



Long Covid, Short Magnesium

Patrick W. Chambers, MD

Department of Pathology, Torrance Memorial Medical Center, Torrance, California
pwc@gte.net

How to cite this paper: Author 1, Author 2 and Author 3 (2022) Paper Title. *Open Access Library Journal*, 9: ****. https://dx.doi.org/10.4236/****.2022.****

Received: **** *, **

Accepted: **** *, **

Published: **** *, **

Copyright © 2022 by author(s) and Open Access Library Inc.

This work is licensed under the Creative Commons Attribution International License (CC BY 4.0).

<http://creativecommons.org/licenses/by/4.0/>



Abstract

Long Covid, now also reported in children, has become increasingly alarming. Perhaps a third of those who develop MIS-C go on to experience Long Covid. Etiology is elusive. The role of vitamin D in bone and immune health has been recognized but magnesium deficiency has escaped attention. A physiologic and biochemical argument for its culpability in Long Covid as well Chronic Fatigue Syndrome, Fibromyalgia, Epstein Barr Virus, and Cytomegalovirus is discussed.

Subject Areas

Pathology

Keywords

gamma interferon, bradykinin, asthma, IgG3, C1-inhibitor, receptor tyrosine kinases

1. Introduction

The definition of Long Covid varies. Some don't differentiate between long primary infection and secondary recrudescence. Some require 60 days post primary infection, others require 90 days. Furthermore, there appear to be two distinct unacknowledged subsets and this has hindered insight into etiology. These will be delineated and physiologically separated. No previous study evaluating the role of vitamin D deficiency in this mentions, much less includes, any appraisal of magnesium status. This is because the active form is Mg^{2+} . Only 1% of total magnesium is circulating but about 50% is bound to carrier proteins, predominantly albumin. This analyte is not even included in the chem panel. Of the 99% intracellular magnesium only 1-2% is ionized and free Mg^{2+} . This is critical because ionized magnesium is the active form and required for the synthesis of active vitamin D.

In view of these difficulties, ignored by previous studies and meta-analyses, a bottom up approach is adopted, one reliant upon symptoms and less on individual lab values. Currently 25(OH)D levels are defined by the average or median population level. Our society over the past century has become increasingly sun shy, driven by both cancer fears and cultural norms. In areas where this is not the mindset, circulating 25(OH)D ranges from 135 to 225 nmol/L (54–90 $\mu\text{g/L}$) [1]. This number represents eons of evolution. Migratory patterns over the past century have further compromised the validity of 20-30 ng/mL (50-75 nmoles/L) as sufficient.

This discussion will be a more complete look at magnesium and Long Covid, including the impact of our deteriorating nutrition, biologic individuality, and related physiology. It will combine the clinical with the technical, absent in previous attempts to discern the nature of Long Covid. The goal is to incentivize all who suffer from Long Covid to include vitamin D and magnesium in their therapeutic regimen.

The link between vitamin D deficiency and rickets was first discovered in the 1920s. It was not until 50 years later, in the 1970s, that the entity, magnesium deficient, vitamin D resistant rickets, was realized. In 1971 Jean Durlach founded the Society for the Development and Research on Magnesium (SDRM). But despite two excellent books on the topic, **The Magnesium Factor** (2003) by Mildred Seelig/Andrea Rosanoff and **The Magnesium Miracle** (2006 first ed., 2017 second ed.) by Carolyn Dean, research has languished (Figure 1).

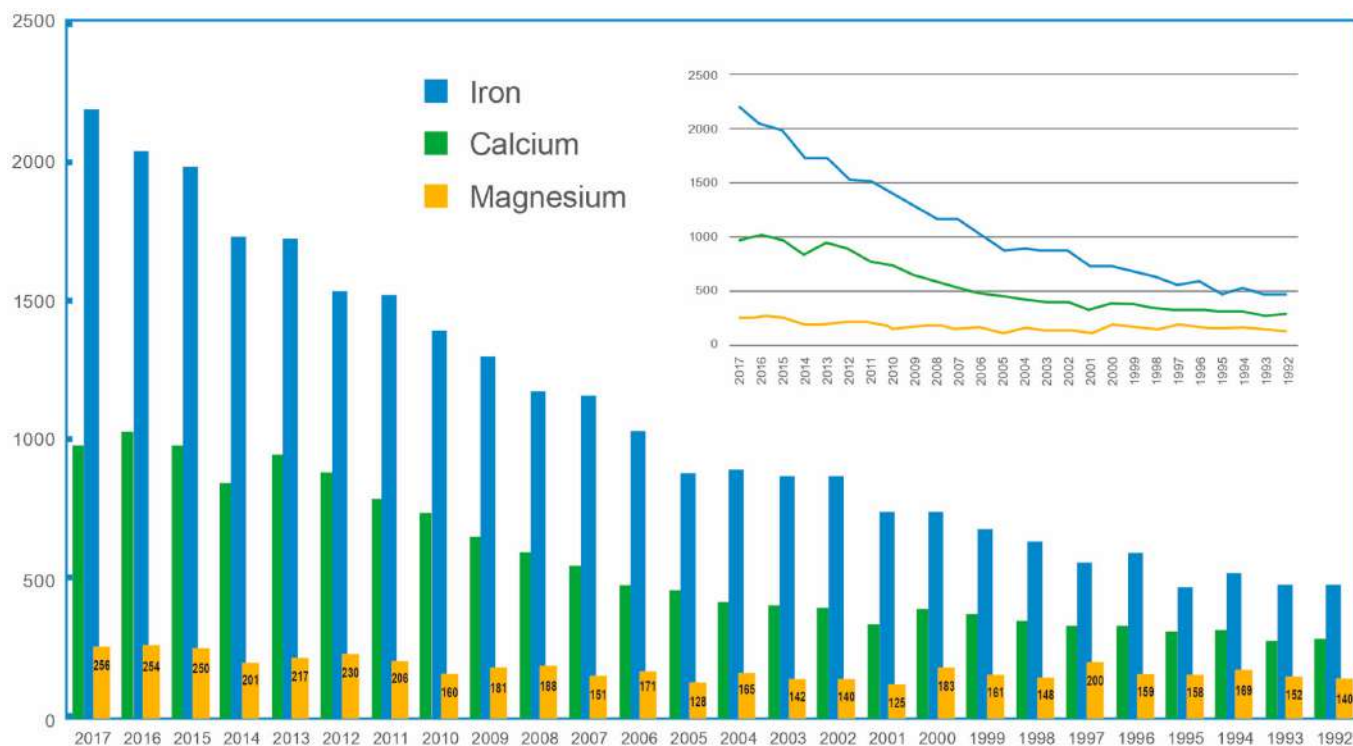


Figure 1. The number of basic and clinical research papers published (Y-axis) on Fe, Ca, and Mg [2].

Magnesium metabolism and requirements are inextricably entwined with vitamin D. One cannot discuss vitamin D without discussing magnesium. Similarly, one cannot correct a vitamin D deficiency associated problem without magnesium sufficiency (Figure 2).

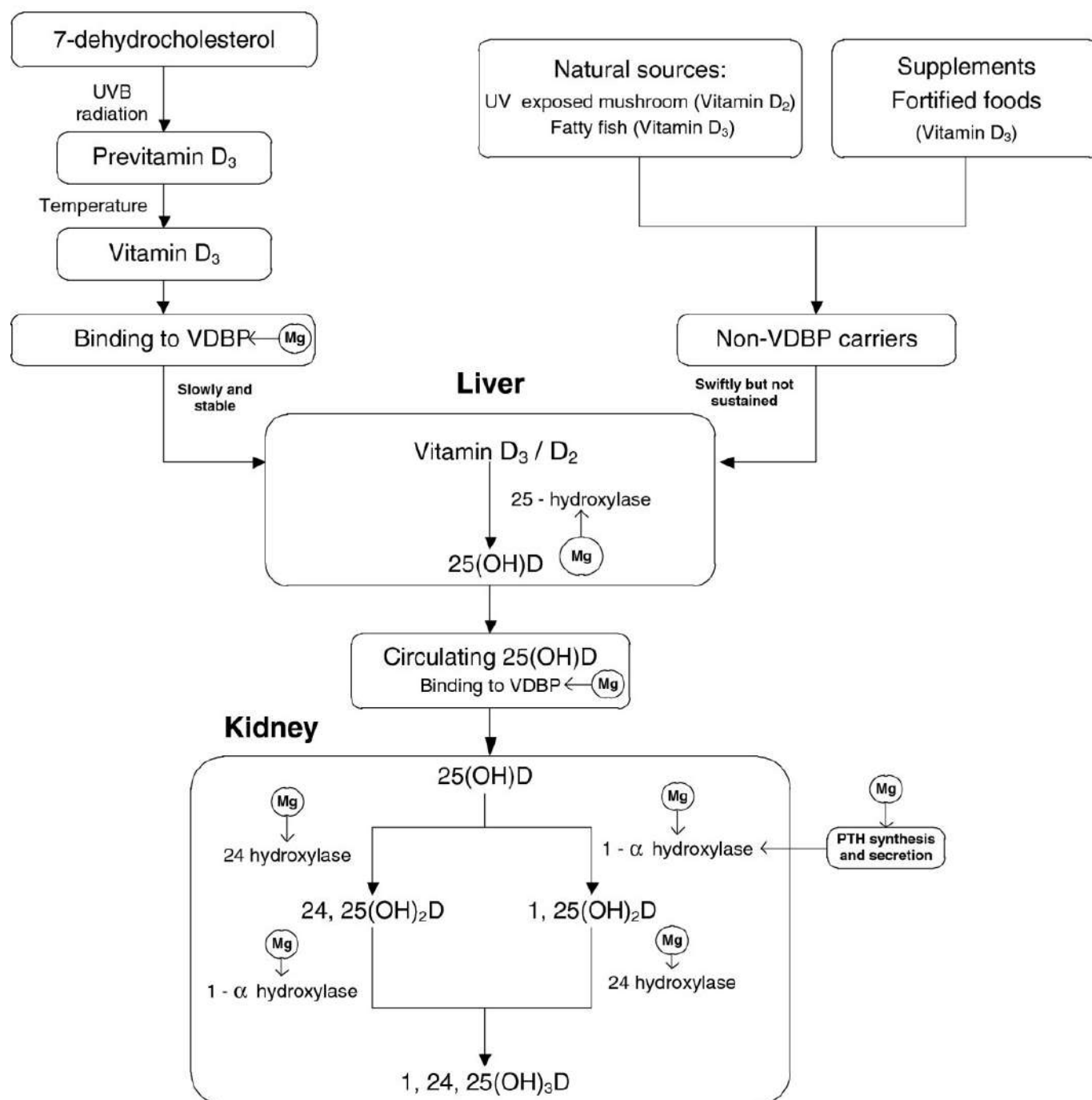
Sunlight/Skin SynthesisDietary Sources
Vitamin D₃ / D₂

Figure 2. Magnesium is not only required for the synthesis of active vitamin D [1,25(OH)₂D] but is also required for the synthesis and secretion of PTH by the parathyroid glands. Synthesis of 7-dehydrocholesterol is also Mg²⁺ dependent.

However, sudden increases in vitamin D intake in the presence of magnesium deficiency can be problematic. Existing free Mg^{2+} could be triaged from low priority functions e.g., neuromuscular, to servicing the added $D_3/25(OH)D_3$. These can manifest as signs and/or symptoms of magnesium deficiency, e.g., worsening constipation or increase in palpitations. It is noteworthy that repleting D alone will deplete Mg^{2+} . This has tarnished the value of vitamin D supplementation in many who are also magnesium deficient. In many the double deficiency persists and future supplementation is then shunned.

2. Hypothesis

Magnesium deficiency is intimately involved in the brain fog, fatigue, post-exertional malaise, headache, dizziness, myalgia and asthma of Long Covid or Post Acute Coronavirus Syndrome (PACS) also known as Post Acute Sequelae of COVID-19 (PASC).

3. Discussion

3.1. Is magnesium deficiency related to vitamin D deficiency?

A recent study demonstrated that dietary magnesium intake is inversely related to serum parathormone (PTH) concentration in the overweight and obese, especially in response to raising serum $25(OH)D$ concentration[3].

Based on dietary magnesium intake, three groups over-weight or obese (n=57) were identified: low Mg intake group (mean 131 mg/day); intermediate intake group (mean 216.9 mg/day); high intake group (mean 376 mg/day). (RDA for magnesium is 310 to 320 for women and 400 to 420 for men). The magnesium intake in the group reporting benefit (lower PTH) approached that recommended by the RDA. The median body mass index (BMI) for all three groups was 27.7-29.0, less than the mean American BMI, which is greater than 29, according to the most recent NHANES survey (2016).

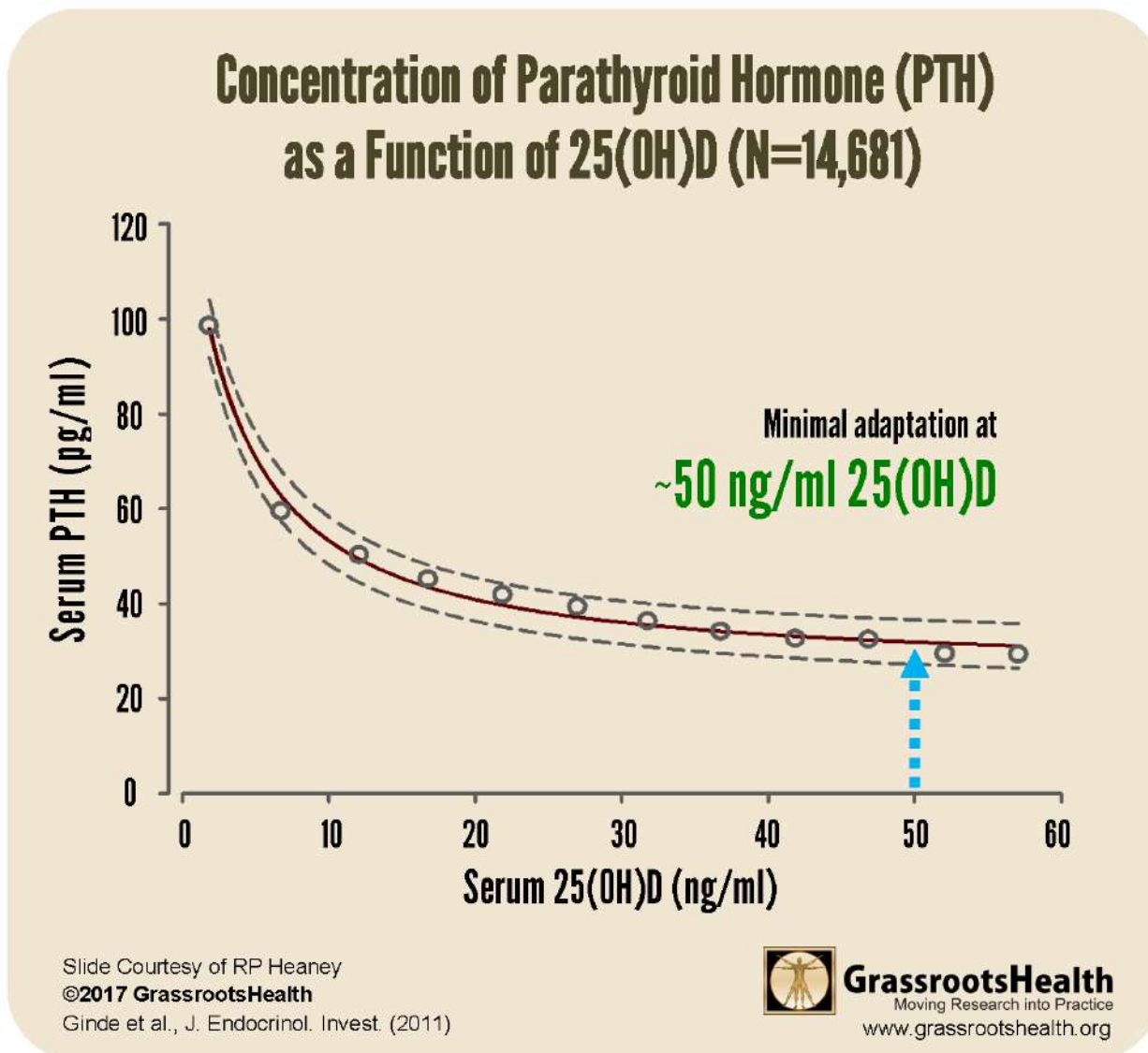


Figure 3. This curve represents the natural/physiological relationship between two hormones with plateauing of the curve when serum 25(OH)D concentration is approximately 50 ng/mL. The dashed lines represent 95% confidence limits. Data is from the 2003-6 NHANES.

The study subjects in the three groups had 25(OH)D levels between 24.6 and 27.1 ng/mL, i.e., all were magnesium deficient. However, according to Figure 3, any value less than 50 ng/mL implies deficiency, since the PTH/25(OH)D relationship is still suboptimal below that amount. Gastrointestinal absorption and renal resorption of Mg^{2+} (and Ca^{2+}) are influenced by vitamin D, which responds inversely to PTH. The latter is predominantly controlled by circulating ionized calcium (Ca^{2+}) and Mg^{2+} to a lesser extent.

The flattening of the curve at serum 25(OH)D concentrations above 50 ng/mL seems to imply an optimum balance between calcium, magnesium, PTH (and calcitonin) above this set point. In the study serum 25(OH)D concentration was inversely associated with PTH only in the high Mg^{2+} intake group. Data from that study have several implications.

- 1) In the low magnesium intake group all the magnesium is consumed by bone needs and the PTH is inappropriately low. This paradox suggests insufficient Mg^{2+} to meet PTH synthesis needs.
- 2) Magnesium is consumed by bone needs and PTH synthesis in the intermediate magnesium intake group, since the PTH was elevated (indicating the presence of some degree of secondary hyperparathyroidism and perhaps, overactive osteoclastic activity), with little magnesium left to synthesize 1,25(OH)₂D to address the osteoporosis. PTH (mean 76.3 pg/ml) and Ca:Mg (mean 3.12) were elevated in this intermediate group. Ironically any increase in magnesium intake could precipitate symptoms of magnesium deficiency due to increased PTH induced suppression of both Vitamin D synthesis and magnesium absorption/resorption.
- 3) In the high intake group not all the magnesium is consumed by bone needs and PTH synthesis. The surplus is directed to vitamin D synthesis (Figure 2). The Ca:Mg plummets, as relatively more Mg^{2+} than Ca^{2+} is absorbed, depressing PTH. Note: At least in the renal tubular cells, PTH enhances the conversion of 25(OH)D into 1,25(OH)₂D (magnesium is a required cofactor), which in turn decreases PTH secretion (Figure 2).

All were vitamin D deficient (< 30 ng/mL). But the study demonstrates that the minimum should be 50 ng/mL (not 50 nmoles/L) 25(OH)D. Vitamin D requirement for the obese is 2 to 3 times greater than that for those of normal average weight[4]. The curve in figure 3 from a 2019 study of 15000 with a mean BMI of 26.9 should be shifted to the right. The mean BMI in 2019 was over 29.

One can appreciate the importance of magnesium and the complexity of its physiology, especially when known and unknown feedback loops, polymorphisms (genes), nutrition, lifestyles, etc., are considered. Randomized clinical trials (RCTs) are rarely comparable; some incorporate controversial assumptions, are expensive, and are time-consuming.

This 50 ng/mL is not a serum concentration recommended by most meta-analyses or some prospective NIH-funded-study, but one ordained by Mother Nature through human evolution. The production of vitamin D₃ (cholecalciferol) in the skin from sunlight is essentially limited to four hours between 10 am and 2 pm. This benefit is also seasonal and needs are directly proportional to BMI. Generally, with the current lifestyles, solar exposure is rarely sufficient and supplementation is rarely adequate. Both routes to the active form are magnesium-dependent (Figure 2).

Once the minimum serum concentration of 50 ng/mL is established, evaluating magnesium status becomes easier. Unfortunately, biologic individuality, e.g., genes or single nucleotide polymorphisms (SNPs), and the complex nature of measuring free intracellular Mg^{2+} make accurate evaluation difficult. Unlike vitamin D, there are no simple laboratory tests that are reliable in this regard. This makes evaluation of symptoms or a bottom-up approach superior to a top-down one (evaluation of lab results).

In 2006 Bruce Ames[5] posited that when micronutrient availability is limited, those functions required for short-term survival take precedence over those less urgent. In the case of magnesium, it appears that skeletal needs for magnesium supersede those needed to produce active vitamin D. After all vitamin D deficient rickets was described in the 1920s. However, magnesium-deficient vitamin D-resistant rickets was not recognized until the 1970s.

The recommended serum 25(OH)D 30 ng/mL is sufficient to avoid rickets in the presence of magnesium sufficiency but is inadequate to avoid secondary hyperparathyroidism and osteoporosis. Furthermore, the minimum magnesium intake for any individual should be that necessary to maintain a 25(OH)D level above 50 ng/mL. Nevertheless, there is no measure estimating whether this amount of magnesium is sufficient to address magnesium needs for a healthy immune system.

Based on the higher incidence of osteoporosis and the lower incidence of COVID-19 in Northern Europe versus the opposite in Southern Europe, any magnesium shortfall is triaged first to bone needs. In second place are Vitamin D synthesis needs, which supersede those of immunomodulation. The high dietary calcium and 25(OH)D levels in Northern Europe create a magnesium shortfall by suppressing PTH. PTH down-regulates vitamin D, decreasing magnesium intestinal absorption and renal resorption, decreasing blood levels of magnesium (innocent bystander), and aggravating osteoporosis. Clearly, adequate vitamin D is more critical to immunomodulation than adequate magnesium, given the low incidence of COVID-19 in Northern Europe.

On the other hand, their Southern cousins have sufficient magnesium to avoid osteoporosis, but not enough to avoid a greater risk of COVID-19. Their 25(OH)D₃ levels are lower and SARS CoV2 is more often severe. There is no significant osteoporosis => vitamin D, calcium, and magnesium needs are in balance, i.e., healthy bone needs for calcium and magnesium have been satisfied, as have magnesium needs for synthesis of active vitamin D. However, there is a problem with immunomodulation compared to their northern neighbors. This confirms that magnesium needs for immunomodulation are subservient to magnesium for healthy bone and vitamin D synthesis (demonstrated in the South) and that vitamin D is more critical to immune function than any solo role in this for magnesium (demonstrated in the North).

Since neuromuscular needs are probably in the runt position, we can only assure sufficient magnesium to fulfill any immunomodulation needs by addressing neuromuscular symptoms often associated with insufficiency, via magnesium supplementation. The contribution of magnesium to immune function independent of vitamin D is vastly under appreciated.

3.2. Why is magnesium deficiency increasing?

It is decreasing because the quality of our food has decreased (Figure 4).

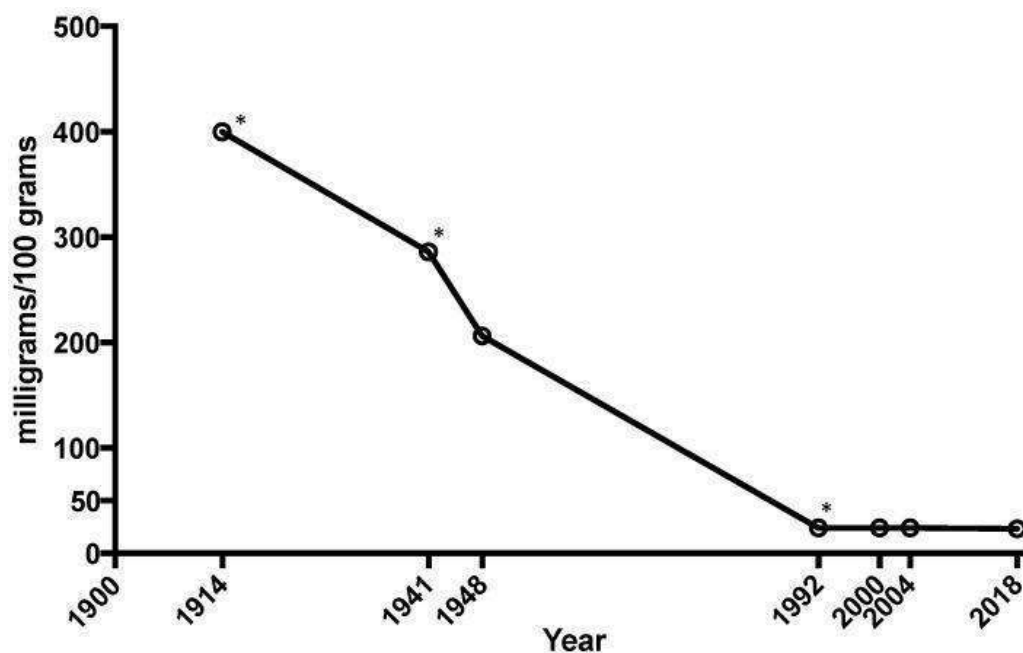


Figure 4. The average mineral content of calcium, magnesium, and iron in cabbage, lettuce, tomatoes, and spinach has dropped 80–90% between 1914 and 2018[1].

Furthermore, an increasingly sedentary lifestyle, now with work at home video-conferencing, precludes adequate sun exposure, aggravating many health issues and compromising vitamin D status. Inflammatory conditions deplete the already low stores of other vital vitamins and minerals, e.g., selenium, vitamin C, zinc,....

Humans in Western countries are consuming four times more calcium than magnesium versus the recommended 2:1 ratio. This is one of the reasons why osteoporosis is so high in those on diets high in dairy. The pharmaceutical industry has been conveniently available to address any symptoms due to a magnesium shortfall and/or any associated pain and suffering with a growing menu of helpful medications. Many of these exacerbate magnesium deficiency. A more recent (Mar 2022) and more relevant assessment of this ratio reveals it to be 6.93 in those dying of Covid versus 4.93 males/3.93 females in the general population[6].

Dehydration is at the center of muscle cramps and headaches, commonly seen in magnesium deficiency. Aldosterone triggers renal resorption of Na^+ and water, but at the expense of K^+ and Mg^{2+} , which are excreted to maintain electrical neutrality. Stress is also a major player. The hormone cortisol from the adrenal cortex exerts aldosterone-like activity.

3.3. What is the role of magnesium outside bone health and vitamin D synthesis?

Magnesium is a critical mineral in the human body and is involved in ~80% of known metabolic functions. Currently 60% of adults do not achieve the average dietary intake (ADI) and 45% of Americans are magnesium deficient[2]. Magnesium is a required cofactor for about 600 enzymatic reactions (many require vitamin B6) and serves as an activator for perhaps an additional 200[7] (many if not all of these involve ATP).

The most significant of these is its role (as an activator) storing and releasing energy generated by ATP (Figure 5). In green plants it is also involved in generating ATP through chlorophyll in photosynthesis. Eating leafy greens is healthy. Chlorophyll is identical to hemoglobin but with Mg^{2+} instead of Fe^{2+} .

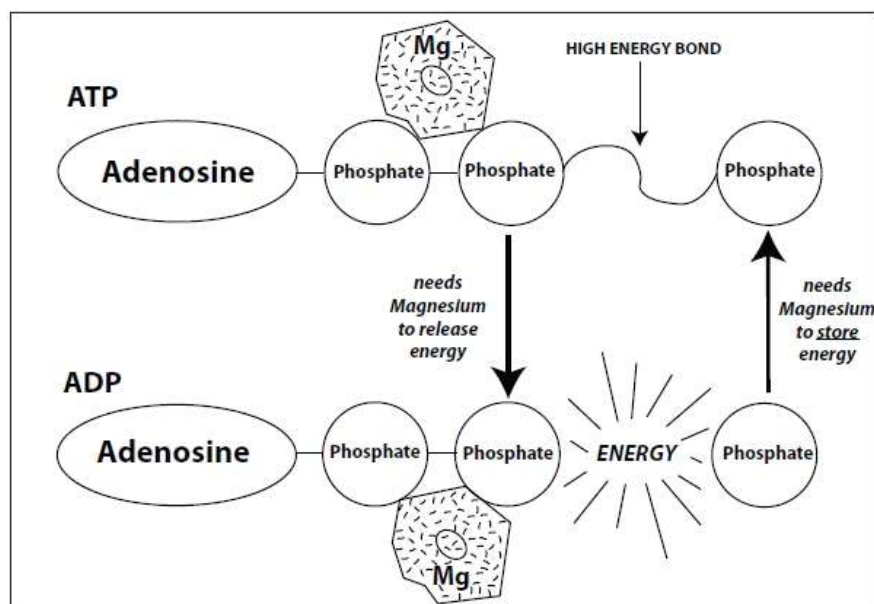


Figure 5. ATP and energy generation cannot proceed without magnesium (from **The Magnesium Factor** by Seelig and Rosanoff).

Magnesium is vital to the conduction of electrical impulses in nerves and muscles. There are three types of muscles - smooth, skeletal, and cardiac. Manifestations of magnesium deficiency in smooth muscle include constipation, bronchial asthma, and vasospasms (migraine headaches and even Prinzmetal angina due to coronary vasospasm). In skeletal muscle, it's cramps and twitches (fasciculations). In heart muscle it's palpitations (premature atrial contractions) and even atrial fibrillation. Any of these symptoms should put a magnesium shortfall on the radar.

In the immune system, the role of vitamin D is well known but poorly embraced. Vitamin D supplementation offers 10 times the efficacy of the flu shot. Magnesium (independent of vitamin D) is required for many disparate functions. But the role of magnesium in immune function is poorly understood and relatively unexplored.

Some well known natural antioxidants, e.g., glutathione and melatonin, require a magnesium cofactor for their synthesis. Melatonin, which decreases with age, also balances Th1 and Th2 cytokine responses, mimicking the benefits of vitamin D[8]. However, the role of magnesium as a receptor activator via ATP in immune function is especially intriguing. These are called receptor tyrosine kinases (RTKs) and include all the interferon receptors[9]. These ATP/Mg dependent RTKs include JAKs and TYK2 (Janus kinases 1,2,3, tyrosine kinase 2) and spotlight a very pertinent role for magnesium in immunomodulation.

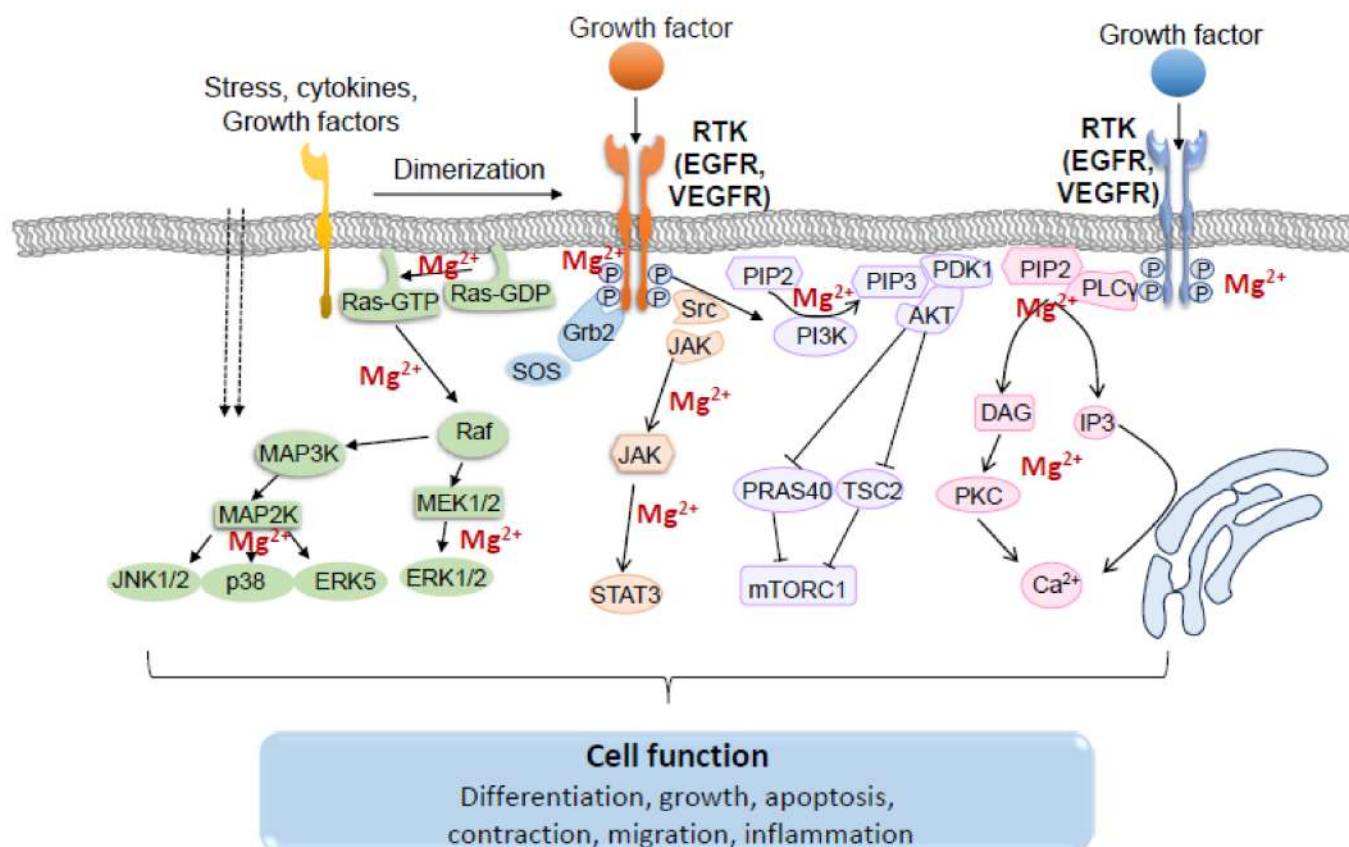


Figure 6. Note the extensive involvement of Mg²⁺[9]

3.4. Might any particular cytokine connect magnesium deficiency to Long Covid?

CD4+ and CD8+ T cell proliferation and activation are greatly reduced in Mg-deficient conditions[10]. These same cells are primarily responsible for the production of types I,II,III interferons.

Secretion of type I interferons (INF- α , INF- β) and type III interferons (INF- λ), which are innate immune cytokines (early), are induced directly by invading viruses (primary release, no interferon receptors required, STAT independent). At the same time, type II interferon gamma (INF- γ) is predominantly an adaptive immune cytokine (secondary release, interferon receptors required, STAT dependent), induced by NK (natural killer) cells (innate) and CD4+/CD8+ T cells (adaptive) via IFNGRs (INF- γ receptors)[11].

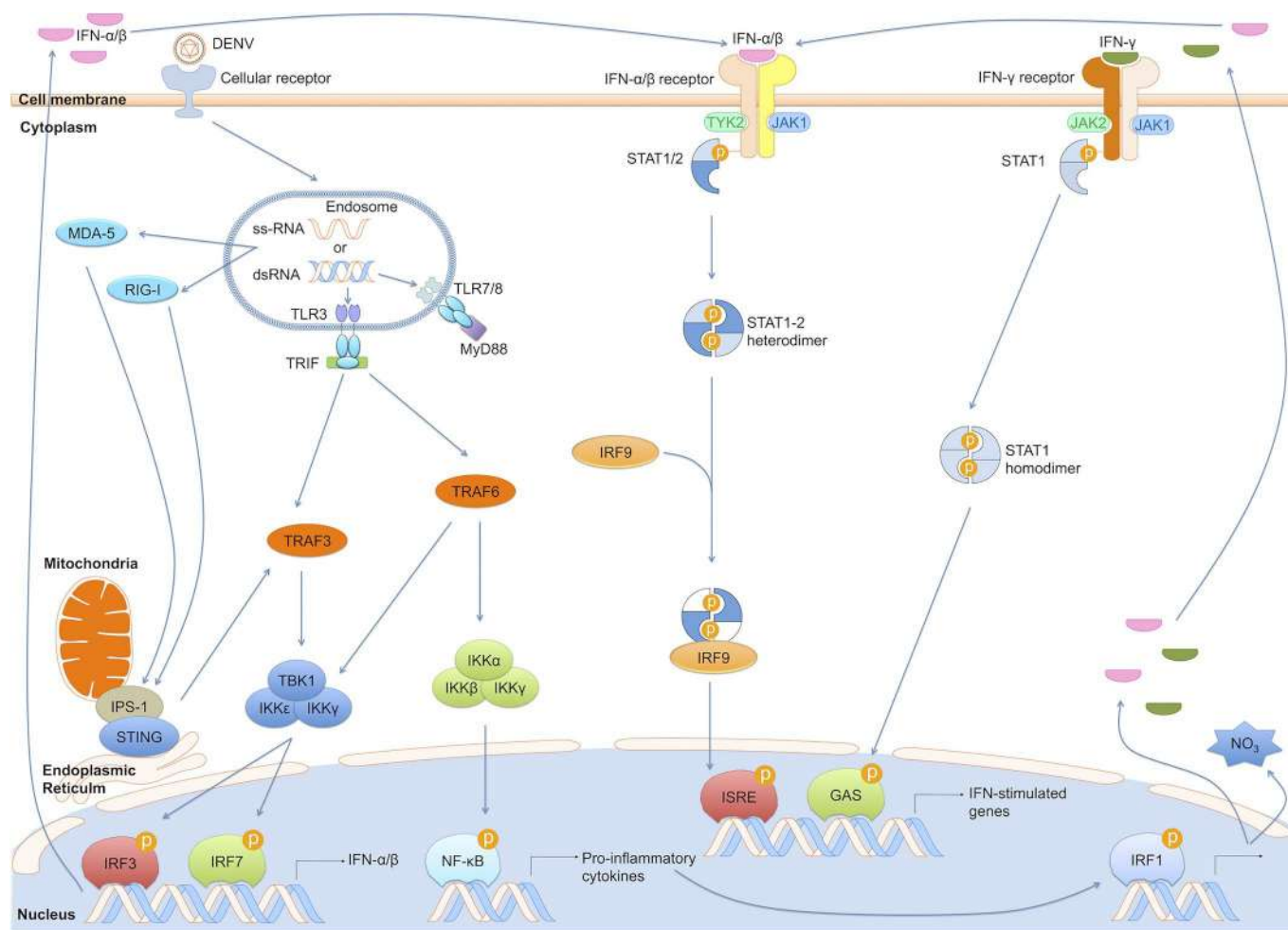


Figure 7. This demonstrates the primary and secondary releases of interferons. Note the orange Ps, which indicate ATP/Mg dependency. JAK1,2 and TYK2 are also similarly dependent [12] (P not shown). The primary release of IFN- α/β is triggered by the virus (STAT independent), while the secondary release of IFN- α/β and primary release of IFN- γ are triggered by IFN- α/β and are STAT dependent.

JAKs1,2, TYK2, STATs1,2 are ATP/Mg dependent, as are all protein kinases. So one can appreciate the overwhelming role of ATP/Mg in not only interferon production, especially IFN- γ , but also the cells (CD4+/CD8+ T cells) that secrete them (Figures 6, 7).

Accordingly, a magnesium shortfall might contribute to a decrease in IFN- γ and adaptive immunity. IFN- γ in particular is fundamental to understanding the symptoms of Long Covid and an alphabet soup of chronic inflammatory conditions (ME/CFS, FM, EBV, CMV) and autoimmune diseases (MS, SLE, RA, DM, ...). These CD4+/CD8+ T cells are the PBMCs (peripheral blood mononuclear cells) that are exhausted during prolonged COVID-19 (lymphopenia). Plasma levels of IFN- γ were significantly reduced in Covid ICU patients [11,13,14]. IFN- γ is a Th1 pro-inflammatory cytokine. But it has several beneficial effects, including blocking differentiation of naive CD4+ T (Th0) cells into Th17 cells and enhancing synthesis of the inhibitor of C1 (C1-INH) of the CCP (Classic Complement Pathway).

3.5. What causes Long Covid?

The diagnosis of Long Covid or PACS has become a bit of a mixed bag that can include those that never recovered from the primary infection, those that were never infected but developed similar symptoms during the prolonged quarantining and social isolation, those that recovered but developed unrelated but attributed symptoms, This complicates rational analysis. Accordingly, discussion is directed primarily toward those never hospitalized for COVID-19 that developed cognitive dysfunction or brain fog. Those in the ICU that developed Long Covid more than 12 weeks after discharge appear to be a separate smaller group (see Summary), probably mediated by TGF beta (transforming growth factor) and treatable by angiotensin receptor blockers (in addition to vitamin D and magnesium).

PACS or Long Covid exhibits a unique immunoglobulin signature (decreased IgM and IgG3)[[15](#)]. Ironically IgG3 and IFN- γ are proportionately elevated in both mild and severe COVID-19 cases[[16](#)]. IFN- γ actually induces IgG3 secretion[[17](#)]. Only IgG1 and IgG3 can activate CCP and only the CCP crosstalks with the KKS (Kallikrein Kinin System). Development of Long Covid may be suspected in those with indeterminate (low) IGRA (IFN- γ release assay) results[[18,19](#)]. Low IgG3 levels have also been linked to chronic fatigue syndrome (CFS)[[20,21](#)], which suggests IFN- γ may also be lower in CFS. IFN γ enhances synthesis of C1-INH in PBMCs and the liver[[22,23](#)], suppressing over-activation of the CCP. So low IgG3 and low IFN- γ in Long Covid and CFS translate to less C1-INH and more C1 activation (Figure 10). Once C1 has been activated, the CCP begins crosstalk with the KKS[[24](#)]. The lectin complement pathway (LCP) and the alternative complement pathway do not cross talk with the KKS, because neither activates C1q.

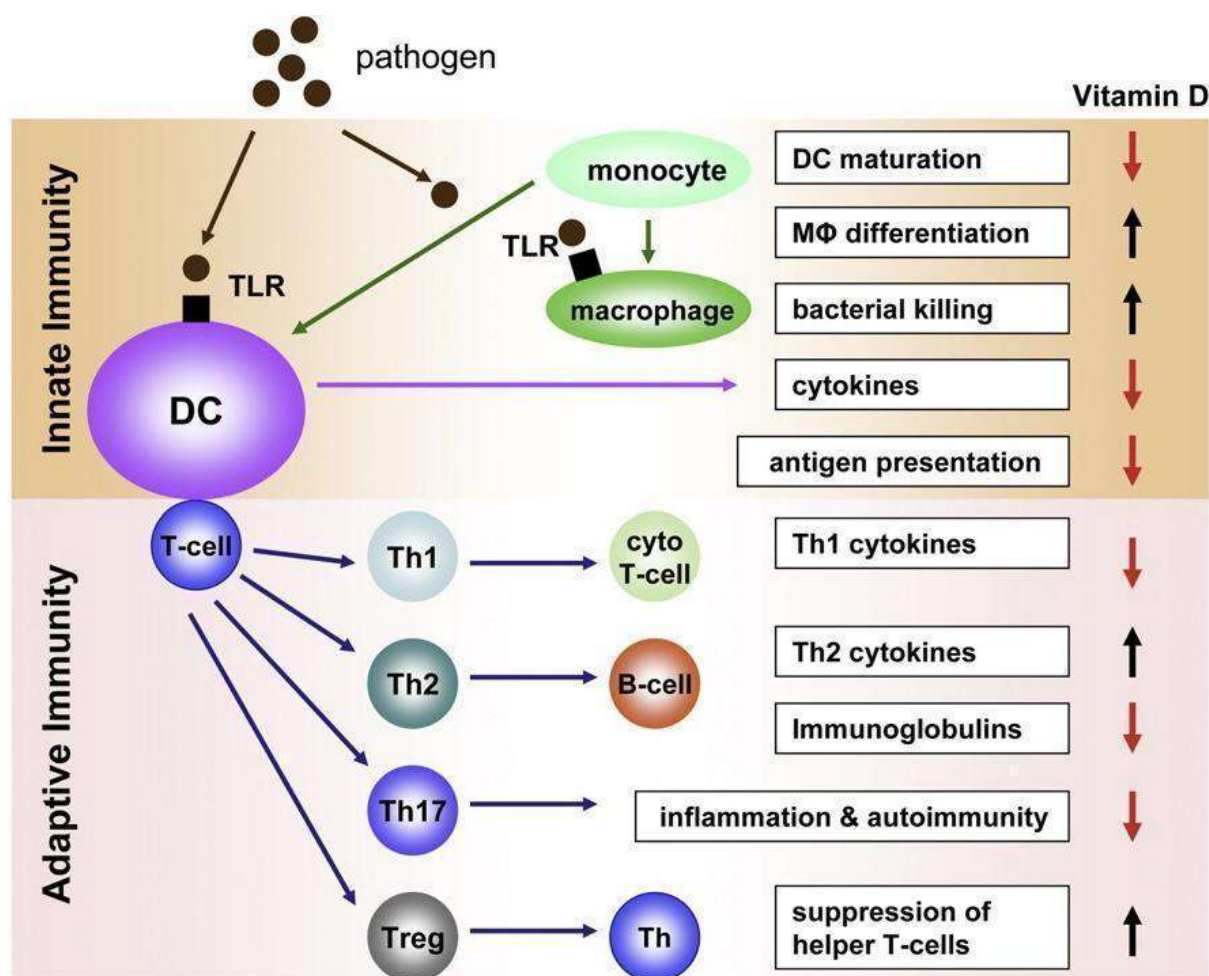


Figure 8. Vitamin D operates in both the innate and adaptive immunity phases, promotes anti-inflammatory cytokines, and balances the Th1/Th2 immune response[25].

There are two types of asthma, allergic and non-allergic. Vitamin D was adequate ($25(\text{OH})\text{D} > 30 \text{ ng/mL}$) in only 15% of pediatric asthmatics v 80% of healthy controls[26]. This suggests that the majority of asthmatics are non-allergic. The risk of severe disease in COVID-19 is increased in non-allergic asthma[27,28]. On the other hand allergic asthma (defined by the presence of eosinophilia) provides protection against COVID-19[29]. Might much of this non-allergic asthma be due to magnesium deficiency causing bronchial smooth muscle spasm[30]? Might this group of asthmatics be at greater risk of Long Covid (and Multisystem Inflammatory Syndrome in Children or MIS-C)[15]?

This is the same pediatric sub-population (asthmatic and vitamin D deficient) that develops MIS-C. So, asthma in these children and adults (MIS-A) may be a marker for magnesium deficiency. Unfortunately in those at risk for MIS-C (and Long Covid) a sudden increase in vitamin D intake without simultaneously adding magnesium could further exacerbate symptoms due to triage. In addition to vitamin D (Figure 8), melatonin also helps balance the Th1/Th2 response[8]. But magnesium is a required cofactor for the synthesis of serotonin, the precursor to melatonin. Melatonin and asthma seem to connect magnesium to Long Covid.

Low IFN γ in COVID-19 is also associated with lung fibrosis[31] => post exertional malaise, breathlessness, fatigue in Long Covid. Toxoplasma gondii, Cryptosporidium, Blastocyst, and Giardia infections downgraded COVID-19 severity via elevation of IFN- γ [32]. This speaks to the beneficial C1 inhibiting properties of IFN- γ , i.e., inhibition of CCP with inhibition of crosstalk to the KKS. Therefore, depleted IFN- γ seems to translate to an acquired angioedema type clinical condition. Long Covid brain fog, fatigue, and breathlessness may be a function of low IFN- γ , causing lung fibrosis, mild angioedema, and less C1 INH (more C1) due to activation of the CCP and crosstalk with the KKS.

Due to the extensive ATP/Mg requirements for activation of naïve CD4+ T (Th0) cells and their release of interferons, magnesium deficiency could easily result in low IFN γ levels/low melatonin levels and mimic or exacerbate Long Covid[33]. Indeed one could probably expand this to include CFS, FM, EBV (chronic phase), and CMV (chronic phase) in combination with magnesium deficiency. All vitamin D receptors (VDRs) require zinc. Zinc deficiency could also masquerade as vitamin D deficiency and Long Covid[34].

MIS-C[35] (and probably Kawasaki's Disease), MIS-A, and Long Covid seem to be products of the classical complement pathway (antibody mediated (exhausted IgG3)) and the KKS. Not surprisingly Long Covid can frequently make a delayed appearance in MIS-C (10-30%)[36]. Asthma is the only reported pre-existing medical condition in pediatric Long Covid[37].

In summary low levels of IFN- γ (due to exhausted CD4+ and CD8+ T cells) with commensurately low levels of C1-INH result in activation of C1 and the CCP with crosstalk to the KKS. This creates an acquired angioedema clinically in those with increased Th1/Th2 and decreased IFN- γ , i.e., those that are vitamin D/Mg deficient and/or T cell exhausted => Long Covid.

3.6. What population does Long Covid target?

If we approach the question from the perspective of an activated KKS, then bradykinin (BKN) should be the starting point.

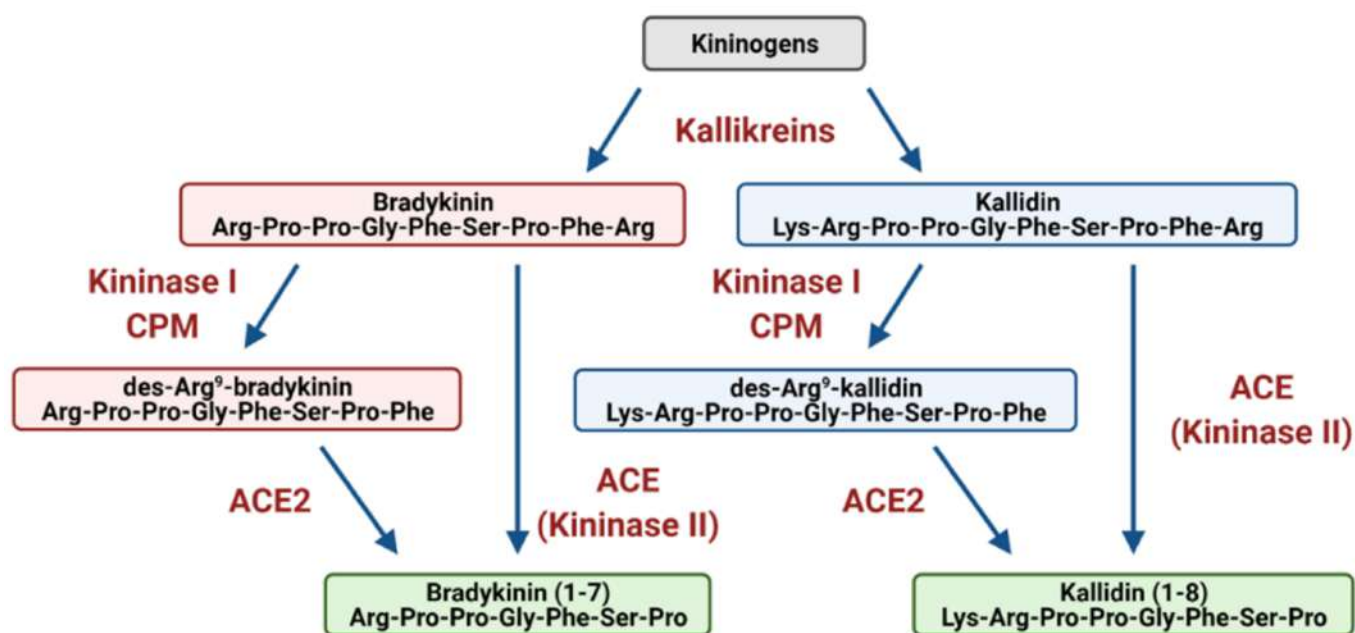


Figure 9. BKN (1-9), BKN (1-8), Kallidin (1-10) or LYS-BKN, and Kallidin (1-9) are all vasoactive peptides. BKN/Kallidin trigger B2 receptors and BKN (1-8)/Kallidin (1-9) trigger B1 receptors. The green boxes are inactive metabolites[38].

ACE is the main enzyme responsible for BKN and LYS-BKN degradation [39]. The half-life of BKN is age independent. In men it is shorter than in women, because estrogen down-regulates ACE levels (vitamin D down-regulates estrogen)[40]. This means that Long Covid is more likely in women[39]. BKN operates via BKN2Rs and causes vascular leakage (Figure 9). Loose endothelial intercellular junctions are associated with brain fog [41,42].

ACE levels for the ACE DD haplotype are up to 70% higher [43,44]. The ACE DD haplotype is more common in African-Americans, which means that they are less likely to develop Long Covid, unless they were in the ICU (see Summary). The evolutionary pressure of falciparum malaria favors the DD haplotype[45] and provides protection against both Covid brain fog and childhood cerebral malaria [45,46]. This explains the mild pulmonary angioedema seen in many hypertensive African Americans on angiotensin converting enzyme inhibitors (ACEIs) [47]. So both the ACE DD haplotype and COVID-19 enhance ACE and RAS activity but reduce BKN and KKS activity. The incidence of the ACE DD haplotype is greater in power sport athletes. On the other hand, a high kinin ACE II haplotype has been associated with enhanced endurance performance at an Olympic level, especially in triathlons(48).

According to a recent study, females appear to be more susceptible to Covid brain fog, 63% v 37% [46], the reverse of the COVID-19 gender breakdown. Age (median 43) and BMI (median 26) had no impact on cognitive function between those PCR+ and those PCR- (non hospitalized) long haulers, first seen for brain fog 5-6 months after onset of COVID-19 symptoms[46]. Covid brain fog seems to prefer Caucasians (88%) over African Americans (6%) [46]. BKN can increase the permeability of the blood brain barrier [46] and the blood-gas barrier (lungs).

ACE/ACE2 provides a balance between angiotensin II and BKN with respect to thrombosis on the one hand and vascular permeability on the other. Too much ACE produces thrombotic microangiopathy (TMA). Too much BKN results in vascular leakage and angioedema. Therefore, Long Covid seems to prefer premenopausal/perimenopausal females with the ACE II haplotype. The increase in osteoporosis risk at menopause may enhance the magnesium shortage due to triage. Severe COVID-19 prefers males with the ACE DD haplotype (and those that live at altitude)[49]. Those that survive the ICU can also develop Long Covid (see Summary). This is a much smaller subset of Long Covid.

The immunological differences between COVID-19 and Long Covid are:

1. Severe COVID-19 represents a problematic immune response, in which Th1>Th2 in responding to an invading pathogen, e.g., antibody independent. It involves mannose binding lectins (MBLs), MBL associated serine protease (MASP2), and the LCP[50] with activation of C2,4. Although it is strongly associated with vitamin D/magnesium deficiency, the KKS is uninvolved and not activated by the LCP (no crosstalk).
2. Long Covid and MIS-C/MIS-A represent a problematic immune response, in which Th1>Th2 in responding to Ag-Ab or immune complex, i.e., antibody dependent. This is a secondary response after mild to moderate primary exposure and recovery. It involves the classical complement pathway[50], activates the KKS via C1 activation of the CCP with crosstalk (Figure 10), and is strongly associated with vitamin D/magnesium deficiency.

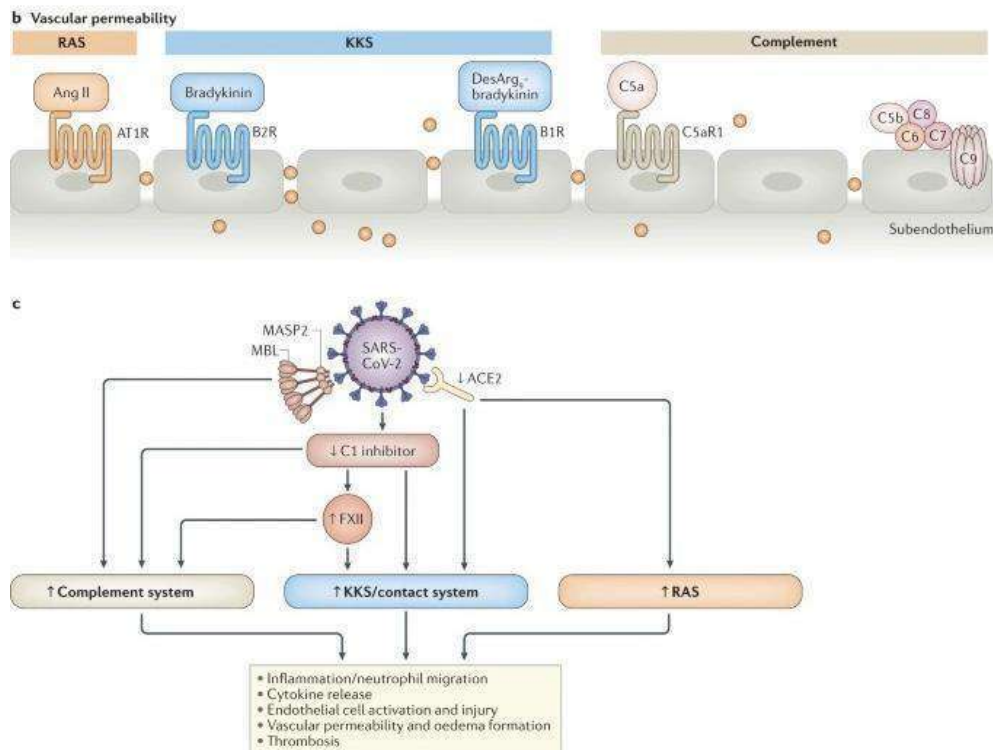


Figure 10. If IFN- γ is decreased and C1-INH with it, both Complement and the KKS are activated. If ACE2 is decreased, B1Rs are also activated (Figure. 9)[51].

3.7. Is Long Covid one of the faces of magnesium deficiency?

Frequent symptoms of magnesium deficiency

- Fatigue
- Migraines
- Sleeplessness
- Stress
- Depression and anxiety
- Hyperalgesia
- Asthma

Frequent symptoms of Long Covid

- Breathlessness
- Fatigue
- Brain fog
- Hyperalgesia
- Sleeplessness
- Headaches
- Asthma

3.8. What other faces does magnesium deficiency wear?

An alphabet soup of chronic inflammatory diseases seem to reflect a vitamin D/magnesium deficiency through decreased IFN- γ expression [52]. IFN- γ signaling seems to be at the heart of many chronic inflammatory conditions, including EBV, CMV, Fibromyalgia, CFS/ME, and Long Covid[53,54,55,56]. Initially IFN- γ levels are high, but then the CD4+/CD8+ T cells producing the IFN- γ become exhausted with decreased IFN- γ . Although IFN- γ plays a prominent role in autoimmune disease, some findings are contradictory[57]. But what is clear is that vitamin D deficiency is involved in the pathogenesis of autoimmune disease[58,59]. Th17 cells and their IL17 cytokine, markers for COVID-19 severity and autoimmune disease[60], are unchallenged (see fig.8).

3.9. How to address Long Covid?

Whether Long Covid is due to a smoldering viral infection and/or sterile inflammation and/or exhaustion of T cells and/or consumption of magnesium is unclear. But biologic individuality dictates a bottom up approach to magnesium with attention to neuromuscular symptoms (“runt” symptoms) to assure coverage of immunomodulation needs.

Upon initiation of vitamin D supplementation magnesium (and vitamin K2) must be included[61] or one risks an exacerbation of magnesium deficiency symptoms (and ectopic calcifications) due to triage, e.g., sleeplessness[62]. Sleeplessness can occur, because magnesium (and vitamin B6) is required for the conversion of glutamate (excitatory) to GABA (calming); both are neurotransmitters. Magnesium also blocks access of glutamate to excitatory NMDA receptors. Others have reported palpitations, constipation, and/or muscle cramps that disappeared after cessation of vitamin D supplementation.

Magnesium supplementation itself must also be approached carefully. Most have a laxative effect, especially magnesium citrate. Exceeding bowel tolerance results in loss of magnesium and potassium. Magnesium in chelated form to malate, taurate, threonate, glycinate, or another amino acid is recommended. An increase in palpitations has been reported with magnesium glutamate and magnesium aspartate. Magnesium oxide is poorly absorbable. Aqueous magnesium (Mg^{2+}) was previously considered highly absorbable, but the size of the hydrated cation compromises passive ion channel passage, which is otherwise responsible for the vast majority of small bowel absorption[2]. Furthermore absorption via active transport requires ATP and is magnesium dependent. If supplementing, it is also important to differentiate the magnesium content by weight per tablet (“elemental Mg” or “Mg as ...”) versus total tablet weight and to note how many tablets per serving. Furthermore, do not overlook the transdermal approach ($MgCl_2$, $MgSO_4$ can be absorbed through hair follicles) Avoid any oral route-related adverse reactions like laxative effect.

4.0. Summary

If 25(OH)D3 blood level is less than 50ng/ml, one is not only vitamin D deficient but also magnesium deficient. A vitamin D problem cannot be fixed in the face of a magnesium problem, e.g., vitamin D resistant magnesium deficient rickets. Modern osteoporosis seems to reflect a vitamin D resistant magnesium deficient entity. Surely this implies the existence of vitamin D resistant magnesium deficient immune dysfunction.

Asthma paradoxically reduces risk for COVID-19 but increases it for MIS-C/MIS-A and Long Covid. But separation of allergic asthma from non-allergic asthma provides clarification. The eosinophils in the former and the smooth muscle bronchospasm in the latter shed light on this.

Magnesium deficiency compromises both CD4+/CD8+ T cell activation/proliferation and interferon production, especially IFN- γ (adaptive immunity). IFN- γ normally signals B lymphocytes to produce IgG3, which may be decreased due to a magnesium shortfall. This decrease in IFN- γ is assisted by exhaustion of CD4+/CD8+ T cells, which are responsible for its production. In those who develop PASC IFN- γ , TNF-alpha, and IL-6 are elevated in early recovery (<90 days) but only IL-6 is persistently elevated in late recovery (>90 days)[63]. The domino effect of low IFN- γ leads to low C1-INH. Decrease in the latter promotes activation of the CCP which “crosstalks” with the KKS. The ACE II haplotype and estrogen then can explain the demographics of Long Covid.

IFN- γ links Long Covid with many other chronic inflammatory diseases. Indeed it links magnesium deficiency to dysfunctional immunomodulation. Vitamin D deficiency has been strongly linked to autoimmune disease[58], but for pleiotropic IFN- γ much of the research has yielded paradoxical results - pro-inflammatory in one circumstance yet anti-inflammatory in another[64,65,66]. IFN- γ can also promote tumor progression in one instance but regression in another[67]. Nonetheless, despite our lack of understanding on this, efforts toward achieving adequate vitamin D and magnesium seem prudent.

This article is more speculative in some ways than definitive but is based on the latest research. There are other opinions on the pathogenesis of Long Covid. For example, EBV inhibits IFN- γ signaling and Long Covid may represent reactivation of EBV, which has remarkably similar symptoms[68,69]. Or EBV could be reactivated by elevated TGF beta[70].

Discussion has been limited to Long Covid in the non-hospitalized. But there appear to be two kinds of Long Covid, both vitamin D/magnesium deficient - white middle aged women (and children) who contracted COVID-19 but were never hospitalized and those with comorbidities who were.

Those that developed Long Covid more than 12 weeks after discharge from the ICU (severe not mild COVID-19) appear to be different (a smaller subset). In addition to low IFN- γ , TGF beta (transforming growth factor) is elevated[71]. TGF beta inhibits IFN- γ [72] and is elevated in diabetics, especially those with nephropathy[73], in hypertensives[74], and in the obese[75]. SARS-CoV-2 in severe COVID-19 induces a TGF- β -dominated chronic immune response[76].

TGF beta is also elevated in POTS, which shares some dysautonomic features with Long Covid[77] and is treated with losartan[78]. Vitamin D deficiency has also been implicated in autonomic dysfunction[79]. Elevated TGF beta also connects CFS/ME with Long Covid[80,81]. High levels of TGF beta are associated with hard to treat asthma attacks, fibrosis in organs such as the liver/kidney/lungs[82], and autoimmunity. The elevated TGF beta in CIRS (Chronic Inflammatory Response Syndrome), which overlaps with Long Covid symptoms, can be lowered with losartan[83].

Ang II induces TGF- β expression via AT1Rs[84] and is treatable by angiotensin receptor blockers[85,86] (in addition to vitamin D/magnesium). Pulmonary fibrosis through activation of the RAS can be seen in chronic vitamin D deficiency[87].

Indeed an elevated TGF-beta/IFN-gamma ratio post COVID-19 might predict those most likely to develop PACS in both those never hospitalized and those that survive the ICU. Perhaps some future meta-analysis or RCT will answer this question.

The role of magnesium in human health cannot be underestimated and its solo role in immune function is complex. This discussion only scratches the surface. Genetic and epigenetic considerations that control Th1 and Th2 responses are in large measure a black box(88).

Ironically the Frontline Covid Critical Care Alliance (FLCCC) makes no mention of magnesium in any of its protocols - general prevention, hospitalized treatment, long haul prevention. In fact only three items appear in all three protocols - vitamin D, vitamin C, and melatonin. Two of these require magnesium for their synthesis. Perhaps that is why they are on all three protocols. Almost everyone is short magnesium.

5.0. Conclusion

The involvement of magnesium in human physiology is so comprehensive as to be almost beyond comprehension. Its role in preventing Long Covid is but a sliver, albeit a hot one at this time. Vaccination status is irrelevant. Whether or not you are taking vitamin D, and you should be, consider adding magnesium to your regimen. It might ameliorate some of your Long Covid-like symptoms and that list is long.

Acknowledgements

The author greatly appreciates the input of Dr. Sunil Wimalawansa.

References

1. Hollis, BW, (2005) "Circulating 25-Hydroxyvitamin D Levels Indicative of Vitamin D Sufficiency: Implications for Establishing a New Effective Dietary Intake Recommendation for Vitamin D" *The Journal of Nutrition*, 135(2):317–322 <https://doi.org/10.1093/jn/135.2.317>
2. Workinger, J. L., R. P. Doyle and J. Bortz (2018). "Challenges in the diagnosis of magnesium status." *Nutrients* 10(9). <https://dx.doi.org/10.3390/nu10091202>
3. Cheung, M. M., R. DeLuccia, R. K. Ramadoss, A. Aljahdali, S. L. Volpe, P. A. Shewokis and D. Sukumar (2019). "Low dietary magnesium intake alters vitamin D-parathyroid hormone relationship in adults who are overweight or obese." *Nutr Res* 69: 82-93. <https://doi.org/10.1016/j.nutres.2019.08.003>
4. Ekwaru JP, Zwicker JD, Holick MF, Giovannucci E, Veugelers PJ (2014). "The Importance of Body Weight for the Dose Response Relationship of Oral Vitamin D Supplementation and Serum 25-Hydroxyvitamin D in Healthy Volunteers." *PLoS ONE* 9(11): e111265. <https://doi.org/10.1371/journal.pone.0111265>
5. Ames, BN (2006). "The "triage theory": micronutrient deficiencies cause insidious damage that accelerates age-associated chronic disease." *PNAS* 103-17589-94 <http://www.bruceames.org/Triage.pdf>
6. Guerrero-Romero F, Mercado M, Rodriguez-Moran M, Ramirez-Renteria C, Martínez-Aguilar G, Marrero-Rodríguez D, et al. (2022) "Magnesium-to-Calcium Ratio and Mortality from COVID-19" *Nutrients* 14(9):1686. <https://doi.org/10.3390/nu14091686>
7. Jeroen H. F. de Baaij, Joost G. J. Hoenderop, and René J. M. Bindels (2015). "Magnesium in Man: Implications for Health and Disease." *Physiological Reviews* 2015 95:1, 1-46 <https://doi.org/10.1152/physrev.00012.2014>

8. Hosseini, A., H. Esmaili Gouvarchin Ghaleh, H. Aghamollaei, M. Fasihi Ramandi, G. Alishiri, A. Shahriary, K. Hassanpour, M. Tat and G. Farnoosh (2021). "Evaluation of Th1 and Th2 mediated cellular and humoral immunity in patients with COVID-19 following the use of melatonin as an adjunctive treatment." *Eur J Pharmacol* 904: 174193. <https://dx.doi.org/10.1016%2Fj.ejphar.2021.174193>
9. Zou Z-G, Rios FJ, Montezano AC, Touyz RM (2019). "TRPM7, Magnesium, and Signaling." *International Journal of Molecular Sciences* 20(8):1877. <https://doi.org/10.3390/ijms20081877>
10. Stefano Iotti, S., Wolf, F., Mazur, A., Maier, JA. (2020) "The COVID-19 pandemic: is there a role for magnesium? Hypotheses and perspectives." *Magnesium Research*. 33(2):21-27. <https://doi.org/10.1684/mrh.2020.0465>
11. Kim, M. H., S. Salloum, J. Y. Wang, L. P. Wong, J. Regan, K. Lefteri, Z. Manickas-Hill, C. Gao, J. Z. Li, R. I. Sadreyev, X. G. Yu, R. T. Chung, M. C. (2021). "Type I, II, and III interferon signatures correspond to coronavirus disease 2019 Severity." *J Infect Dis* 224(5): 777-782. <https://doi.org/10.1093/infdis/jiab288>
12. Adam Taylor, Suan-Sin Foo, Roberto Bruzzone, Luan Vu Dinh, Nicholas J. C. King, Suresh Mahalingam (2015) "Fc receptors in antibody-dependent enhancement of viral infections" *Immun Rev* 268(1):340-68. <https://doi.org/10.1111/imr.12367>
13. Goletti, D., L. Petrone, D. Manissero, A. Bertoletti, S. Rao, N. Ndunda, A. Sette, V. Nikolayevskyy et al. (2021) "The potential clinical utility of measuring severe acute respiratory syndrome coronavirus 2-specific T-cell responses." *Clin Microbiol Infect*. 2021 Dec; 27(12): 1784–1789. <https://doi.org/10.1016/j.cmi.2021.07.005>
14. Ling, N., C. Meng-Li, F. Yu, Z. Hui, L. Jingyuan, Y. Fang, Y. Qing, Z. Gengzhen, et al. (2022) "Impaired Cellular Immunity to SARS-CoV-2 in Severe COVID-19 Patients." *Front.Immunol*. 12:603563 <https://dx.doi.org/10.3389%2Ffimmu.2021.603563>
15. Cervia, C., Zurbuchen, Y., Taeschler, P. et al. (2022) "Immunoglobulin signature predicts risk of post-acute COVID-19 syndrome." *Nat Commun* 13:446 <https://doi.org/10.1038/s41467-021-27797-1>
16. Luo H, Jia T, Chen J, Zeng S, Qiu Z, Wu S, Li X, Lei Y, et al (2021) "The Characterization of Disease Severity Associated IgG Subclasses Response in COVID-19 Patients." *Front. Immunol*. 12:632814. <https://dx.doi.org/10.3389%2Ffimmu.2021.632814>
17. Morales-Núñez,J.J., Muñoz-Valle, J.F., Torres-Hernández, P.C., Hernández-Bello, J. (2021) Overview of Neutralizing Antibodies and Their Potential in COVID-19. *Vaccines* 2021, 9, 1376. <https://doi.org/10.3390/vaccines9121376>
18. Palacios-Gutiérrez, JJ, A Rodríguez-Guardadob, M Arias-Guilléc, R Alonso-Ariasd, S Palacios-Penedoe, J-M García-García, et al (2022) "Clinical and epidemiological correlates of low IFN-gamma responses in mitogen tube of QuantiFERON assay in tuberculosis infection screening during the COVID-19 pandemic: A population-based marker of COVID-19 mortality?" *Arch Bronconeumol*. <https://archbronconeumol.org/en-clinical-epidemiological-correlates-low-ifn-gamma-avance-S0300289622000825>
19. Borekci, S., FG Karakas, S Sirekbasan, B Kubat, R Karaali, G (2021) "The Relationship between Pre-Pandemic Interferon Gamma Release Assay Test Results and COVID-19 Infection: Potential Prognostic Value of Indeterminate IFN-γ Release Assay Results." *Canadian Journal of Infectious Diseases and Medical Microbiology* Volume 2021, Article ID 1989277, 9 pages <https://dx.doi.org/10.1155%2F2021%2F1989277>
20. Löbel, M., Mooslechner, A.A., Bauer, S. et al. (2015). "Polymorphism in COMT is associated with IgG3 subclass level and susceptibility to infection in patients with chronic fatigue syndrome." *J Transl Med* 13, 264 <https://doi.org/10.1186/s12967-015-0628-4>

21. Hilgers A, Frank J. (1994) "Chronic fatigue syndrome: immune dysfunction, role of pathogens and toxic agents and neurological and cardiac changes." *Wien Med Wochenschr.* 1994;144(16):399-406.
<http://www.ncbi.nlm.nih.gov/pubmed/7856214>
22. Lotz M, Zuraw BL. (1987) "IFN- γ is a major regulator of C1-inhibitor synthesis by human blood monocytes." *J Immunol.* 139(10):3382-3387. <https://pubmed.ncbi.nlm.nih.gov/3119706/>
23. Zuraw BL, Lotz M. (1990) "Regulation of the hepatic synthesis of C1 inhibitor by the hepatocyte stimulating factors interleukin 6 and interferon gamma." *J Biol Chem.* 265(21):12664-12670. <https://pubmed.ncbi.nlm.nih.gov/1695634/>
24. Bossi, F., El Peerschke, B Ghebrehiwet, F Tedesco (2011) "Cross-talk between the complement and the kinin system in vascular permeability." *Immunology Letters* 140(1–2):7-13 <https://doi.org/10.1016/j.imlet.2011.06.006>
25. Hewison, M. (2010) "Vitamin D and the Immune System: New Perspectives on an Old Theme, Endocrinology and Metabolism." *Clinics of North America* 39(2):365-379 <https://doi.org/10.1016/j.ecl.2010.02.010>
26. Maalmi H, Berraïes A, Tanguouru E, Ammar J, Abid H, Hamzaoui K, Hamzaoui A. (2012) "The impact of vitamin D deficiency on immune T cells in asthmatic children: a case-control study." *J Asthma Allergy.* 5:11-19
<http://dx.doi.org/10.2147/JAA.S29566>
27. Agnes Hamzaoui, A. Berraïes, B. Hamdi, W. Kaabachi, J. Ammar, K. Hamzaoui (2014) "Vitamin D reduces the differentiation and expansion of Th17 cells in young asthmatic children." *Immunobiology* 219(11):873-879
<https://doi.org/10.1016/j.imbio.2014.07.009>
28. Zhu, Z., K. Hasegawa, B. Ma, M. Fujiogi, CA Camargo Jr., L. Liang (2020) "Association of asthma and its genetic predisposition with the risk of severe COVID-19." *Journal of Allergy and Clinical Immunology* 146(2):327–329.
<https://doi.org/10.1016/j.jaci.2020.06.001>
29. Ferastraoar D, Hudes G, Jerschow E, Jariwala S, Karagic M, de Vos G, Rosenstreich D, Ramesh M. (2021) "Eosinophilia in Asthma Patients Is Protective Against Severe COVID-19 Illness." *J Allergy Clin Immunol Pract.* 9(3):1152-1162.
<https://doi.org/10.1016/j.jaip.2020.12.045>
30. Shaikh, MN, Malapati, BR, Gokani, R, Patel, B, Chatriwala, M (2016) "Serum Magnesium and Vitamin D Levels as Indicators of Asthma Severity." *Pulm Med.* 2016:1643717. <https://dx.doi.org/10.1155%2F2016%2F1643717>
31. Zhong-Jie, H., X. Jia, Y. Ji-Ming, L. Li, H. Wei, Z. Li-Li, Z. Zhen, et al. (2020) "Lower Circulating Interferon-Gamma Is a Risk Factor for Lung Fibrosis in COVID-19 Patients." *Frontiers in Immunology* 11:585647.
<https://dx.doi.org/10.3389%2Ffimmu.2020.585647>
32. Abdel-Hamed, E.F., Ibrahim, M.N., Mostafa, N.E. et al. (2021) "Role of interferon gamma in SARS-CoV2 positive patients with parasitic infections." *Gut Pathog* 13:29 <https://doi.org/10.1186/s13099-021-00427-3>
33. Sapkota, H.R., Nune, A. (2022) "Long COVID from rheumatology perspective — a narrative review." *Clin Rheumatol* 41:337–348 <https://dx.doi.org/10.1007%2Fs10067-021-06001-1>
34. 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." *Clin Mol Allergy* 19:21.
<https://doi.org/10.1186/s12948-021-00161-w>
35. Porritt, RA, A Binek, L Paschold, MN Rivas, A McArdle, LM Yonker, et al. (2021) "The autoimmune signature of hyperinflammatory multisystem inflammatory syndrome in children." *J Clin Invest.* 131(20):e151520.
<https://doi.org/10.1172/JCI151520>
36. Rubin L, Subramony A, Kothare S. (2022) "Patients Diagnosed with Multisystem Inflammatory Syndrome in Children Have Persistent Neurologic, Sleep, and Psychiatric Symptoms After Hospitalization" *J Child Neurol.* 24:8830738221075924. <https://doi.org/10.1177/08830738221075924>

37. Zimmermann, P., Pittet, LF, Curtis, N., (2021) "How Common is Long COVID in Children and Adolescents?" The Pediatric Infectious Disease Journal: December 40(12):e482-e487 <https://dx.doi.org/10.1097%2FINF.0000000000003328>
38. Cooper, S.L.; Boyle, E.; Jefferson, S.R.; Heslop, C.R.A.; Mohan, P.; Mohanraj, G.G.J. et al. (2021) "Role of the Renin–Angiotensin–Aldosterone and Kinin–Kallikrein Systems in the Cardiovascular Complications of COVID-19 and Long COVID" *Int. J. Mol. Sci.* 22(15):8255. <https://doi.org/10.3390/ijms22158255>
39. Cyr, M., Y. Lepage, C. Blais, Jr., N. Gervais, M. Cugno, J-L. Rouleau, A.Adam (2001) "Bradykinin and des-Arg⁹-bradykinin metabolic pathways and kinetics of activation of human plasma." *American Journal of Physiology-Heart and Circulatory Physiology* 281(1):H275-H283 <https://doi.org/10.1152/ajpheart.2001.281.1.H275>
40. Gallagher, P. E., Li, P., Lenhart, J. R., Chappell, M. C., K. B. Brosnihan (1999) "Estrogen Regulation of Angiotensin-Converting Enzyme mRNA." *American Heart Association* 33(1):323-328. <https://doi.org/10.1161/01.hyp.33.1.323>
41. Schwaninger, M., S. Sallmann, N. Petersen, A. Schneider, S. Prinz, T.A. Libermann, M. Spranger (1999) "Bradykinin Induces Interleukin-6 Expression in Astrocytes Through Activation of Nuclear Factor- κ B." *J. Neurochem.* 73,1461–1466 <https://doi.org/10.1046/j.1471-4159.1999.0731461.x>
42. Bas, M., TK Hoffmann, B Tiemann, VTV Dao, C Bantis, V Balz, H-J Schultz-Coulon, T Stark, et al. (2010) "Potential genetic risk factors in angiotensin-converting enzyme-inhibitor-induced angio-oedema." *Br J Clin Pharmacol* 69(2):179–186 <https://doi.org/10.1111/j.1365-2125.2009.03567.x>
43. Biller, H., Zissel, G., Ruprecht, B., Nauck, M., Busse Grawitz, A., Müller-Quernheim, J. (2006) "Genotype-corrected reference values for serum angiotensin-converting enzyme." *European Respiratory Journal* 28:1085-1091. <https://doi.org/10.1183/09031936.00050106>
44. Rigat, B., Corvol, P., Soubrier, F. (1990) "An insertion/deletion polymorphism in the angiotensin I converting enzyme gene accounting for half the variance of serum enzyme levels." *J Clin Invest.* 86(4):1343-1346. <https://doi.org/10.1172/JCI114844>
45. Gallego-Delgado, J., Walther, T., Rodriguez, A. (2016) "The High Blood Pressure-Malaria Protection Hypothesis." *Circulation Research.* 119:1071–1075 <https://doi.org/10.1161/CIRCRESAHA.116.309602>
46. Graham, EL, Clark, JR, Orban, ZS, Lim, PH, Szymanski, AL, et al, (2021) "Persistent neurologic symptoms and cognitive dysfunction in non hospitalized Covid19 long haulers." *Annals of Clinical and TranslationalNeurology*2021; 8(5): 1073–1085. <https://doi.org/10.1002/acn3.51350>
47. Teuwen, LA., Geldhof, V., Pasut, A. et al. (2020) "COVID-19: the vasculature unleashed." *Nat Rev Immunol* 20, 389–391 <https://doi.org/10.1038/s41577-020-0343-0>
48. Puthuchery, Z., Skipworth, J.R.A., Rawal, J. et al. (2011) "The ACE Gene and Human Performance." *Sports Med* 41:433–448 <https://doi.org/10.2165/11588720-000000000-00000>
49. Chambers, P.W. (2022) "COVID-19: From Cough to Coffin." *Open Access Library Journal*, 9:1-24. <https://doi.org/10.4236/oalib.1108300>
50. Java, A., AJ Apicelli, K Liszewski, A Coler-Reilly, JP Atkinson, AHJ Kim, HS Kulkarni (2020) "The complement system in COVID-19: friend and foe?" *JCI Insight.* 5(15):e140711 <https://doi.org/10.1172/jci.insight.140711>
51. Bekassy, Z., Lopatko Fagerström, I., Bader, M. et al. (2021) "Crosstalk between the renin–angiotensin, complement and kallikrein–kinin systems in inflammation." *Nat Rev Immunol.* <https://doi.org/10.1038/s41577-021-00634-8>
52. Schoenborn, J.R., CB Wilson. (2007) "Regulation of Interferon- γ During Innate and Adaptive Immune Responses." *Advances in Immunology* 96:41-101 [https://doi.org/10.1016/s0065-2776\(07\)96002-2](https://doi.org/10.1016/s0065-2776(07)96002-2)

53. Rosa Bellmann-Weiler, Katharina Schroecksadel, Claudia Holzer, Clara Larcher, Dietmar Fuchs, Guenter Weiss (2008) "IFN-gamma mediated pathways in patients with fatigue and chronic active Epstein Barr virus-infection." *Journal of Affective Disorders* 108(1-2):171-176 <https://doi.org/10.1016/j.jad.2007.09.005>
54. Sinclair, E., D Black, CL Epling, A Carvidi, SZ Josefowicz, BM Bredt, MAVJacobson (2004) "CMV Antigen-Specific CD4+ and CD8+ T Cell IFN γ Expression and Proliferation Responses in Healthy CMV-Seropositive Individuals." *Viral Immunology* 17(3):445-454 <https://dx.doi.org/10.1089%2F0882824041857049>
55. Björkander, S., M Ernberg, I Bileviciute-Ljungar (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>
56. Deumer, U.-S., Varesi, A., Floris, V., Savioli, G., Mantovani, E., López-Carrasco, P., Rosati, G.M., Prasad, S., Ricevuti, G. (2021) "Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS): An Overview." *J. Clin. Med.* 10:4786. <https://dx.doi.org/10.3390%2Fjcm10204786>
57. Arellano G, Ottum PA, Reyes LI, Burgos PI and Naves R (2015) "Stage-specific role of interferon-gamma in experimental autoimmune encephalomyelitis and multiple sclerosis." *Front. Immunol.* 6:492. <https://doi.org/10.3389/fimmu.2015.00492>
58. Passwater, M. (2022) "It's Official: Vitamin D Reduces the Incidence of Autoimmunity." *Orthomolecular.org* v18(9) <http://orthomolecular.org/resources/omns/v18n09.shtml>
59. Zhao R, Zhang W, Ma C, Zhao Y, Xiong R, Wang H, Chen W, Zheng SG (2021) "Immunomodulatory Function of Vitamin D and Its Role in Autoimmune Thyroid Disease." *Front. Immunol.* 12:574967. <https://dx.doi.org/10.3389%2Ffimmu.2021.574967>
60. Pourgholaminejad A., S.Pahlavanneshan, M. Basiri (2022) "COVID-19 immunopathology with emphasis on Th17 response and cell-based immunomodulation therapy: Potential targets and challenges." *Scand J Immunol.* 95:e13131. <https://doi.org/10.1111/sji.13131>
61. Pramod, R., Edwards, L. (2019) "Magnesium Supplementation in Vitamin D Deficiency" *American Journal of Therapeutics.* 26(1):e124-e132 <https://doi.org/10.1097/MJT.0000000000000538>
62. Mason, C., Tapsoba, JD, Duggan, C., Ching-Yun Wang, Korde, L., McTiernan, A. (2016) "Repletion of vitamin D associated with deterioration of sleep quality among postmenopausal women" . *Preventive Medicine.* 93:166-170 <https://doi.org/10.1016/j.ypmed.2016.09.035>
63. Peluso, MJ, Lu, S, Tang, AF, Durstenfeld, MS, Hsi-en Ho, H, Goldberg, SA, et al (2021) "Markers of immune activation and inflammation in individuals with post-acute sequelae of SARS-CoV-2 infection" *The Journal of Infectious Diseases,* 224(11):1839–1848, <https://doi.org/10.1093/infdis/jiab490>
64. Zhang J. (2007) "Paradoxical roles of interferon- γ in autoimmune disease." *Expert Review of Clinical Immunology,* 3(1):35-38 <https://doi.org/10.1586/1744666x.3.1.35>
65. Kelchtermans, H., A Billiau, P Matthys (2008) "How interferon- γ keeps autoimmune diseases in check." *Trends in Immunology* 29(10):479-486. <https://doi.org/10.1016/j.it.2008.07.002>
66. Ottum P A., G Arellano, LI Reyes, M Iruretagoyena, Rodrigo N (2015) "Opposing Roles of Interferon-Gamma on Cells of the Central Nervous System in Autoimmune Neuroinflammation." *Frontiers in Immunology* 6:539. <https://doi.org/10.3389/fimmu.2015.00539>
67. Mandai, M., Hamanishi, J., Abiko, K., Matsumura, N., Baba, T., & Konishi, I. (2016). "Dual Faces of IFN γ in Cancer Progression: A Role of PD-L1 Induction in the Determination of Pro- and Antitumor Immunity." *Clinical cancer research (an official journal of the American Association for Cancer Research)* 22(10):2329–2334. <https://doi.org/10.1158/1078-0432.CCR-16-0224>

68. Morrison, TE, Mauser, A., Wong, A., Ting, Jenny PYT, Kenney, KC, et al (2001) "Inhibition of IFN-gamma Signaling by an Epstein-Barr Virus Immediate-Early Protein" *Immunity* 15:787–799 [https://doi.org/10.1016/S1074-7613\(01\)00226-6](https://doi.org/10.1016/S1074-7613(01)00226-6)
69. Gold JE, Okyay RA, Licht WE, Hurley DJ. (2021) Investigation of Long COVID Prevalence and Its Relationship to Epstein-Barr Virus Reactivation. *Pathogens*. 10(6):763. <https://doi.org/10.3390/pathogens10060763>
70. Liang, CL, Chen, JL, Hsu, YPP, Ou, JT, Chang, YS (2002) "Epstein-Barr Virus BZLF1 Gene Is Activated by Transforming Growth Factor- β through Cooperativity of Smads and c-Jun/c-Fos Proteins" *Journal of Biological Chemistry* 277(26):23345-57 <https://doi.org/10.1074/jbc.M107420200>.
71. Oronsky, B., Larson, C., Hammond, T.C. et al. (2021) "A Review of Persistent Post-COVID Syndrome (PPCS)" *Clinic Rev Allerg Immunol* (2021). <https://doi.org/10.1007/s12016-021-08848-3>
72. Barros-Martins, J., Förster, R. & Bošnjak, B. (2022) "NK cell dysfunction in severe COVID-19: TGF- β -induced downregulation of integrin beta-2 restricts NK cell cytotoxicity" *Sig Transduct Target Ther* v7, article 32 <https://dx.doi.org/10.1038%2Fs41392-022-00892-5>
73. Qiao, Yong-Chao, Chen, Yin-Ling, Pan, Yan-Hong, Ling, Wei, Tian, Fang, et al (2017) "Changes of transforming growth factor beta 1 in patients with type 2 diabetes and diabetic nephropathy" *Medicine* 96(15):e6583 <https://doi.org/10.1097/md.0000000000006583>
74. Laviades, C, Varo, N, Díez, J. (2000) "Transforming Growth Factor β in Hypertensives With Cardiorenal Damage" *Hypertension*. 2000;36:517–522 <https://doi.org/10.1161/01.HYP.36.4.517>
75. Woo, J, Koziol-White, C, Panettieri, R, Jude, J. (2021) "TGF- β : The missing link in obesity-associated airway diseases?" *Current Research in Pharmacology and Drug Discovery*, v2, 2021, 100016 <https://doi.org/10.1016/j.crphar.2021.100016>
76. 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" *Nat Commun* 12:1961. <https://doi.org/10.1038/s41467-021-22210-3>
77. Johansson, M, Ståhlberg, M, Runold, M, Nygren-Bonnier, M, Nilsson, J, 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(4):573-580 <https://doi.org/10.1016/j.jaccas.2021.01.009>
78. Stewart, JM, Taneja, I, Glover, J, Medow, MS (2008) "Angiotensin II type 1 receptor blockade corrects cutaneous nitric oxide deficit in postural tachycardia syndrome" *Am J Physiol Heart Circ Physiol*. 2008 294(1):H466–H473. <https://doi.org/10.1152/ajpheart.01139.2007>
79. Wadhwanian R. (2017) "Is Vitamin D deficiency implicated in autonomic dysfunction?" *J Pediatr Neurosci* 12:119-23 https://doi.org/10.4103/jpn.JPN_1_17
80. McCarthy, MJ (2022) "Circadian rhythm disruption in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Implications for the post-acute sequelae of COVID-19" *Brain, Behavior, & Immunity - Health* 20:2022,100412 <https://doi.org/10.1016/j.bbih.2022.100412>
81. Zhang, HY, Liu, ZD, Hu, CJ, Wang, DX, Zhang, YB, Li, YZ (2011) "Up-regulation of TGF- β 1 mRNA expression in peripheral blood mononuclear cells of patients with chronic fatigue syndrome" *Journal of the Formosan Medical Association* 110(11):701-704 <http://dx.doi.org/10.1016/j.jfma.2011.09.006>
82. Meng, Xm., Nikolic-Paterson, D. & Lan, H. (2016) "TGF- β : the master regulator of fibrosis" *Nat Rev Nephrol* 12:325–338 <https://doi.org/10.1038/nrneph.2016.48>
83. Hoffman Centre for Integrative and Functional Medicine March 9, 2021 by Dr. Bruce Hoffman <https://hoffmancentre.com/chronic-inflammatory-response-syndrome-cirs-evaluation-and-treatment/>
84. Mahmudpour, M, Roozbeh, J, Keshavarz, M, Farrokhi, S, Nabipour, I. (2020) "COVID-19 cytokine storm: The anger of inflammation" *Cytokine* v133, 2020,155151 <https://doi.org/10.1016/j.cyto.2020.155151>

85. Ehanire, T., Ren, L., Bond, J. et al. (2015) "Angiotensin II stimulates canonical TGF- β signaling pathway through angiotensin type 1 receptor to induce granulation tissue contraction" *J Mol Med* 93:289–302. <https://doi.org/10.1007/s00109-014-1211-9>
86. Lanz, TV, Ding, Z, Ho, PP, Luo, J, Agrawal, AN, Srinagesh, H, et al. (2010) "Angiotensin II sustains brain inflammation in mice via TGF- β " *J. Clin. Investig.*, 120 (8) (2010), pp. 2782-2794 <https://doi.org/10.1172/JCI41709>
87. Shi, Y., Liu, T., Yao, L. et al. (2017) Chronic vitamin D deficiency induces lung fibrosis through activation of the renin-angiotensin system *Sci Rep* 7:3312. <https://doi.org/10.1038/s41598-017-03474-6>
88. Sanders, VM (2006) "Epigenetic regulation of Th1 and Th2 cell development." *Brain, Behavior, and Immunity* 20(4):317-324 <https://doi.org/10.1016/j.bbi.2005.08.005>