indoles are longevity agents produced by gut microbiota. Their healthful benefits depend on the aryl hydrocarbon receptor (AhR)[79]. Not only are indoles and butyrate AhR ligands[80],

but their subsequent AhR activation induces Mg dependent cytochrome CYP450 enzymes that facilitate gut absorption of indoles[81]. All CYP450 enzymes are Mg dependent[72]. Like Ozempic, butyrate is also a GLP-1 (glucagon-like peptide) agonist[82], albeit natural. Both are longevity indicators. Probiotics, rich in butyrogenic bacteria, are also associated with longevity[83] and Mg enhances their efficacy[84]. Butyrate produced by gut bacteria via vagal afferents may increase HRV[85] [86], linked to longevity.

Gut microbiota cannot produce SCFAs in the absence of Mg[87], but they can produce tryptophan[88], another longevity agent. Candida yeast and hyphal forms produce their own form of IDO[89] that competes with host IDO. It enhances degradation of tryptophan to kynurenine (K/T) and accelerates the kynurenine pathway, increasing K/T, especially under the direction of interferon-gamma[90]. Any shortfall in Mg can increase subsequent neurotoxic metabolites and decrease NAD^+ production[2]. The K/T ratio is negatively linked to the health of the gut microbiome[90]. Lactobacilli and Bifidobacteria boost plasma tryptophan levels[88]. They also produce lactate, which can crossfeed butyrogenic bacteria[91]. Gut microbes provide most of our circulating tryptophan. However, in order to absorb it intestinal epithelial cells rely on B^0AT, a neutral or nonpolar amino acid transporter, that works in concert with ACE2 receptors[92]. This puts those with Covid-19, long Covid, or Candida overgrowth at risk for gut dysbiosis, compromising the enormous benefits of VD and Mg.

V. Therapeutic Interventions

1. Probiotics, e.g., yogurt, alone are insufficient, if diet is suboptimal. The "good" bacteria must be fed and require fiber or indigestible carbohydrates, i.e., prebiotic, e.g., d-mannose. Butyrate is a commercially available postbiotic
2. Target a Ca:Mg of 2.0, either by weight of intake or by serum cation mM values. If elevated, lower dietary Ca, e.g., dairy products, sardines, first and then increase dietary Mg, e.g., nuts, seeds, leafy greens, avocados. The damage due to an elevated ratio is greatly underappreciated[38]
3. After improving Ca:Mg supplement D3 to attain a serum level of at least 50 ng/mL (125mM) 25(OH) D3 (see figure 2)[93][94].
4. Take supplemental Mg with pyridoxal phosphate and perhaps D3, the active form of B6. Mg is required for the hydroxylation of D3 in the liver (storage form). Taking pyridoxal phosphate concomitantly with magnesium can enhance absorption and availability of magnesium[95][96]. Not only does pyridoxal phosphate enhance cellular uptake of magnesium but magnesium enhances that of pyridoxal phosphate[97]. Several studies have challenged this[98][99]. But both employed the inactive form - pyridoxine.
5. Avoid simultaneous Ca and Mg intake. Although CaSRs are primarily found in the parathyroid gland and the kidney, they are also present in many other organs, including the alimentary canal[100].
6. Avoid simultaneous processed food/soft drinks and Mg intake. The former contain phosphates, which bind magnesium, limiting absorption.
7. Exercise induced elevation of lactate may enhance serum butyrate. Lactate may permeate intestinal endothelial and epithelial cells into the alimentary canal, where it can crossfeed butyrogenic bacteria[91].
8. Pay close attention to proper hydration. Dehydration triggers release of aldosterone, which increases renal reabsorption of Na+ and urinary excretion of Mg++ and K+. Cortisol possesses similar aldosterone properties and can to a lesser degree trigger this same cationic exchange. Stress induced cortisol can lead to Mg deficiency, while magnesium deficiency in turn enhances the body's susceptibility to stress[101].
9. Increase VD intake with age and increasing morbidity.

10. Replenish water soluble B vitamins that require Mg for activation and are required for synthesis of 7-dehydrocholesterol from acetate, enabling solar conversion to D3, (see figure 1).

Conclusion

Magnesium may be to VD what the gut microbiome is to general health. One is indispensable to the other. This review presents benefits of VD and magnesium on gut microbiome dependent longevity agents. Many indirect benefits of this partnership are not included, e.g., maintenance of intestinal integrity[84][102]. VD and magnesium are inextricably entwined. Thirty ng/mL of 25(OH) D3 and 0.75 mg/dL of Mg are insufficient. Mg is indispensable for not only the synthesis of VD's solar substrate and the storage/active forms of VD from D3 but also the synthesis and secretion of PTH. A healthy gut microbiome is also required to fully realize the benefits of both. Furthermore, there are many other gut microbiome related micronutrients and vitamins that depend on VD and Mg for their healthful effects and vice versa. Indeed there are myriad extraskeletal and extra-intestinal benefits of both.

The interdependencies are both legion and complex. Many have only recently been discovered and much remains hidden. The balance between Ca and Mg is increasingly recognized as critical to attaining optimal levels of 25(OH)D3 (see figure 3). Traditional graphs demonstrate a hyperbolic curve with PTH decreasing as 25(OH)D3 increases. But figure 3 appears to contradict this, when Ca:Mg is greater than 3.5. Insufficient Mg translates to insufficient PTH synthesis (for feedback inhibition of Ca absorption/resorption) and insufficient Mg for synthesis of VD => elevated Ca:Mg, depressed 25(OH)D3 and PTH. On the other hand, insufficient Ca should trigger PTH secretion, but genetic, cultural, socioeconomic, and dietary conditions may conspire to deny the intake of Ca and/or VD (or its synthesis) => depressed Ca:Mg, depressed 25(OH)D3, elevated PTH (see figures 3,4). The vertical axis on figure 3 may also directly reflect gut microbiome quality and optimal health (see figure 6).

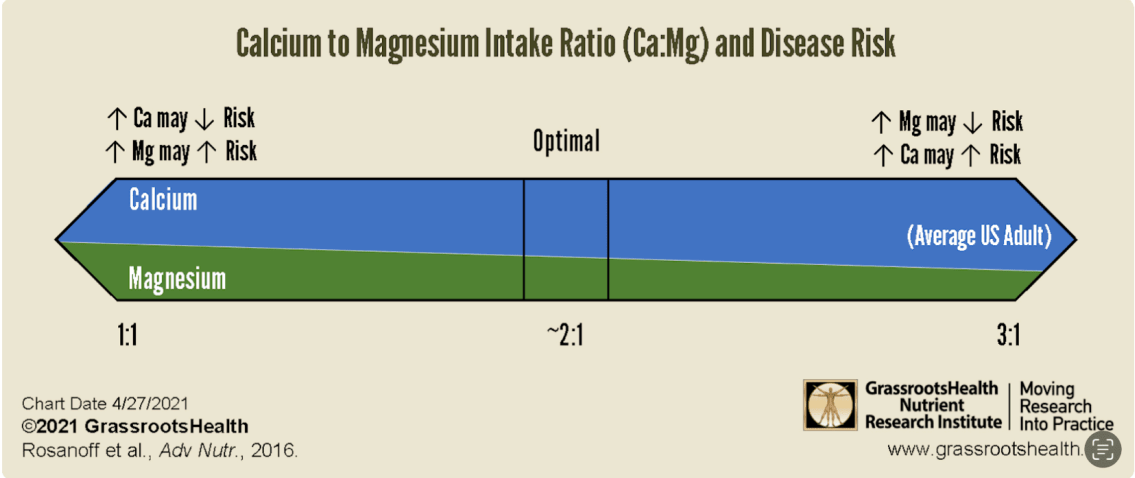

Figure 6. This figure is from Rosanoff *et al.*[103].

The contributions of the gut microbiome are massively underappreciated. The increasingly sedentary Western lifestyle, the deteriorating quality of food, the abundant use of antibiotics and certain other medications, e.g., proton pump inhibitors and some antihypertensives, have conspired to challenge the quality of our gut microbiome. Not surprisingly the benefits of fecal microbiota transplantation have rapidly expanded from its initial treatment for fulminant pseudomembranous colitis due to Clostridium difficile to an emerging tool for alleviating diseases related to a problematic gut microbiome. VD efficacy is tightly linked to Ca:Mg and VD studies that normalize for race, ethnicity, culture, socioeconomic status, and diet may be more elucidating.

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