Open Access Library Journal
2022, Volume 9, e9249
ISSN Online: 2333-9721
ISSN Print: 2333-9705

Ca:Mg + D, the Shield that Interdicts the Crown Viruses and Vaccines

Patrick Chambers

Department of Pathology, Torrance Memorial Medical Center, Torrance, USA
Email: pwc@gte.net

How to cite this paper: Chambers, P. (2022) Ca:Mg + D, the Shield that Interdicts the Crown Viruses and Vaccines. *Open Access Library Journal*, **9**: e9249.
https://doi.org/10.4236/oalib.1109249

Received: August 24, 2022
Accepted: September 17, 2022
Published: September 20, 2022

Abstract

The calcium to magnesium ratio plus adequate vitamin D greatly determine success or not in the immune battle against pathogens and cancer, not to mention cardiovascular disease. Ionized calcium and magnesium in normal, healthy individuals can be calculated and a ratio determined from serum levels. Using widely accepted laboratory reference range values and NHANES data, the recommended daily allowances from the Institute of Medicine of the National Academy of Sciences for calcium, magnesium, and D3 (cholecalciferol) are objectively refuted mathematically and physiologically. Midrange values for both cations, despite RDA sufficiency, are shown to be unattainable without secondary hyperparathyroidism (high parathormone (PTH), low D) or hypoparathyroidism (low PTH, high iCa:iMg) at the officially designated level of 25(OH)D sufficiency (30 ng/mL). Calcium and magnesium utilize the same calcium sensing receptor (CaSR) not only on cell membranes but also on organelle membranes. Intra-mitochondrial hydroxylation of cholecalciferol can become compromised. An imbalanced intake of calcium and magnesium can impact the efficacy of vitamin D supplementation. Several pertinent articles underscoring these conclusions are analyzed in detail. The impact of an imbalanced Ca:Mg ratio on Covid-19, Long Covid and vaccination is also discussed.

Subject Areas

Pathology

Keywords

Magnesium, Parathormone, NHANES, Kallikrein-Kinin, Glutathione

1. Introduction

Western Societies have seen a steady escalation in their calcium to magnesium

ratio, due in large part to increasing dietary calcium relative to magnesium and decreasing magnesium content in their food. The mineral content of vegetables has declined by as much as 80% - 90% in the last 100 years [1]. There has also been considerable controversy over what blood level of 25(OH)D and intake of D3 constitute adequacy for skeletal and extraskeletal health [2].

This controversy has only become more heated with the advent of Covid-19 and the pandemic. D3 intake directly affects the iCa:iMg ratio. But this has garnered little attention and the interplay has been overlooked. The benefits of vitamin D are slowly adulterated as this ratio rises and is reflected in rates of colorectal cancer [3] [4] [5], prostate cancer [5] [6], esophageal cancer [5], cardiovascular disease (CVD) [5], metabolic syndrome [5], total mortality [5], and cognitive function [7] [8].

Like calcium, only the ionized form of magnesium (Mg^{++} or iMg) is physiologically active. Unlike calcium, magnesium is primarily an intracellular resident. Magnesium is not a hormone like vitamin D, but does play an integral role in the function of neurotransmitters and intracellular signaling.

Vitamin D not only identifies as a hormone with endocrine features but also boasts intracrine and paracrine capabilities. The latter are vital to both innate and adaptive immune function. Vitamin D deficient rickets was first discovered in the 1920s. Not until the 1970s was the entity vitamin D resistant magnesium deficient rickets recognized.

Is magnesium integral to optimal immune function as well? Or is its primary role only to support vitamin D? Is there a vitamin D resistant magnesium deficient immune dysfunction? And if so, at what level of magnesium is this problem avoided? We know that magnesium is vital to immune function independent of vitamin D. Its role in methylation to prevent mutations and to stabilize DNA are under-appreciated. Is there a way to evaluate the vitamin D/magnesium partnership directly? Using widely accepted laboratory reference ranges for serum Ca, Mg, PTH and several clinical studies involving Ca, Mg, PTH, and 25(OH)D, this article will demonstrate the critical roles in immune function both magnesium and vitamin D play, together and independently. A serum iCa:iMg of about 2.0 with a 25(OH)D of at least 50 ng/mL translates to optimal health.

2. Serum iMg and iCa:iMg, the Laboratory Perspective

Establishing magnesium sufficiency in the hospital setting can be difficult. Most of the authorities on the topic cannot agree on the best method. Evaluating the urine for the concentration of magnesium after a loading dose seems to be the most popular at present. However, this is expensive and time consuming, not to mention inconvenient. Many others prefer to measure magnesium content within RBCs (red blood cells) and/or PBMCs (peripheral blood mononuclear cells). In the healthy (no meds, no renal disease, normal albumin, no known relevant polymorphisms) establishing magnesium sufficiency is much easier. Se-

rum iMg can be calculated, as will be shown.

The Ca:Mg appears to differ depending on the population studied, and diet seems to be the primary determinant of this variance. Jean Durlach, founder of the Society for the Development of Research on Magnesium (SDRM) over 50 years ago recommended 2.0 as the proper target.

The active forms of calcium and magnesium are its cations (iCa, iMg). The screening serum lab value for each includes both bound and unbound components. Normal range for serum calcium is about 2.2 - 2.7 mM (8.5 - 10.5 mg/dL or 4.3 - 5.3 mEq/L) with a median of about 2.45 mM (mg/mL). If serum albumin is midrange, then ~50% is ionized => median iCa is about 1.22 mM. Normal range for serum magnesium is about 0.75 - 0.95 mM (1.8 - 2.2 mg/dL or 1.5 - 1.9 mEq/L) with a median of 0.85 mM. Serum iMg is 55% - 70% of total serum Mg (tMg) [9] [10] [11]. What % is "normal"?

Serum iMg is held within a narrow range (0.53 - 0.67 mmol/L by ion sensitive probe) in normal, healthy subjects [12]. Therefore, in normal, healthy subjects about 70% of serum magnesium must be ionized in order to remain within the reference range, *i.e.*, 70% of 0.75 mM = 0.525 mM (v 0.53 mM) and 70% of 0.95 mM = 0.665 mM (v 0.67 mM). This implies a median iMg of about 0.60 mM and a median iCa:iMg of 2.03 (1.22/0.60), close to Durlach's recommendation of twice as much dietary calcium as magnesium. This number is not some government derived result, but one derived physiologically based on millions of control specimens. Therefore, in normal, healthy subjects with normal renal function and without medications, when serum Mg is within normal limits, most of the time serum iMg can be easily determined from tMg without ion sensitive probes.

Serum tMg and iMg can be further refined in a healthy population by reconfiguring the lower reference limit of serum magnesium from 0.75 mM to 0.85 mM. Serum magnesium values of less than 0.85 mM are associated with increased health risks. The lower limit of the reference range should be raised to 0.85 mM [13] [14]. This reference interval (0.75 - 0.95 mM) was derived from NHANES (National Health and Nutrition Examination Survey) I data (1974) and the recommended iCa:iMg of 2.6 was derived from NHANES II (1977). Both were based on the distribution of serum magnesium in a normal population rather than one based on clinical outcomes. Due to funding shortages NHANES has not determined serum magnesium levels in its participants since 1974 [15]. All data is based on food frequency questionnaires.

Many have called for a change in the serum tMg reference range, all have been ignored [16] [17]. Many have noted that using a cut-off of 0.75 mmol/L for magnesium deficiency misses 50% of those with true magnesium deficiency. For example, no change of iMg in plasma was observed during the menstrual cycle in controls and PMS (premenstrual syndrome) patients. However, in the PMS group the overall monocyte iMg and to a lesser extent the RBC iMg were significantly lower than in controls [18]. Another study on migraine patients, as compared to controls, demonstrated a lower intracellular magnesium content only

[19]. Subsequent increase in magnesium intake only increased intracellular content (erythrocytes and lymphocytes) without any change in plasma magnesium.

Any serum iMg shortfall is seemingly replenished in part from intra-erythrocytic iMg stores, where iMg varies between 0.4 - 0.6 mM [20] [21]. This is close to the serum iMg range of 0.53 - 0.67 mM [12], which suggests simple passive diffusion. Interestingly, intra-erythrocytic iMg also reflects memory and recognition [22] and intra-erythrocytic iMg appears to decline with age [23]. Changing the reference range lower limit for serum magnesium would uncover these diagnostic shortfalls. Mansmann christened this occult (migraines) and subclinical (PMS) normomagnesemia magnesium deficiency (MgD) [24]. Normomagnesemia MgD can also be seen in pre-eclampsia [25]. Even below the existing lower limit of 0.75 mM, symptoms may be absent [26].

3. Vitamin D and Parathormone, the Clinical Perspective

PTH, which responds to both blood iCa and iMg, should be about 20 - 30 pg/ml (see **Figure 1**), when serum (or plasma) tCa (total calcium) is at its median of 2.45 mM or 9.5 mg/dL.

One study [27] evaluated a group with "high" magnesium intake (n = 19) in which 1) the RDA for magnesium was met by FFQ (food frequency questionnaire), 2) the calcium intake was twice that of magnesium, 4) the vitamin D was 27 ng/mL (near its official sufficiency level of 30 ng/mL), 5) iMg was 0.537 mM,

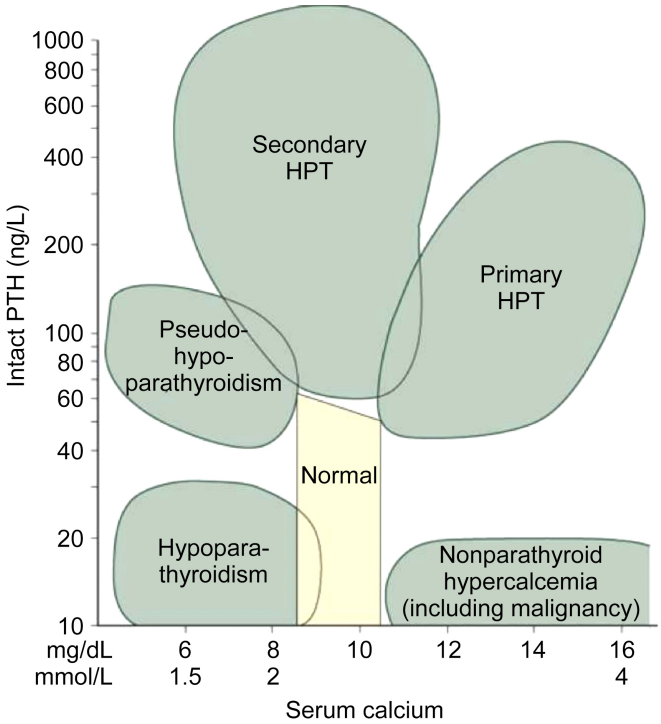

Figure 1. The sweet spot for PTH is about 30 pg/mL.

and 5) the iCa:iMg ratio was an optimal 1.85 (=> iCa was about 1.0 mM, since serum calcium was not measured). Both iCa and iMg were low, despite a PTH of 60 pg/mL. The sufficiency level of 30 ng/mL 25(OH)D requires a PTH of 40 pg/mL (see Figure 2). This indicates some degree of secondary hyperparathyroidism in this "high" mag group. Ca and Mg need to increase and a vitamin D level of 30 ng/mL is insufficient to meet that need. The set point (27-D, 60-PTH) in this group represents their mean in this study. The PTH of 60 pg/mL on the curve (see Figure 2) corresponds to a 25(OH)D of less than 10 ng/mL (not 27 ng/mL). This level of PTH is too high (secondary hyperparathyroidism) and must be suppressed by increasing magnesium and calcium intake and their absorption/resorption. Increasing intake of D3 both increases calcium/magnesium and suppresses PTH. This shifts the curve to the right by about 20 ng/mL (27 ng/mL - ~7 ng/mL). The recommended 30 ng/mL 25(OH)D becomes about 50 ng/mL and the PTH becomes about 30 pg/mL. But the 2:1 intake ratio must be maintained. The 25(OH)D can then approach its minimal adaptation of 50 ng/mL (see Figure 2). This 50 ng/mL is not some arbitrary number determined by the Institute of Medicine (IOM) (mathematically proven to be in error by an order of magnitude) [28]. This number has been determined physiologically by serum samples from a large control group (n = 14,681). About 75% of all adults worldwide have serum 25(OH)D levels less than 30 ng/mL [29]. According to the NHANES (2003-6) about 95% of Americans have serum 25(OH)D levels less than 40 ng/mL [30].

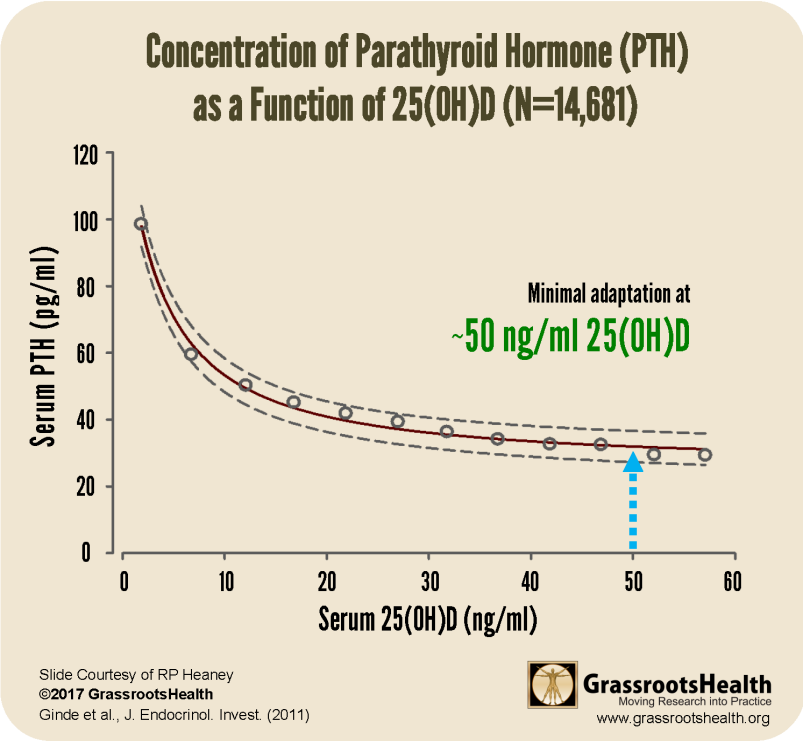

Figure 2. Any 25(OH)D level less than 50 ng/mL implies some degree of secondary hyperparathyroidism.

Another recent study of 180 participants (see **Figure 3**) [31] revealed that increasing magnesium intake, when serum 25(OH)D > 30 ng/mL, may be ineffective and even counterproductive.

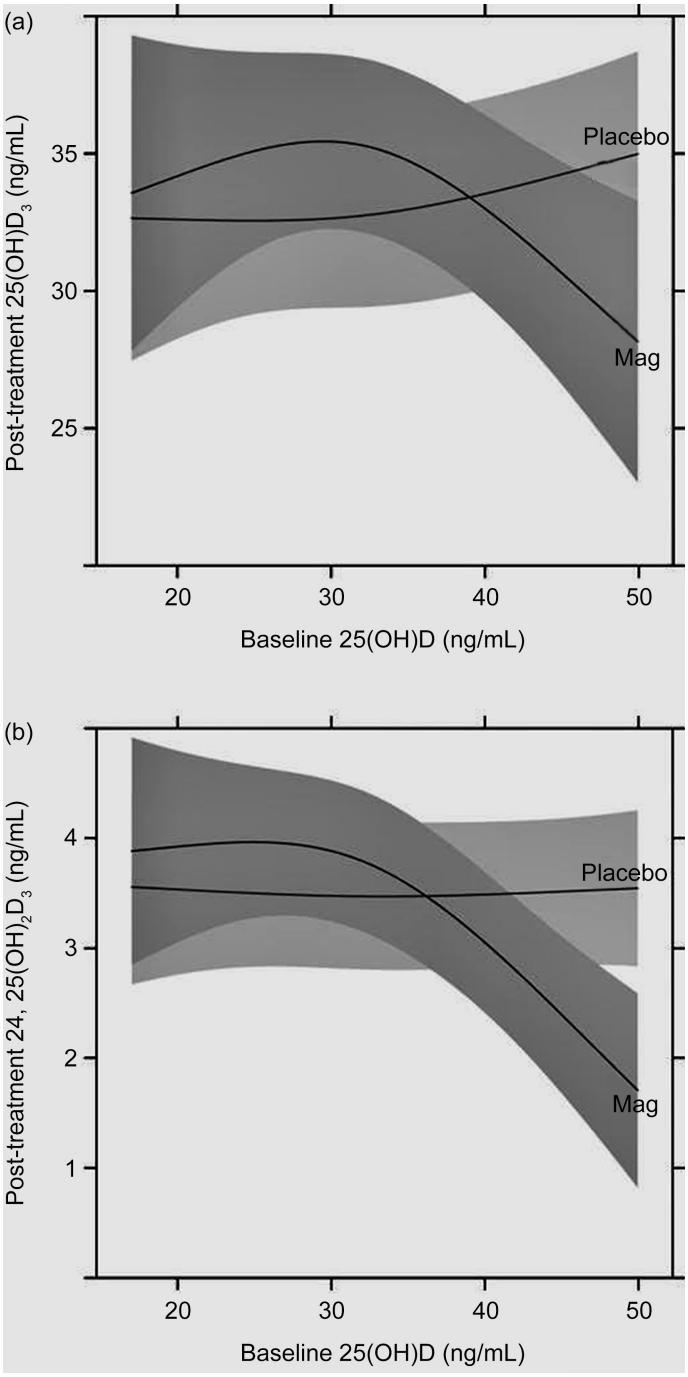

Figure 3. In A magnesium supplementation (v placebo) suppresses PTH and with it 25(OH)D3 levels, when baseline is greater than 30 ng/mL [31]. In B this supplementation unsurprisingly also initiates degradation of 25(OH)D3 in the same group. But both the placebo and target groups had significantly elevated Ca:Mg ratios and the CaSRs (calcium sensing receptors) on cell/organelle membranes were overloaded with iCa—not much room for iMg, which uses the same receptor.

In this study magnesium supplementation was beneficial if initial baseline 25(OH)D3 was between 15 ng/mL and 30 ng/mL, but had a negative effect if baseline was between 30 and 50. But closer scrutiny reveals that the Ca:Mg ratios for the target group and the placebo group were 3.7 and 3.9 respectively (serum calcium must be elevated and PTH must be suppressed). Any increase in either calcium or magnesium further suppresses PTH (negative feedback) and with it the synthesis of vitamin D, which is degraded to $24,25(OH)_2D3$ at a 3.5 + Ca:Mg. The PTH (not measured) must be allowed to increase by decreasing Ca intake. An elevated Ca:Mg cannot be lowered by increasing magnesium supplementation alone. An isolated increase in magnesium intake will only further depress PTH. A combined approach will facilitate the availability to Mg of CaSRs in the intestines, kidneys, bone, and parathyroids, shared by both calcium and magnesium. Increased Mg intake can be accommodated with less risk of the laxative effect. But calcium intake must be curtailed simultaneously!

As has been shown, midrange iCa and iMg and a 2:1 ratio cannot be attained at a level of 40 ng/mL for 25(OH)D. From this graph (see **Figure 1**, **Figure 2**) the difference in PTH values above or below 30 pg/mL reflects a Ca:Mg ratio below or above 2.0 respectively. If iCa and iMg are midrange and dietary calcium to magnesium intake approaches 2 to 1, then the full benefit of increasing vitamin D can be realized even to 80 ng/mL without increasing serum calcium [32].

The beneficial effect of lowering the Ca:Mg ratio below 2.6 (see **Figure 4**) applies to many forms of cancer, CVD, total mortality, and cognitive function.

But there is a lower limit and it appears to be 1.7 [3] [4] [33] [34]. In a study on Chinese [33] with a low Ca/Mg intake ratio (a median of 1.7 vs around 3.0 in US populations), intakes of Mg greater than US Recommended Daily Allowance (RDA) levels (320 mg/day among women and 420 mg/day among men) were related to increased risks of total mortality for both women and men. Mortality was predominantly CVD and CRC [33], which were also seen in those who increased calcium intake, when their Ca:Mg exceeded 2.6. Perhaps the dairy diet of the West (more disposed to calcium) might explain this discrepancy. Increasing calcium intake has been encouraged in China [34]. Increased magnesium intake has been encouraged in the West [35].

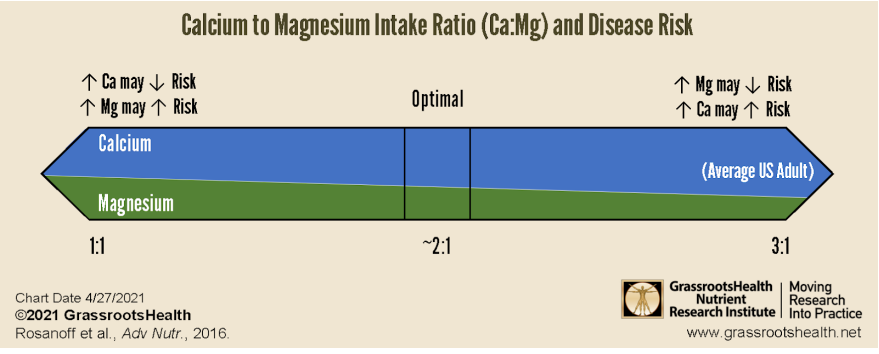

Figure 4. Optimal Ca:Mg is around 2.0, slightly more in the West and slightly less in the East.

According to NHANES (1999-2000), 79% of US adults did not meet the RDA of magnesium. US population Ca:Mg for 2000 and later has been greater than 3.0 with a mean ratio as high as 3.7 in women supplementing with calcium [36].

The inverse association between calcium and distal CRC was found only in participants with a Ca:Mg ratio between 1.7 and 2.5. Interestingly, in one study on this 25(OH)D levels were higher in those with Ca:Mg greater than 2.636 in both the placebo and target groups [4]. Clearly vitamin D supplementation in a vacuum has drawbacks.

According to NHANES 2009-2010 data, more than 76% had calcium-to-magnesium intake ratios ≥2.6… A Ca:Mg ratio range of 1.70 - 2.60 has been proposed as an optimum range. Data from NHANES surveys have shown the mean Ca:Mg intake ratio from foods alone for US adults has been >3.00 since 2000. Furthermore, a review of supplements containing calcium or magnesium available to the American public found a mean ratio of 2.90 [5].

4. Discussion

The journey to determine optimum Ca:Mg and its relationship to vitamin D has been tortuous and torturous.

1) The RDA for D3 determined by the IOM of the National Academy of Sciences, issued in 2014, was shown to be in error by an order of magnitude [28]. Instead of 600 to 800 IUs D3 per day, it should be 6000+. Instead of 30 ng/mL blood level of 25(OH)D, it should be 50+ ng/mL.

2) Calculation of the NNT (number needed to treat) reveals the efficacy of vitamin D for viral respiratory infections during the flu season [37] to be ten times that of the flu shot, according to the CDC's own data for 2017-18 [38]. Yet this fact languishes in clinical application.

Many conditions challenge magnesium adequacy. Dehydration triggers aldosterone, which has a magnesiuretic effect [39]. The symptoms of dehydration overlap with those of magnesium deficiency—headaches, cramps. Stress triggers cortisol, which also causes magnesiuresis [40]. Due to these factors and many others, e.g., alcohol, proton pump inhibitors, certain antibiotics, …, magnesium status can slowly deteriorate, yet remain unrecognized. Many of its signs and symptoms are nonspecific and overlap with those of aging, including alopecia, a common symptom in Long Covid. Magnesium deficiency is an underappreciated and unwelcome diagnosis hiding in plain sight. It has as deep a connection to vitamin D, as does calcium. The serum iCa:iMg serves as a reliable proxy for their working partnership [41]. Calcium and magnesium compete for the same receptor (CaSR) in the intestines, bone, kidney, and the chief cells of the parathyroid glands. Vitamin D and magnesium are also inextricably linked. Magnesium is required for multiple enzymes in the synthesis of vitamin D and PTH (see **Figure 5**). Even the substrate (7-dehydrocholesterol), utilized by the sun to produce D3, requires magnesium as a cofactor.

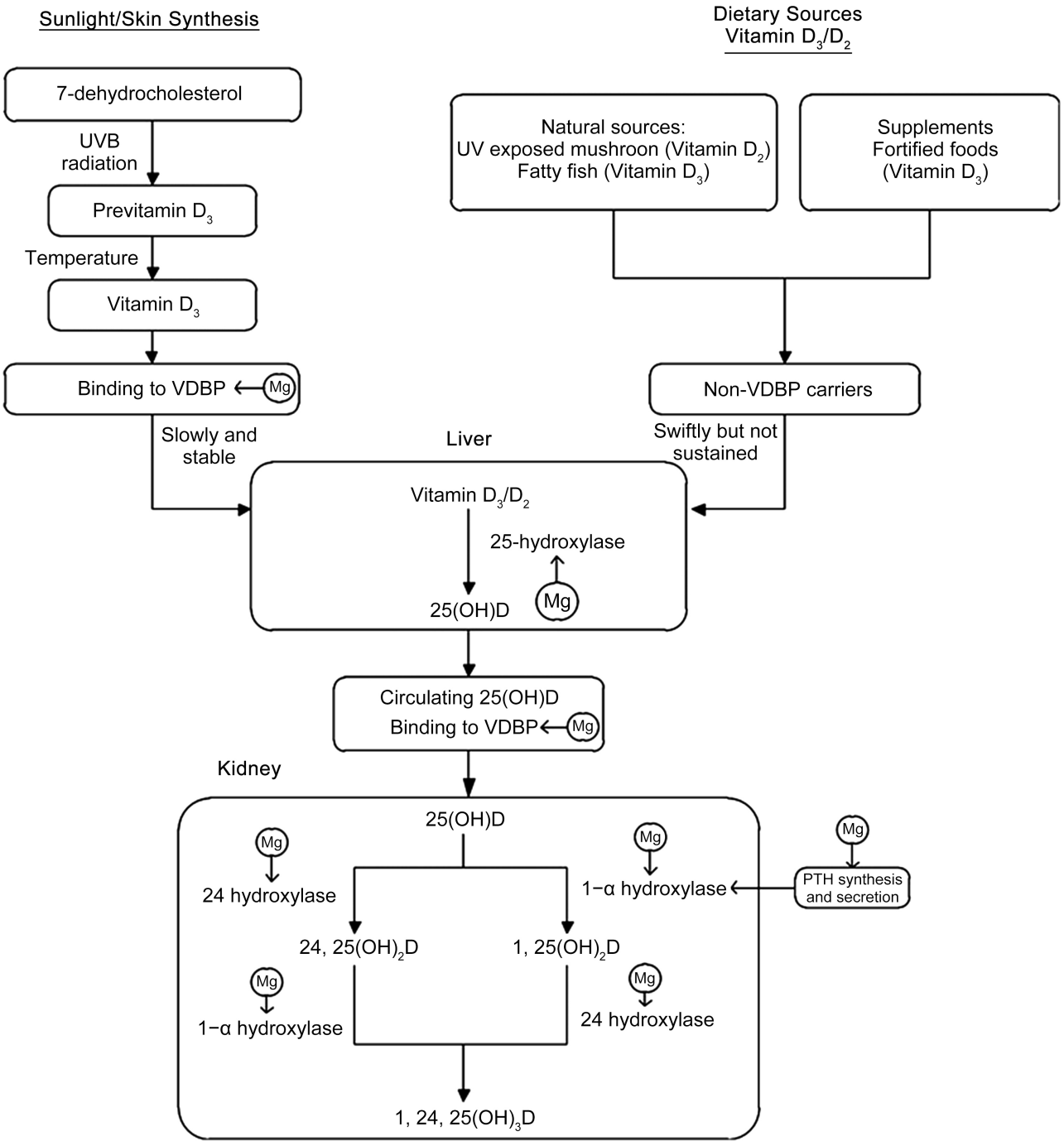

Figure 5. PTH synthesis also requires magnesium, as does binding to vitamin D binding protein (VDBP).

Magnesium can also act independent of vitamin D. We know that it is critical for natural killer (NK) and CD8+ cell activation [42] [43] [44]. Magnesium is also required for synthesis of SAMe (S-adenosyl methionine), the universal source for the body's methylation needs, essential to cancer prevention and other probable long term complications of Covid-19 and/or its vaccines, including cognitive function. DNA is hypomethylated in both Alzheimer's [7] and Lewy Body Dementia [8].

Magnesium is essential to the synthesis of the powerful antioxidants glutathione (see Figure 6) and melatonin. These two antioxidants are frequently mentioned in the treatment of Covid-19 [45] [46]. NAC (N-acetyl cysteine) efficacy has also been reported [47] [48]. Magnesium (and B6) are also required cofactors for aromatic L-amino acid decarboxylase (AAAD), which directly produces serotonin and dopamine. An imbalance or deficiency between the two is closely associated with depression and many symptoms that overlap with Long Covid.

To produce melatonin requires methylation (with B5 as cofactor) of serotonin. SAMe is the sine qua non for synthesis of both glutathione (see Figure 6) [49] and melatonin. NAC can replenish glutathione [47] [48]. Glutathione also regulates transforming growth factor-beta (TGFβ) [50], a cytokine critical to Covid-19 and some forms of Long Covid.

Myalgic encephalomyelitis/chronic fatigue syndrome (CFS) [51], fibromyalgia [52], Epstein-Barr virus (EBV) [53], cytomegalovirus [54], mast cell activation syndrome (MCAS) [55], and postural orthostatic tachycardia syndrome (POTS or dysautonomia) are all associated with magnesium deficiency. Excess histamine characterizes MCAS. Magnesium is required for both pathways to degradation

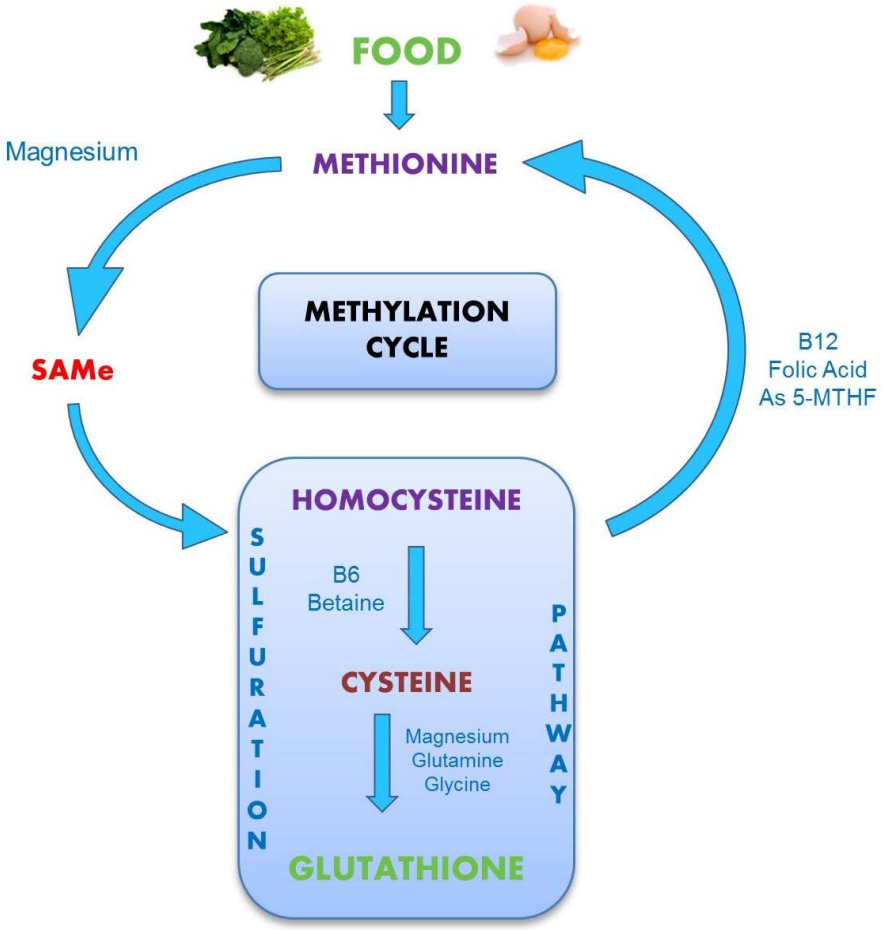

Figure 6. Magnesium is required for two steps (SAMe and cysteine to glutathione).

of histamine (SAMe and diamine oxidase (DAO)). There are reports of successful treatment of Long Covid with antihistamines. Autoimmune diseases (multiple sclerosis, systemic lupus erythematosus, rheumatoid arthritis, diabetes mellitus (DM)) [56] [57] [58] are also directly or indirectly associated with magnesium deficiency.

The CD147 epitope on the spike protein S of SARS-CoV2 or its vaccines [59] [60] combines with CD147 receptors on immune cells, erythrocytes, platelets, and endothelial cells. ACE2 receptors are prominent in the lungs, but the CD147 receptor becomes the major player once the blood-gas barrier has been breached. Vaccination bypasses this immune barrier. Increasing D3 supplementation in the face of an imbalanced calcium intake, three times greater than that for magnesium, impedes the contribution of magnesium to immune function and can compromise the benefits of vitamin D. Calcium and magnesium are both integral to immune function, but as the iCa:iMg increases above its natural, Mother Nature derived ratio of 2.0, efficacy slowly decreases.

The magnesium dependent 1α-hydroxylase, which produces the active form of vitamin D, is active not only in renal cells but also in lung, prostate, brain, immune cells, and placenta for synthesis of active vitamin D with paracrine and intracrine effects that are not impacted by circulating PTH [61]. These cells need plenty of intracellular Mg^{++} to enable intracellular reactions, e.g., PTH production in the cytosol and vitamin D related hydroxylations in the mitochondria. Increasing intracellular iCa compromises this [62] via competition for mitochondrial membrane CaSRs. This might explain why so many symptoms of magnesium deficiency involve smooth, skeletal, or cardiac muscle, all rich in mitochondria.

- "Every known illness is associated with a magnesium deficiency". Norman Shealy (father of holistic medicine);
- "Magnesium is involved in ~80% of known metabolic functions". Jayme Workinger.

5. Covid-19, the Short and the Long of It

5.1. The Short

Awareness of magnesium deficiency in Covid-19 is vastly under-appreciated. Magnesium methylates and deactivates transmembrane serine protease 2 (TMPRSS2), essential to SARS-CoV2 entry [63]. Even its content in water directly dictates the impact of Covid-19 [64].

The cytokine that dominates the clinical picture is TGFβ. Elevated TGFβ is a hallmark of severe Covid-19 [65]. TGFβ 1) compromises function of NK cells (innate) and CD8+ T cells (adaptive); 2) suppresses gamma interferon (IFN-γ) produced primarily by NK cells and CD8+ T cells [66]; 3) stimulates fibrosis; 4) compromises NKG2D (a receptor on NK and CD8+ cells and master regulator of immune function); 5) is associated with CFS, EBV reactivation, cancer, and autoimmune disease.

1) TGFβ restricts the cytotoxicity of natural killer cells and CD8+ T cells [67] [68] [69].

Vitamin D suppresses TGF-β [70] [71] [72] [73]. It regulates the cytotoxicity of NK cells and especially CD8+ T cells [45] [46] [47]. TGFβ is elevated in all the comorbidities—DM, obesity, hypertension [74]. Angiotensin II stimulates TGF-β release via AT1Rs [75] [76]. ARBs (angiotensin receptor blockers) have shown some efficacy [77] in Covid-19. Vitamin D down regulates renin and NF-κB. Magnesium decreases cytokine production [78].

2) TGFβ suppresses IFN-γ

TGFβ inhibits IFN-γ and downregulates NK cell cytotoxicity [79]. This IFN-γ inhibition leads to loss of its inhibitory effect on C1 of the classic complement pathway (CCP) [80]. TGFβ inhibits IFN-γ expression on CD4+ T cells [81]. Activation of C1 and the CCP initiates crosstalk with the KKS (Kallikrein Kinin Systems) [80] and seemingly brain fog type of Long Covid. Vitamin D modulates IFN-γ production by PBMCs [82]. Deficiency of either Mg or vitamin D translates to less IFN-γ (see **Figure 7**).

Interferon receptors depend on the actions of magnesium dependent kinases (JAKs and TYK2). Magnesium deficiency compromises interferon production, especially IFN-γ [84].

3) TGFβ stimulates fibrosis [85] [86].

TGFβ up-regulates fibrosis in lungs [87] [88], liver, kidney [89], and heart [90]. The profibrotic TGF-β has been implicated in obesity associated diseases, especially asthma. Circulating TGFβ levels were higher in severe post-Covid-19 patients with pulmonary and renal fibrosis events [87] [89]. Vitamin D modulates the production of TGFβ and fibrosis [75], especially in the lungs [70], liver [91], and kidney [92]. Magnesium arrests pulmonary [93] and hepatic [94] fibrosis by inhibiting TGFβ/SMAD signaling.

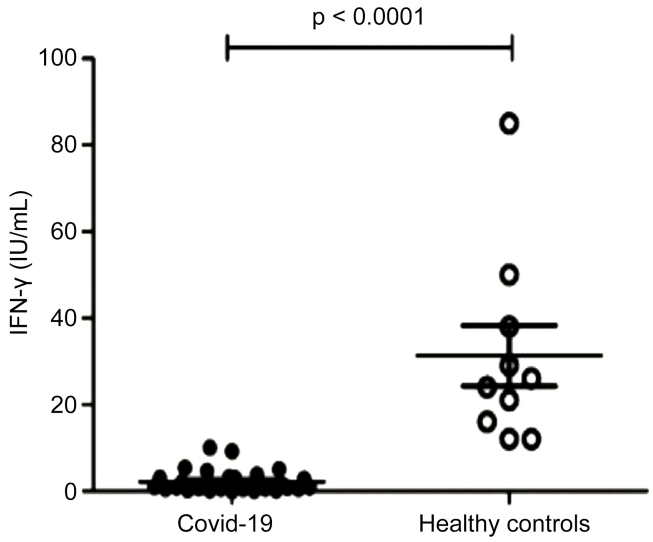

Figure 7. IFN-γ release in 31 patients with moderate to severe Covid-19 and 10 healthy controls [83].

4) TGFβ compromises NKG2D

NKG2D, the master regulator of immune cell responsiveness [95], is abundantly present on all NK cells, NK T cells, and CD8+ T cells and facilitates the immune response [96]. Magnesium is critical for the assembly of the NKG2D-DAP10 receptor complex [97]. TGFβ impairs the function of NKG2D [98]. TGF-β, produced by immune cells, plays a key role in blunting NKG2D-mediated surveillance [98].

5) Up-regulated TGFβ is associated with CFS [99], EBV reactivation [100] [101] [102], cancer [103] [104], and autoimmune disease [60] [61].

Vitamin D and magnesium deficiencies play prominent roles in these long term consequences of Covid-19 and/or its vaccines/boosters. TGF-β has a role in the differentiation of Th17 cells from naive CD4+ T-cells [60]. Th17 cells are a marker for autoimmune disease [61]. Vitamin D rebalances Th17/Treg.

5.2. The Long

There appear to be two kinds of Long Covid, both vitamin D/magnesium deficient—white middle aged women who contracted Covid-19 but were never hospitalized and those with comorbidities who were.

5.2.1. Long Covid and the KKS

Long Covid brain fog type is probably a manifestation of mild immune dysfunction due to a predominant shortage of magnesium. It is more common in Caucasians than African-Americans, despite greater vitamin D deficiency in the latter. It is more common in women than men, the opposite of that for Covid-19 (see **Figure 8**). It appears to be more connected to the KKS [84] than to the RAS.

The young often do not meet the EAR (estimated average requirement) for magnesium and are especially vulnerable to post Covid brain fog and fatigue.

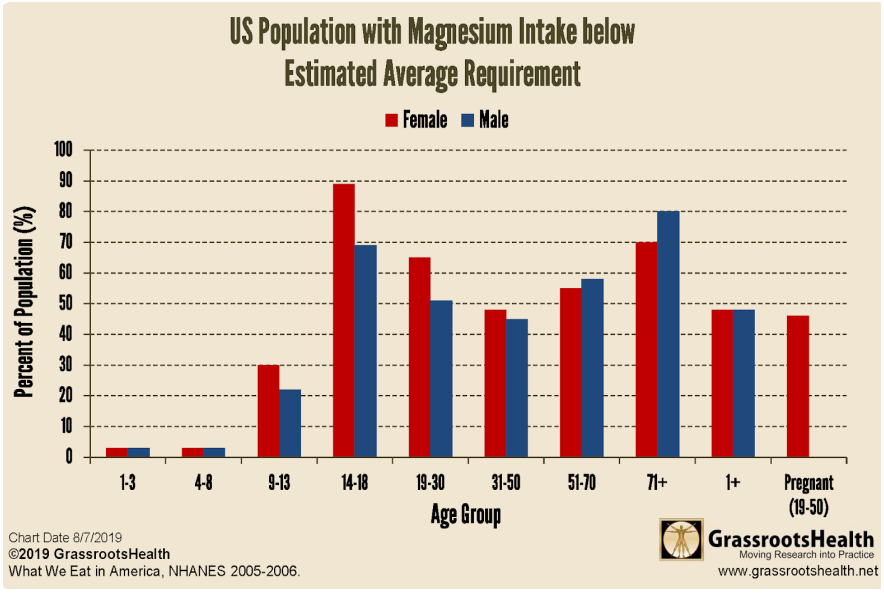

Figure 8. An EAR shortfall primarily afflicts young women and children and old men.

Its symptoms are seen in many conditions that overlap with Long Covid (and magnesium deficiency), including CFS, FM, MCAS, and (POTS) [105]. A very small subset of this brain fog type of Long Covid resembles MCAS [106] and, as already stated, may be due to inadequate magnesium [107]. Histamine is upregulated in magnesium deficiency. Magnesium deficiency not only increases histamine but also increases mast cells [108]. Mast cells can also produce TGFβ [109]. Antihistamines might prove helpful [110].

5.2.2. Long Covid and the RAS

Those that developed Long Covid more than 12 weeks after discharge from the ICU (severe not mild Covid-19) appear to be a different group, especially the elderly (see **Figure 8**). Some of their symptoms appear more connected to the RAS than the KKS and point to a vitamin D deficiency. For example, POTS shares some dysautonomic features with Long Covid [111] and is treated with Losartan [112]. Vitamin D deficiency has also been implicated in autonomic dysfunction [113]. CIRS (Chronic Inflammatory Response Syndrome), which overlaps with Long Covid, can be lowered with losartan [114]. Chronic vitamin D deficiency induces lung fibrosis through activation of the RAS [115]. Ang II induces TGF-β expression via AT1Rs [80] and is treatable by angiotensin receptor blockers [116].

6. Conclusions

In summary, calcium, magnesium and vitamin D are essential to good health. The iCa:iMg ratio is the best measure of the efficacy of this working partnership. The present reference range for normal serum tMg (0.75 - 0.95 mM) includes many with subclinical diseases. In healthy, normal individuals tMg can provide specific insight to iMg, especially if the tMg normal range is modified to 0.85 - 0.95 mM. The laboratory reference range values for serum Mg and Ca imply a midrange iCa:iMg of about 2.05 which contradicts official RDA recommendation from the IOM for calcium and magnesium, which is about 3.0 (1200 mg/400 mg). A review of supplements containing calcium or magnesium available to the American public found a mean ratio of 2.90 [5]. Furthermore, the RDA of 600 - 800 IU/d for vitamin D from the IOM was discovered to be in error by an order of magnitude (2014) and has not been rectified over the ensuing 8 years [30]. The target ratio of 2.0 cannot be attained at this RDA.

To attain the laboratory reference range dictated ratio of 2.05 for iCa:Mg requires a PTH of about 30 pg/mL (see **Figure 1**), a similar 2.0 dietary intake ratio for calcium and magnesium, and a 25(OH)D level of at least 50 ng/mL. Any PTH above this level implies some degree of secondary hyperparathyroidism (elevated PTH and depressed 25(OH)D). Any PTH level below this implies some degree of secondary hypoparathyroidism (depressed PTH and elevated iCa:iMg). Some symptoms of mild hypoparathyroidism, e.g., fatigue, weakness, cramps, fasciculations, overlap with those of magnesium deficiency.

Indeed both the correction of the IOM error [30] and evidence presented in this article point to a sufficiency level of at least 50 ng/mL 25(OH)D (see **Figure 9**).

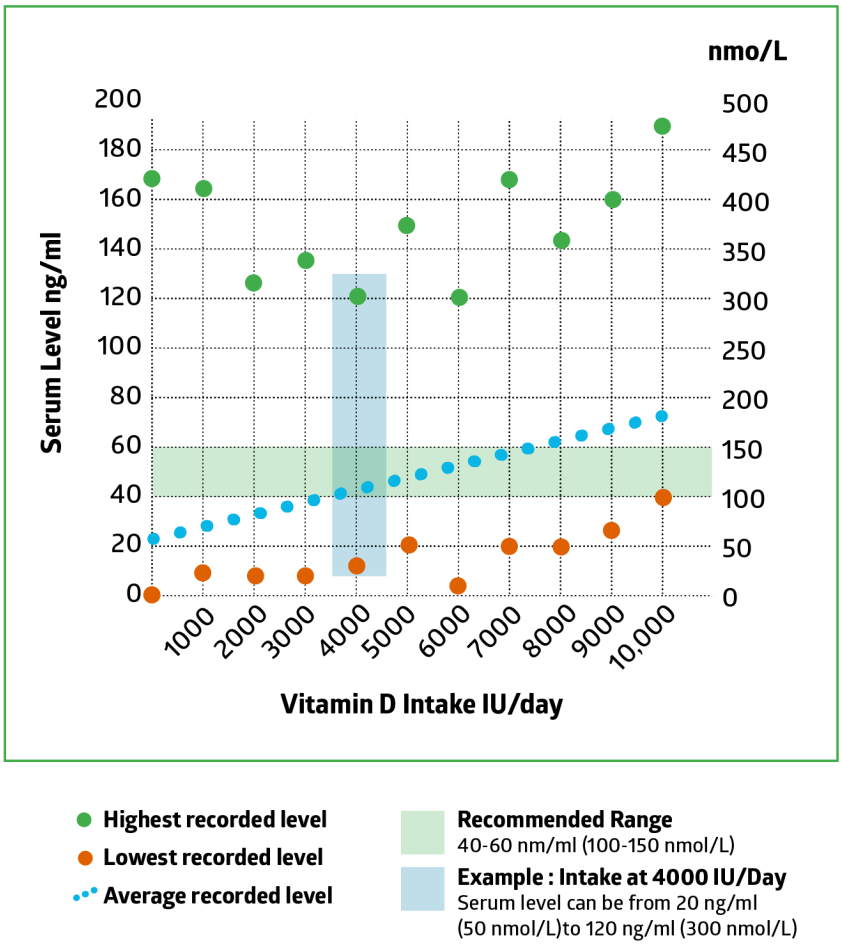

Figure 9. Even the officially recommended 600 - 800 IUs daily intake of D (cholecalciferol) is insufficient to attain the officially sufficient serum 30 ng/mL [117].

Magnesium deficiency, including that associated with an elevated iCa:iMg, combined with CD147 receptor mediated consumption of NK cells and CD8+ T cells, creates severe Covid-19. The CD147 epitope, present on the spike protein S [59] [60], engages CD147 receptors on these two classes of immune cells.

NK cells and CD8+ T cells produce the predominance of IFN-γ and its removal activates the KKS, brain fog type Long Covid [84]. The other less frequent comorbidity type Long Covid is characterized by increased TGFβ. This cytokine opposes IFN-γ and is increased in all with comorbidities. Its release is triggered by angiotensin II and AT1Rs, and arises in an upregulated RAS environment.

Maintaining a dietary Ca:Mg intake roughly 2:1 (dairy has a Ca:Mg of about 12:1) and a 25(OH)D level of at least 50 ng/mL optimizes the vitamin D, calcium, magnesium interplay. Between 1977 and 2012, US calcium intakes increased at a rate 2 - 2.5 times that of magnesium intakes [118]. Got milk?

Perhaps a "Long Covid panel" or "immune panel" with serum 25(OH)D, calcium, and magnesium might become popular. This approach shields the individual from not only the crown viruses and their vaccines but also DNA mutations and cancer, cardiovascular disease, and immune dysfunction in general.

Conflicts of Interest

The author declares no conflicts of interest.

References

[1] Workinger, J.L., Doyle, R.P. and Bortz, J. (2018) Challenges in the Diagnosis of Magnesium Status. *Nutrients*, **10**, Article 1202. https://doi.org/10.3390/nu10091202

[2] Wacker, M. and Holick, M.F. (2018) Vitamin D—Effects on Skeletal and Extraskeletal Health and the Need for Supplementation. *Nutrients*, **5**, 111-148. https://doi.org/10.3390/nu5010111

[3] Zhao, J., Giri, A., Zhu, X., *et al.* (2019) Calcium: Magnesium Intake Ratio and Colorectal Carcinogenesis, Results from the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial. *British Journal of Cancer*, **121**, 796-804. https://doi.org/10.1038/s41416-019-0579-2

[4] Dai, Q., Sandler, R., Barry, E., Summers, R., Grau, M. and Baron, J. (2012) Calcium, Magnesium, and Colorectal Cancer. *Epidemiology*, **23**, 504-505. https://doi.org/10.1097/EDE.0b013e31824deb09

[5] Costello, R., Rosanoff, A., Dai, Q, Saldanha, L.G. and Potischman, N.A. (2021) Perspective: Characterization of Dietary Supplements Containing Calcium and Magnesium and Their Respective Ratio—Is a Rising Ratio a Cause for Concern? *Advances in Nutrition*, **12**, 291-297. https://doi.org/10.1093/advances/nmaa160

[6] Dai, Q., Motley, S.S., Smith Jr., J.A., Concepcion, R., Barocas, D., Byerly, S. and Fowke, J.H. (2011) Blood Magnesium, and the Interaction with Calcium, on the Risk of High-Grade Prostate Cancer. *PLOS ONE*, **6**, e18237. https://doi.org/10.1371/journal.pone.0018237

[7] Zhu, X., Borenstein, A.R, Zheng, Y., Zhang, W., Seidner, D.L., Ness, R., *et al.* (2020) Ca:Mg Ratio, *APOE* Cytosine Modifications, and Cognitive Function: Results from a Randomized Trial. *Journal of Alzheimer's Disease*, **75**, 85-98. https://doi.org/10.3233/JAD-191223

[8] Tulloch, J., Leong, L., Chen, S., Keene, C.D., Millard, S., Shutes-David, A., *et al.* (2018) APOE DNA Methylation Is Altered in Lewy Body Dementia. *Alzheimer's and Dementia*, **14**, 889-894. https://doi.org/10.1016/j.jalz.2018.02.005

[9] Gröber, U., Schmidt, J. and Kisters, K. (2015) Magnesium in Prevention and Therapy. *Nutrients*, **7**, 8199-8226. https://doi.org/10.3390/nu7095388

[10] Rooney, M.R., Rudser, K.D., Alonso, A., Harnack, L., Saenger, A.K. and Lutsey, P.L. (2020) Circulating Ionized Magnesium: Comparisons with Circulating Total Magnesium and the Response to Magnesium Supplementation in a Randomized Controlled Trial. *Nutrients*, **12**, Article 263. https://doi.org/10.3390/nu12010263

[11] Mathew, A.A. and Panonnummal, R. (2021) 'Magnesium'—The Master Cation—As a Drug—Possibilities and Evidence. *Biometals*, **34**, 955-986. https://doi.org/10.1007/s10534-021-00328-7

[12] Altura, B.T., Shirey, T.L., Young, C.C., *et al.* (1994) Characterization of a New Ion Selective Electrode for Ionized Magnesium in Whole Blood, Plasma, Serum, and Aqueous Samples. *Scandinavian Journal of Clinical and Laboratory Investigation*, **54**, 21-36. https://doi.org/10.3109/00365519409095208

[13] Micke, O., Vormann, J., Kraus, A. and Kisters, K. (2021) Serum Magnesium: Time for a Standardized and Evidence-Based Reference Range. *Magnetic Resonance*, **34**, 84-89. https://www.magnesium-ges.de/Micke_et_al._2021.pdf

[14] Rosanoff, A., West, C., Elin, R.J., *et al.* (2022) Recommendation on an Updated

Standardization of Serum Magnesium Reference Ranges. *European Journal Nutrition*, **61**, 3697-3706. https://doi.org/10.1007/s00394-022-02916-w

[15] Rosanoff, A., Weaver, C.M. and Rude, R.K. (2012) Suboptimal Magnesium Status in the United States: Are the Health Consequences Underestimated? *Nutrition Reviews*, **70**, 153-164. https://doi.org/10.1111/j.1753-4887.2011.00465.x

[16] Costello, R.B., Elin, R.J., Rosanoff, A., Wallace, T.C., Guerrero-Romero, F., Hruby, A., *et al.* (2016) Perspective: The Case for an Evidence-Based Reference Interval for Serum Magnesium: The Time Has Come. *Advances in Nutrition*, **7**, 977-993. https://doi.org/10.3945/an.116.012765

[17] Liebscher, D.H. and Liebscher, D.E. (2004) About the Misdiagnosis of Magnesium Deficiency. *Journal of the American College of Nutrition*, **23**, 730S-731S. https://doi.org/10.1080/07315724.2004.10719416

[18] Facchinetti, F., Borella, P., Fioroni, L., Pironti, T. and Genazzani, A.R. (1990) Reduction of Monocyte Magnesium in Patients Affected by Premenstrual Syndrome. *Journal of Psychosomatic Obstetrics & Gynecology*, **11**, 221-229. https://doi.org/10.3109/01674829009084417

[19] Thomas, J., Millot, J.M., Sebille, S., Delabroise, A.M., Thomas, E. and Manfait, M. (2000) Free and Total Magnesium in Lymphocytes of Migraine Patients—Effect of Magnesium-Rich Mineral Water Intake. *Clinica Chimica Acta*, **295**, 63-75. https://doi.org/10.1016/S0009-8981(00)00186-8

[20] Razzaque, M.S. (2018) Magnesium: Are We Consuming Enough? *Nutrients*, **10**, Article 1863. https://doi.org/10.3390/nu10121863

[21] Mulquiney, Peter J., and Kuchel, Philip W. (1997) Free Magnesium-Ion Concentration in Erythrocytes by 31P NMR: The Effect of Metabolite: Hemoglobin Interactions. *NMR in Biomedicine*, **10**, 129-137. https://www.deepdyve.com/lp/wiley/free-magnesium-ion-concentration-in-erythrocytes-by-31-p-nmr-the-MAOMj0MQ1C

[22] Xiong, W., Liang, Y., Li, X., *et al.* (2016) Erythrocyte Intracellular Mg^{2+} Concentration as an Index of recognition and Memory. *Scientific Reports*, **6**, Article No. 26975. https://doi.org/10.1038/srep26975

[23] Ulger, Z., Ariogul, S., Cankurtaran, M., *et al.* (2020) Intra-Erythrocyte Magnesium levels and Their Clinical Implications in Geriatric Outpatients. *Journal of Nutrition, Health and Aging*, **14**, 810-814. https://doi.org/10.1007/s12603-010-0121-y

[24] Mansmann, H.C. (1993) Consider Magnesium Homeostasis: II: Staging of Magnesium Deficiencies. *Pediatric Allergy, Immunology and Pulmonology*, **7**, 211-215. https://doi.org/10.1089/pai.1993.7.211

[25] Kisters, K., Niedner, W., Fafera, I., and Zidek, W. (1990) Plasma and Intracellular Mg^{2+} Concentrations in Pre-Eclampsia. *Journal of Hypertension*, **8**, 303-306. https://doi.org/10.1097/00004872-199004000-00002

[26] Sales, C.H., Nascimento, D.A., Medeiros, A.C.Q., Lima, K.C., and Pedrosa, L.F.C. (2014) There Is Chronic Latent Magnesium Deficiency in Apparently Healthy University Students. *Nutricion Hospitalaria*, **30**, 200-204.

[27] Cheung, M.M., DeLuccia, R., Ramadoss, R.K., Aljahdali, A., Volpe, S.L., Shewokis, P.A. and Sukumar, D. (2019) Low Dietary Magnesium Intake Alters Vitamin D—Parathyroid Hormone Relationship in Adults Who Are Overweight or Obese. *Nutrition Research*, **69**, 82-93. https://doi.org/10.1016/j.nutres.2019.08.003

[28] Veugelers, P.J. and Ekwaru, J.P. (2014) A Statistical Error in the Estimation of the Recommended Dietary Allowance for Vitamin D. *Nutrients*, **6**, 4472-4475. https://doi.org/10.3390/nu6104472

[29] Reddy, P. and Edwards, L.R. (2019) Magnesium Supplementation in Vitamin D Deficiency. *American Journal of Therapeutics*, **26**, e124-e132. https://doi.org/10.1097/MJT.0000000000000538

[30] Ginde, A.A., Wolfe, P., Camargo, C.A., *et al.* (2012) Defining Vitamin D Status by Secondary Hyperparathyroidism in the U.S. Population. *Journal of Endocrinological Investigation*, **35**, 42-48.

[31] Dai, Q., Zhu, X., Manson, J.E., Song, Y., Li, X., Franke, A., *et al.* (2018) Magnesium Status and Supplementation Influence Vitamin D Status and Metabolism: Results from a Randomized Trial. *The American Journal of Clinical Nutrition*, **108**, 1249-1258. https://doi.org/10.1093/ajcn/nqy274

[32] Kimball, S.M., Burton, J.M., O'Connor, P.G., and Vieth, R. (2011) Urinary Calcium Response to High Dose Vitamin D3 with Calcium Supplementation in Patients with Multiple Sclerosis. *Clinical Biochemistry*, **44**, 930-932. https://doi.org/10.1016/j.clinbiochem.2011.04.017

[33] Dai, Q., Shu, X.O., Deng, X., Xiang, Y.B., Li, H., Yang, G., *et al.* (2013) Modifying Effect of Calcium/Magnesium Intake Ratio and Mortality: A Population-Based Cohort Study. *BMJ Open*, **3**, e002111. https://doi.org/10.1136/bmjopen-2012-002111

[34] Huang, F., Wang, Z., Zhang, J., Du, W., Su, C. and Jiang, H. (2018) Dietary Calcium intake and Food Sources among Chinese Adults in CNTCS. *PLOS ONE*, **13**, e0205045. https://doi.org/10.1371/journal.pone.0205045

[35] Wark, P.A., Lau, R., Norat, T. and Kampman, E. (2012) Magnesium Intake and Colorectal Tumor Risk: A Case-Control Study and Meta-Analysis. *The American Journal of Clinical Nutrition*, **96**, 622-631. https://doi.org/10.3945/ajcn.111.030924

[36] Connor, T. (2020) The Importance of the Calcium-to-Magnesium Ratio. https://thepaleodiet.com/the-importance-of-the-calcium-to-magnesium-ratio

[37] Martineau, A.R., Jolliffe, D.A., Hoope, R.L., Greenberg, L., Aloia, J.F. and Bergman, P. (2017) Vitamin D Supplementation to Prevent Acute Respiratory Tract Infections: Systematic Review and Meta-Analysis of Individual Participant Data. *BMJ*, **356**, i6583. https://www.bmj.com/content/356/bmj.i6583

[38] CDC. Centers for Disease Control and Prevention. Influenza (Flu). https://www.cdc.gov/flu/about/burden/index.html

[39] Matsuoka, H. (2005) Aldosterone and Magnesium. *Clinical Calcium*, **15**, 187-191. https://pubmed.ncbi.nlm.nih.gov/15692156/

[40] Pickering, G., Mazur, A., Trousselard, M., Bienkowski, P., Yaltsewa, N., Amessou, M., *et al.* (2020) Magnesium Status and Stress: The Vicious Circle Concept Revisited. *Nutrients*, **12**, Article 3672. https://doi.org/10.3390/nu12123672

[41] Kelly, O.J., Gilman, J.C. and Ilich, J.Z. (2018) Utilizing Dietary Micronutrient Ratios in Nutritional Research May Be More Informative than Focusing on Single Nutrients. *Nutrients*, **10**, Article 107. https://doi.org/10.3390/nu10010107

[42] DiNicolantonio, J.J. and O'Keefe, J.H. (2021) Magnesium and Vitamin D Deficiency as a Potential Cause of Immune Dysfunction, Cytokine Storm and Disseminated Intravascular Coagulation in Covid-19 Patients. *Missouri Medicine*, **118**, 68-73. http://www.ncbi.nlm.nih.gov/pmc/articles/pmc7861592/

[43] Bird, L. (2022) Magnesium: Essential for T Cells. *Nature Reviews Immunology*, **22**, 144-145.

[44] Vardhana, S. and Dustin, M.L. (2022) Magnesium for T Cells: Strong to the Finish! *Trends in Immunology*, **43**, 277-279. https://doi.org/10.1016/j.it.2022.02.004

[45] Polonikov, A. (2020) Endogenous Deficiency of Glutathione as the Most Likely

Cause of Serious Manifestations and Death in COVID-19 Patients. *ACS Infectious Diseases*, **6**, 1558-1562. https://doi.org/10.1021/acsinfecdis.0c00288

[46] Shchetinin, E., Baturin, V., Arushanyan, E., Bolatchiev, A. and Bobryshev, D. (2022) Potential and Possible Therapeutic Effects of Melatonin on SARS-CoV-2 Infection. *Antioxidants*, **11**, Article 140. https://doi.org/10.3390/antiox11010140

[47] Shi, Z., and Puyo, C.A. (2020) N-Acetylcysteine to Combat COVID-19: An Evidence Review. *Therapeutics and Clinical Risk Management*, **16**, 1047-1055. https://doi.org/10.2147/TCRM.S273700

[48] Schwalfenberg, G.K. (2021) N-Acetylcysteine: A Review of Clinical Usefulness (An Old Drug with New Tricks). *Journal of Nutrition and Metabolism*, **2021**, Article ID: 9949453. https://doi.org/10.1155/2021/9949453

[49] Twelve Steps to Optimize Your Methylation Process. https://practitionerselect.wordpress.com/2015/05/10/12-steps-to-optimize-your-methylation-process/

[50] Liu, R.M., Liu, Y., Forman, H.J., Olman, M. and Tarpey, M.M. (2004) Glutathione Regulates Transforming Growth Factor-β-Stimulated Collagen Production in Fibroblasts. *American Journal of Physiology-Lung Cellular and Molecular Physiology*, **286**, L121-L128. https://doi.org/10.1152/ajplung.00231.2003

[51] Deumer, U.-S., Varesi, A., Floris, V., Savioli, G., Mantovani, E., López-Carrasco, P., *et al.* (2021) Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS): An Overview. *Journal of Clinical Medicine*, **10**, Article 4786. https://doi.org/10.3390/jcm10204786

[52] Björkand, S., Ernberg, M. and Bileviciute-Ljungard, I. (2022) Reduced Immune System Responsiveness in Fibromyalgia—A Pilot Study. *Clinical Immunology Communications*, **2**, 46-53. https://doi.org/10.1016/j.clicom.2022.02.003

[53] Morrison, T.E., Mauser, A., *et al.* (2001) Inhibition of IFN-γ Signaling by an Epstein-Barr Virus Immediate-Early Protein. *Immunity*, **15**, 787-799. https://doi.org/10.1016/S1074-7613(01)00226-6

[54] Sinclair, E., Black, D., Epling, C.L., Carvidi, A., Josefowicz, F.Z., Bredt, B.M., *et al.* (2004) CMV Antigen-Specific $CD4^+$ and $CD8^+$ T Cell IFNγ Expression and Proliferation Responses in Healthy CMV-Seropositive Individuals. *Viral Immunology*, **17**, 445-454. https://doi.org/10.1089/vim.2004.17.445

[55] Crook, H., Raza, S., Nowell, J., Young, M. and Edison, P. (2021) Long Covid-Mechanisms, Risk Factors, and Management. *BMJ*, **374**, n1648. https://doi.org/10.1136/bmj.n1648

[56] Ghorbani, Z., Rafiee, P., Haghighi, S., *et al.* (2021) The Effects of Vitamin D3 Supplementation on TGF-β and IL-17 Serum Levels in Migraineurs: Post Hoc Analysis of a Randomized Clinical Trial. *Journal of Pharmaceutical Health Care and Sciences*, **7**, Article No. 9.https://doi.org/10.1186/s40780-021-00192-0

[57] Yasuda, K., Takeuchi, Y. and Hirota, K. (2019) The Pathogenicity of Th17 Cells in Autoimmune Diseases. *Semin Immunopathol*, **41**, 283-297. https://doi.org/10.1007/s00281-019-00733-8

[58] Dankers, W., Colin, E.M., van Hamburg, J.P. and Lubberts, E. (2017) Vitamin D in Autoimmunity: Molecular Mechanisms and Therapeutic Potential. *Frontiers in Immunology*, **7**, Article 697. https://doi.org/10.3389/fimmu.2016.00697

[59] Wang, K., Chen, W., Zhang, Z., *et al.* (2020) CD147-Spike Protein Is a Novel Route for SARS-CoV-2 Infection to Host Cells. *Signal Transduction and Targeted Therapy*, **5**, Article 283. https://doi.org/10.1038/s41392-020-00426-x

[60] Chambers, P.W. (2021) Basigin Binds Spike S on SARS-CoV2. *Open Access Library Journal,* **8**, e8064. https://doi.org/10.4236/oalib.1108064

[61] Bivona, G., Agnello, L. and Ciaccio, M. (2018) The Immunological Implication of the New Vitamin D Metabolism. *Central-European Journal of Immunology*, **43**, 331-334. https://doi.org/10.5114/ceji.2018.80053

[62] Watanabe, M., Nakamura, K., Kato, M., Okada, T., and Iesaki, T. (2021) Chronic Magnesium Deficiency Causes Reversible Mitochondrial Permeability Transition Pore Opening and Impairs Hypoxia Tolerance in the Rat Heart. *Journal of Pharmacological Sciences*, **148**, 238-247. https://doi.org/10.1016/j.jphs.2021.12.002

[63] Fan, L., Zhu, X., Zheng, Y., Zhang, W., *et al.* (2021) Magnesium Treatment on Methylation Changes of Transmembrane Serine Protease 2 (TMPRSS2). *Nutrition*, **89**, Article ID: 111340. https://doi.org/10.1016/j.nut.2021.111340

[64] Tian, J., Tang, L., Liu, X., Li, Y., Chen, J., Huang, W. and Liu, M. (2022) Populations in Low-Magnesium Areas Were Associated with Higher Risk of Infection in COVID-19's Early Transmission: A Nationwide Retrospective Cohort Study in the United States. *Nutrients*, **14**, Article 909. https://doi.org/10.3390/nu14040909

[65] Wang, E., Chen, H., Sun, B., Wang, H., Qu, H.Q., Liu, Y., *et al.* (2021) TGF Beta Levels Correlate with Covid-19 Severity. *FEBS Letters*, **595**, 2844-2844. https://doi.org/10.1002/1873-3468.14104

[66] Sun, J. and Lanier, L. (2011) NK Cell Development, Homeostasis and Function: Parallels with $CD8^+$ T Cells. *Nature Reviews Immunology*, **11**, 645-657. https://doi.org/10.1038/nri3044

[67] Ferreira-Gomes, M., Kruglov, A., Durek, P., *et al.* (2021) SARS-CoV-2 in Severe COVID-19 Induces a TGF-β-Dominated Chronic Immune Response that Does Not Target Itself. *Nature Communications*, **12**, Article 1961. https://doi.org/10.1038/s41467-021-22210-3

[68] Witkowski, M., Tizian, C., Ferreira-Gomes, M., *et al.* (2021) Untimely TGFβ Responses in COVID-19 Limit Antiviral Functions of NK Cells. *Nature*, **600**, 295-301. https://doi.org/10.1038/s41586-021-04142-6

[69] Bi, J. (2022) NK Cell Dysfunction in Patients with COVID-19. *Cellular and Molecular Immunology*, **19**, 127-129. https://doi.org/10.1038/s41423-021-00825-2

[70] Jiang, F., Yang, Y., Xue, L., Li, B. and Zhang, Z. (2017) 1α,25-Dihydroxyvitamin D3 Attenuates TGF-β-Induced Pro-Fibrotic Effects in Human Lung Epithelial Cells through Inhibition of Epithelial-Mesenchymal Transition. *Nutrients*, **9**, Article 980. https://doi.org/10.3390/nu9090980

[71] Fischer, K.D. and Agrawal, D.K. (2014) Vitamin D Regulating TGF-β Induced Epithelial-Mesenchymal Transition. *Respiratory Research*, **15**, Article 146. https://doi.org/10.1186/s12931-014-0146-6

[72] Isik, S., Ozuguz, U., Tutuncu, Y.A., Akbaba, G., Helvaci, N., Guler, S., *et al* (2011) Serum Transforming Growth Factor-Beta Levels in Patients with Vitamin D Deficiency. *European Journal of Internal Medicine*, **23**, 93-97. https://doi.org/10.1016/j.ejim.2011.09.017

[73] Yadav, H., Quijano, C., Kamaraju, A.K., Gavrilova, O., Malek, R., Chen, W., *et al.* (2011) Vitamin D Supplementation Decreases TGF-β1 Bioavailability. Protection from Obesity and Diabetes by Blockade of TGF-β/Smad3 Signaling. *Cell Metabolism*, **14**, 67-79. https://doi.org/10.1016/j.cmet.2011.04.013

[74] Yong-Chao, Q., Chen, Y.-L., Pan, Y.-H., Ling, W., Tian, F., Zhang, X.X., *et al.* (2017) Changes of Transforming Growth Factor Beta 1 in Patients with Type 2 Diabetes and Diabetic Nephropathy: A PRISMA-Compliant Systematic Review and

Meta-Analysis. *Medicine*, **96**, e6583. https://doi.org/10.1097/MD.0000000000006583

[75] Mahmudpour, M., Roozbeh, J., Keshavarz, M., Farrokhi, S. and Nabipour, I. (2020) Angiotensin II Stimulates Canonical TGF-β Signaling Pathway through Angiotensin Type 1 Receptor to Induce Granulation Tissue Contraction. *Journal of Molecular Medicine*, **93**, 289-302. https://doi.org/10.1007/s00109-014-1211-9

[76] Mahmudpour, M., Roozbeh, J., Keshavarz, M., Farrokhi, S.and Nabipour, I. (2020) COVID-19 Cytokine Storm: The Anger of Inflammation. *Cytokine*, **133**, Article ID: 155151. https://doi.org/10.1016/j.cyto.2020.155151

[77] Elkahloun, A.G. and Saavedra, J.M. (2020) Candesartan Could Ameliorate the COVID-19 Cytokine Storm. *Biomedicine & Pharmacotherapy*, **131**, Article ID: 110653. https://doi.org/10.1016/j.biopha.2020.110653

[78] Sugimoto, J., Romani, A.M., Valentin-Torres, A.M., Luciano, A.A., Ramirez Kitchen, C.M. and Funderburg, N. (2012) Magnesium Decreases Inflammatory Cytokine Production: A Novel Innate Immunomodulatory Mechanism. *The Journal of Immunology*, **188**, 6338-6346. https://doi.org/10.4049/jimmunol.1101765

[79] Barros-Martins, J., Förster, R. and Bošnjak, B. (2022) NK Cell Dysfunction in Severe COVID-19: TGF-β-Induced Downregulation of Integrin Beta-2 Restricts NK Cell Cytotoxicity. *Signal Transduction and Targeted Therapy*, **7**, Article 32. https://doi.org/10.1038/s41392-022-00892-5

[80] Chambers, P.W. (2022) Long Covid, Short Magnesium. *Open Access Library Journal*, **9**, e8736. https://doi.org/10.4236/oalib.1108736

[81] Lin, J.T., Martin, S.L., Xia, L. and Gorham, J.D. (2005) TGF-β1 Uses Distinct Mechanisms to Inhibit IFN-γ Expression in $CD4^+$ T Cells at Priming and at Recall: Differential Involvement of Stat4 and T-bet. *The Journal of Immunology*, **174**, 5950-5958. https://doi.org/10.4049/jimmunol.174.10.5950

[82] Raga, D., Soliman, D., Samaha, D. and Yassin, A. (2016) Vitamin D Status and Its Modulatory Effect on Interferon Gamma and Interleukin-10 Production by Peripheral Blood Mononuclear Cells in Culture. *Cytokine*, **85**, 5-10. https://doi.org/10.1016/j.cyto.2016.05.024

[83] Dhanda, A.D., Felmlee, D., Boeira, P., Moodley, P., Tan, H., *et al.* (2022) Patients with Moderate to Severe COVID-19 Have an Impaired Cytokine Response with an Exhausted and Senescent Immune Phenotype. *Immunobiology*, **227**, Article 152185. https://doi.org/10.1016/j.imbio.2022.152185

[84] Nabi-Afjadi, M., Karami, H., Goudarzi, K., *et al.* (2021) The Effect of Vitamin D, Magnesium and Zinc Supplements on Interferon Signaling Pathways and Their Relationship to Control SARS-CoV-2 Infection. *Clinical and Molecular Allergy*, **19**, Article 21. https://doi.org/10.1186/s12948-021-00161-w

[85] Meng, X., Nikolic-Paterson, D. and Lan, H. (2016) TGF-β: The Master Regulator of Fibrosis. *Nature Reviews Nephrology*, **12**, 325-338. https://doi.org/10.1038/nrneph.2016.48

[86] Frangogiannis, N.G. (2020) Transforming Growth Factor-β in Tissue Fibrosis. *Journal of Experimental Medicine*, **217**, e20190103. https://doi.org/10.1084/jem.20190103

[87] Woo, J., Koziol-White, C., Panettieri Jr., R. and Judea, J. (2021) TGF-β: The Missing Link in Obesity-Associated Airway Diseases? *Current Research in Pharmacology and Drug Discovery*, **2**, Article 100016. https://doi.org/10.1016/j.crphar.2021.100016

[88] Colarusso, C., Maglio, A., Terlizzi, M., Vitale, C., Molino, A., Pinto, A., *et al.* (2021) Post-COVID-19 Patients Who Develop Lung Fibrotic-Like Changes Have Lower Circulating Levels of IFN-β but Higher Levels of IL-1α and TGF-β. *Biomedicines,* **9**,

Article 1931. https://doi.org/10.3390/biomedicines9121931

[89] Sutariya, B., Jhonsa, D. and Saraf, M.N. (2016) TGF-β: The Connecting Link between Nephropathy and Fibrosis. *Immunopharmacology and Immunotoxicology*, **38**, 39-49. https://doi.org/10.3109/08923973.2015.1127382

[90] Katwa, L.C., Mendoza, C. and Clements, M. (2022) CVD and COVID-19: Emerging Roles of Cardiac Fibroblasts and Myofibroblasts. *Cells*, **11**, Article 1316. https://doi.org/10.3390/cells11081316

[91] Beilfuss, A., Sowa, J., Sydor, S., *et al.* (2015) Vitamin D Counteracts Fibrogenic TGF-β Signalling in Human Hepatic Stellate Cells both Receptor-Dependently and Independently. *Gut*, **64**, 791-799. https://doi.org/10.1136/gutjnl-2014-307024

[92] Li, X.H., Huang, X.P., Pan, L., *et al.* (2026) Vitamin D Deficiency May Predict a Poorer Outcome of IgA Nephropathy. *BMC Nephrology*, **17**, Article No. 164. https://doi.org/10.1186/s12882-016-0378-4

[93] Luo, X., Deng, Q., Xue, Y., Zhang, T., Wu, Z., Peng, H., *et al.* (2021) Anti-Fibrosis Effects of Magnesium Lithospermate B in Experimental Pulmonary Fibrosis: By Inhibiting TGF-βRI/Smad Signaling. *Molecules*, **26**, Article 1715. https://doi.org/10.3390/molecules26061715

[94] Tee, J.K., Peng, F., Tan, Y.L., Yu, B. and Ho, H.K. (2018) Magnesium Isoglycyrrhizinate Ameliorates Fibrosis and Disrupts TGF-β-Mediated SMAD Pathway in Activated Hepatic Stellate Cell Line LX2. *Frontiers in Pharmacology*, **9**, Article 1018. https://doi.org/10.3389/fphar.2018.01018

[95] Wensveen, F.N., Jelenčić, V. and Polić, B. (2018) NKG2D: A Master Regulator of Immune Cell Responsiveness. *Frontiers in Immunology*, **9**, Article 441. https://doi.org/10.3389/fimmu.2018.00441

[96] Iotti, S., Wolf, F., Mazur, A. and Maier, J.A. (2020) The COVID-19 Pandemic: Is There a Role for Magnesium? Hypotheses and Perspectives. *Magnesium Research*, **33**, 1-7. https://www.jle.com/10.1684/mrh.2020.0465

[97] Lanier, L.L. (2015) NKG2D Receptor and Its Ligands in Host Defense. *Cancer Immunology Research*, **3**, 75-582. https://doi.org/10.1158/2326-6066.CIR-15-0098

[98] Lazarova, M. and Steinle, A. (2019) Impairment of NKG2D-Mediated Tumor Immunity by TGF-β. *Frontiers in Immunology*, **10**, Article 2689. https://doi.org/10.3389/fimmu.2019.02689

[99] Zhang, H.-Y., Liu, Z.-D., Hu, C.-J., Wang, D.-X., Zhang, Y.-B. and Li, Y.-Z. (2011) Up-Regulation of TGF-β1 mRNA Expression in Peripheral Blood Mononuclear Cells of Patients with Chronic Fatigue Syndrome. *Journal of the Formosan Medical Association*, **110**, 701-704. https://doi.org/10.1016/j.jfma.2011.09.006

[100] Iempridee, T., Das, S., Xu, I. and Mertz, J.E. (2011) Transforming Growth Factor β-Induced Reactivation of Epstein-Barr Virus Involves Multiple Smad-Binding Elements Cooperatively Activating Expression of the Latent-Lytic Switch BZLF1 Gene. *American Society for Microbiology Journal of Virology*, **85**, 7836-7848. https://doi.org/10.1128/JVI.01197-10

[101] Xu, J., Ahmad, J., Jones, J.F., Dolcetti, R., Vaccher. E., *et al.* (2000) Elevated Serum Transforming Growth Factor β1 Levels in Epstein-Barr Virus-Associated Diseases and Their Correlation with Virus-Specific Immunoglobulin A (IgA) and IgM. *American Society for Microbiology Journal of Virology*, **74**, 2443-2446. https://doi.org/10.1128/JVI.74.5.2443-2446.2000

[102] Chaigne-Delalande, B., Li, F.-Y., O'Connor, G.M., *et al.* (2013) Mg^{2+} Regulates Cytotoxic Functions of NK and CD8 T Cells in Chronic EBV Infection through NKG2D. *Science*, **341**, 186-191. https://doi.org/10.1126/science.1240094

[103] Mirzaei, H. and Faghihloo, E. (2018) Viruses as Key Modulators of the TGF-β Pathway; A Double-Edged Sword Involved in Cancer. *Reviews in Medical Virology*, **28**, e1967. https://doi.org/10.1002/rmv.1967

[104] Chung, J.Y.F., Chan, M.K.K., Li, J.S.-F., Chan, A.S.-W., Tang, P.C.-T., Leung, K.-T., *et al.* (2021) TGF-β Signaling: From Tissue Fibrosis to Tumor Microenvironment. *International Journal of Molecular Sciences*, **22**, Article 7575. https://doi.org/10.3390/ijms22147575

[105] Theoharides, T., Stewart, J.M., Hatziagelaki, E. and Kolaitis, G. (2015) Brain "Fog," Inflammation and Obesity: Key Aspects of Neuropsychiatric Disorders Improved by Luteolin. *Frontiers in Neuroscience*, **9**, Article 225. https://doi.org/10.3389/fnins.2015.00225

[106] Weinstock, L.B., Brook, J.B., Walters, A.S., Gorisd, A., Afrine, L.B. and Molderings, G.J. (2021) Mast Cell Activation Syndrome (MCAS) Symptoms Are Prevalent in Long-COVID. *International Journal of Infectious Diseases*, **112**, 217-226. https://doi.org/10.1016/j.ijid.2021.09.043

[107] Nishio, A., Ishiguro, S. and Miyao, N. (1987) Specific Change of Histamine Metabolism in Acute Magnesium-Deficient Young Rats. *Drug-Nutrient Interactions*, **5**, 89-96. https://pubmed.ncbi.nlm.nih.gov/3111814/

[108] Takemoto, S., Yamamoto, A., Tomonaga, S., Funaba, M. and Matsui, T. (2013) Magnesium Deficiency Induces the Emergence of Mast Cells in the Liver of Rats. *Journal of Nutritional Science and Vitaminology*, **59**, 560-563. https://doi.org/10.3177/jnsv.59.560

[109] Kaieda, S., Fujimoto, K., Todoroki, K., Abe, Y., Kusukawa, J., Hoshino, T., *et al.* (2022) Mast Cells Can Produce Transforming Growth Factor B1 and Promote Tissue Fibrosis during the Development of Sjögren's Syndrome-Related Sialadenitis. *Modern Rheumatology*, **32**, 761-769. https://doi.org/10.1093/mr/roab051

[110] Pinto, M.D., Lambert, N., Downs, C.A., Abrahim, H., Hughes, T.D. and Rahmani, A.M. (2022) Antihistamines for Post Acute Sequelae of SARS-CoV-2 Infection. *The Journal for Nurse Practitioners*, **18**, 335-338. https://doi.org/10.1016/j.nurpra.2021.12.016

[111] Johansson, M., Ståhlberg, M., Runold, M., *et al.* (2021) Long-Haul Post-COVID-19 Symptoms Presenting as a Variant of Postural Orthostatic Tachycardia Syndrome: The Swedish Experience. *JACC: Case Reports*, **3**, 573-580. https://doi.org/10.1016/j.jaccas.2021.01.009

[112] Stewart, J.M., Taneja, I., Glover, J. and Medow, M.S. (2008) Angiotensin II type 1 Receptor Blockade Corrects Cutaneous Nitric Oxide Deficit in Postural Tachycardia Syndrome. *American Journal of Physiology-Heart and Circulatory Physiology*, **294**, H466-H473. https://doi.org/10.1152/ajpheart.01139.2007

[113] Wadhwania, R. (2017) Is Vitamin D Deficiency Implicated in Autonomic Dysfunction? *Journal of Pediatric Neurosciences*, **12**, 119-123. https://doi.org/10.4103/jpn.JPN_1_17

[114] Hoffman, B. (2021) Hoffman Centre for Integrative and Functional Medicine. https://hoffmancentre.com/chronic-inflammatory-response-syndrome-cirs-evaluation-and-treatment

[115] Shi, Y., Liu, T., Yao, L., *et al.* (2017) Chronic Vitamin D Deficiency Induces Lung Fibrosis through Activation of the Renin-Angiotensin System. *Scientific Reports*, **7**, Article No. 3312. https://doi.org/10.1038/s41598-017-03474-6

[116] Lanz, T.V., Ding, Z., Ho, P.P., Luo, J., Agrawal, A.N., Srinagesh, H., *et al.* (2010) Angiotensin II Sustains Brain Inflammation in Mice via TGF-β. *The Journal of*

Clinical Investigation, **120**, 2782-2794. https://doi.org/10.1172/JCI41709

[117] Krishna, A.R. (2020) Can You Overdose on One-Size-Fits-All Multivitamins? https://blog.ginihealth.com/can-you-overdose-on-multivitamins/

[118] Rosanoff, A., Dai, Q. and Shapses, S.A. (2016) Essential Nutrient Interactions: Does Low or Suboptimal Magnesium Status Interact with Vitamin D and/or Calcium Status? *Advances in Nutrition*, **7**, 25-43. https://doi.org/10.3945/an.115.008631