Research Article

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Long Covid and Neurodegenerative Disease

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Abstract

Brain fog with compromised ability to concentrate has been the most frequent Long Covid (LC) complaint. This is due to an increased TGF beta/IFN gamma with consequently increased bradykinin (BKN), especially in Caucasian females. Brain and lung blood vessels "leak." This same ratio is increased in Alzheimer's disease (AD), but decreased in Parkinson's disease (PD), because CD4$^+$ and CD8$^+$ T cells are differentially affected by the invading associated viruses, e.g., SARS CoV2, HIV, Varicella zoster (VZV).... In Covid-19 CD147 receptors on immune cells are critical in generating the increased TGF beta/IFN gamma and those on endothelial cells, platelets, and erythrocytes are critical to the abnormal microvascular blood flow. ACE2 receptors on pneumocytes and enterocytes enable pulmonary and GI entry, initiating gut dysbiosis. Epigenetics, methylation, magnesium, vitamin D, the B vitamins, and antioxidants suggest that these issues can be surmounted. Biochemical, physiologic, and epidemiologic data are analyzed to answer these questions. An LC model is presented and discussed in the context of the most recent research. Suggestions to avoid these and other worrisome concerns are included. Other topics discussed include estrogen, the gut microbiome, type 2 diabetes (T2D), and homocysteine.

Keywords: Homocysteine, Estrogen, Bradykinin, Magnesium, Vitamin D, CD147

Introduction

Long Covid (LC) has replaced Covid-19 as the topic du jour. Long term LC risks are unknown but have stoked growing concern. The neurodegenerative and tumorigenic implications are at the top of this list. Unfortunately, the wide spectrum of LC symptoms has defied mechanistic attempts to link their pathogenesis. There are clearly multiple factors involved, complicating these attempts. The male dominated Covid-19 stands in stark contrast to the female dominated LC. "Evidence based" efforts investigating such issues have traditionally relied on Random Clinical Trials (RCTs) and meta-analyses - the top down approach. Two inherent problems are loss of timeliness (RCTs) and diluted results (meta-analyses). A bottom up approach based on biochemistry, physiology, and epidemiology may be more advantageous, given the urgency of and universal interest in LC. This is an opinion piece aided by the deluge of recent research on this burgeoning problem.

LC Model

• CD147 receptors on T cells bind CD147 epitopes (the falciparum antigen) on the spike protein S (no ACE2 receptors on circulating immune cells or on erythrocytes) [1-5].

• Subsequently SARS CoV2 overwhelms and exhausts CD4+ and CD8+ T cells and Natural Killer cells (NKs)

• Persistent chronic lymphopenia after Covid-19 lowers secretion of IFN gamma (type II IFN), produced only by T cells and NK cells, especially CD4+ T cells [6-8].

• Decreased secretion of IFN gamma implies less hepatic synthesis of C1-INH [9]

• Uninhibited C1 triggers the Classic Complement Pathway (CCP) and crosstalk with the Kallikrein Kinin System (KKS) [10].

• The consequently increased bradykinin (BKN) is normally catabolized by angiotensin converting enzyme (ACE)

• Estrogen downregulates ACE and prolongs BKN half life. This makes estrogen an ACE inhibitor of sorts and increases the risk of some cancers [11,14].

• BKN enhances vascular permeability creating "leaks" primarily in lungs15 and brain16 linking brain fog and dyspnea/post exertional malaise [15,16].

• IL-1beta, prominent in LC, potentiates the BKN induced microvascular leakage18 and brain fog primarily in Caucasian females [17,18].

• The ACE DD genotype in African Americans, an evolutionary adaptation to falciparum malaria, downregulates this leakage (tighter endothelial junctions) and elevates the relative frequency of LC in Caucasian females

• IFN gamma and TGF beta counterbalance each other and the loss of IFN gamma secreted by CD4+ and CD8+ T cells leaves an environment of unopposed TGF beta [19,20].

• Chronic low-grade IL-1beta and TNF alpha redirect pleiotropic TGF beta from wound healing fibrosis to endothelial mesenchymal transition (End MT)/epithelial mesenchymal transition (EMT) and from tumor suppressor to tumor promoter [21-23].

• The switch of pleiotropic TGF beta from anti-inflammatory to proinflammatory appears to be more organ specific, e.g., neurovascular pericytes [24].

• Implications
• Long term LC may drive an increase in sporadic/late onset AD due to an elevated TGF beta/IFN beta [25-27].
• Late onset AD may appear earlier
• AD frequency in Caucasian females, especially in those also on HRT, may approach that in African American females [28, 29].
• Cancer risk/progression and fibrosis may also increase in Caucasian females
• CD147 is the primary receptor involved in the pathogenesis of ASCVD and LC long term may increase its incidence [30,31].
• The presence of CD147 receptors (but not those of ACE2) on platelets (and erythrocytes) creates platelet aggregates, further complicating the microcirculation (elevated mean platelet volume (MPV)) [32].
• The presence of the CD147 epitope on the spike protein S portends dire consequences involving microvascular thrombosis in the short term for all exposed to the spike protein S.
• The incidence of PD in those with LC may increase, as LC increases risk for T2D, which predisposes to PD.

Discussion

To LC and Beyond

Viral load and TGF-β/IFN-γ ratio determine Covid-19 symptoms (or not). This ratio decreases notably from the control group, passing through asymptomatic, up to symptomatic SARS-CoV-2 individuals [33]. But as IFN gamma secreting T cells are lost to the invading virus (see figure 1), this ratio inverts (increases). An depressed TGF beta/IFN gamma is affiliated with PD [34, 35]. An elevated ratio is affiliated with AD [25,26]. This bodes ill for those with LC with respect to fibrosis [36,37].

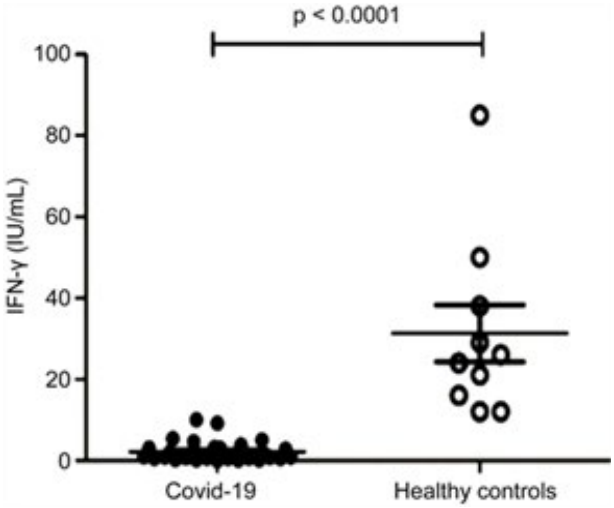


Figure 1: SARS CoV2 destroys IFN gamma producing cells [38].

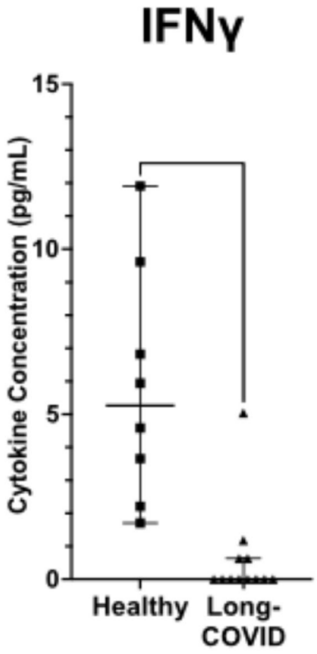


Figure 2: Low levels of IFN gamma persist into the LC phase [39].

The cytokines of LC provide insight to possible future complications. TGF beta and IFN gamma are pleiotropic LC linked cytokines that can work in either direction, i.e., anti- to proinflammatory, suppressing to promoting EMT or tumor for TGF beta and anti- to proliferative, pro-apoptotic to necrotic, antitumor to tumor for IFN gamma. However, it appears that the deleterious effects of the switch are more significant for TGF beta. IFN gamma appears to retain a net positive effect [40]. TGF beta functions initially as an anti-inflammatory, keeping the inflammatory response of IFN gamma under control. Under chronic inflammatory conditions TNF alpha is elevated and can upregulate TGF beta, which opposes IFN gamma.

Chronic low doses of TGF beta when combined with chronic low doses of TNF alpha facilitate the switch of TGF beta from suppressing to promoting tumor23. This also appears to be the case for switching TGF-beta from wound healing fibrosis to endothelial or epithelial mesenchymal transition (EndMT or effect [40]. Therefore, it seems reasonable to assume that TNF alpha (chronic inflammation) might redirect TGF beta from anti-inflammatory to pro-inflammatory and open the door to neurodegenerative disease. The constant stimulus to chronic inflammation posed by residual spike protein S could easily trigger this (see figure 3)

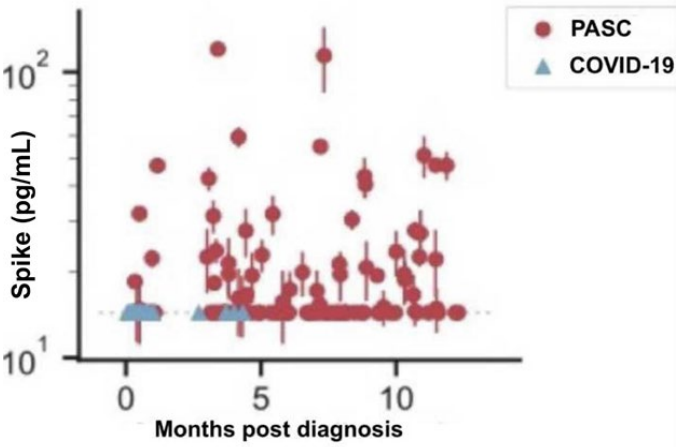


Figure 3: LC is characterized by persistence of the spike protein S [43].

AD, PD, and LBD

The three primary forms of accelerated pre-senile dementia are AD, PD, and LBD. AD, the predominant form of pre-senile dementia, is more common in females while PD is more common in males. LBD is intermediate [44]. AD Is characterized by an elevated TGF beta/IFN gamma Onset of PD in females is later and less severe than that in men and might be due to benefits from premenopausal estrogen or hormone replacement therapy [45, 46]. Although protective against PD, estrogen possesses ACE inhibitor properties that elevate BKN. Lung and brain BKN induced leakage contributes to LC and AD. African American females appear to be less affected by LC but suffer the highest incidence of AD (by gender or race). At first this seems contradictory for two reasons. First, in African American but not in Caucasian female's estrogen levels decrease with increasing premenopausal age and BMI decreasing their risk of LC [47]. Secondly, the incidence of the ACE DD genotype (tighter endothelial junctions) is higher, also decreasing their risk of LC. However, according to a recent NHANES survey the incidence of obesity in African American females was 50% greater than that in Caucasian males, Caucasian females, or African-American males. This is presumed to be due to dietary factors, possibly monosodium glutamate (MSG) [48].

Perhaps escalating dietary MSG, induced by obesity and diabetes, overwhelms the protective properties of the ACE DD genotype, yielding more AD in African-American [49,50]. Obesity and diabetes also up regulate TGF beta, increasing the risk of AD [51]. Individuals with diabetes are up to four times more likely to develop LC [49, 51] Although homocysteine is elevated and contributes to the development of AD, LBD, and PD, PD is different. It is in some ways the opposite of AD, e.g., TGF beta/IFN gamma is depressed, not elevated. AD, LBD, and PD all feature extra cellular plaques - amyloid beta in AD, alpha-synuclein in LBD and PD. IFN gamma, elevated in PD, triggers microglial removal of amyloid [52,53]. PD also exhibits abnormal tryptophan metabolism due to increased IFN gamma and perhaps P5P deficiency [54] (see figure 4).

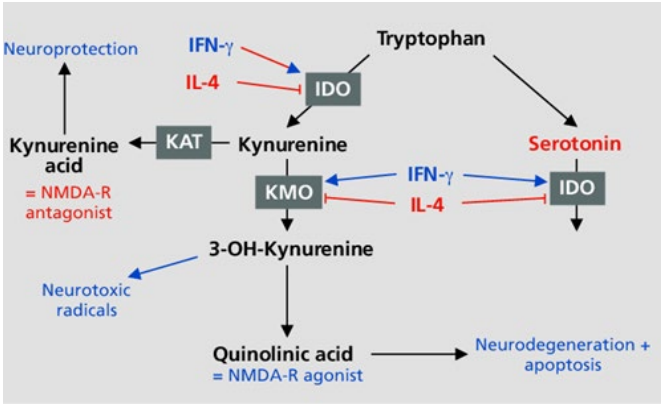


Figure 4: IFN gamma shunts tryptophan away from serotonin synthesis and production of melatonin [55,56].

P5P is a required cofactor for aromatic amino acid decarboxylase (AADC), which produces dopamine and serotonin. Additionally, magnesium is a required cofactor for the synthesis of melatonin from serotonin. All three hormones are deficient in PD. $CD4^+$ (superior producers of IFN gamma) and not $CD4^+$ T cells appear to be responsible for the increased IFN gamma in PD [57,58]. SARS CoV2 preferentially attacks "HIV is tightly linked to hepatitis C virus (HCV) and hepatitis B virus (HBV). Viral hepatitis and alcohol induced hepatitis elicit elevated IFN-γ. On the other hand, SARS CoV2 and TGF-β have been linked to non-alcoholic steatohepatitis (NASH) aka non-alcoholic fatty liver disease (NAFLD). Liver resident CD8+ T cells appear to be responsible for the elevated IFN-γ [57,58]. CD8+ T cells produce the majority of IFN-γ [59]. CD8+ T cells increase in frequency in the aging brain and become a major source of IFNγ [60]. Loss of CD4+ T cells appears to potentiate CD8+ T cells [57]. IFN-γ causes blood-brain barrier leakage [61] and connects chronic alcoholism, viral hepatitis, and HIV to PD (depressed brain TGF-β/IFN-γ). SARS CoV2 preferentially attacks CD8+ T cells [62] (no ACE2 receptors [63) restricting IFN-γ synthesis."

TGF and IFN

"HIV preferentially destroys CD4+ T cells [64], accentuating the IFN-γ response from cytopathic CD8+ T cells [57]. The HIV induced IFN-γ then increases the risk of viral hepatitis, PD [65] and autoimmune disease [66]. T2D also increases the risk of PD [67,68]. IFN-γ induces loss of dopamine neurons and nigrostriatal degeneration [69]. HIV increases the incidence of T2D [70]. The most recent research suggests that Parkinson's is an autoimmune disease, which conforms to the well known linkage between IFN-γ and autoimmune disease. Abnormal tryptophan metabolism exhibited in Parkinson's disease, due to an IFN-γ imbalance, is also seen in T2D and HIV [71].

In summary brain TGF-β is a key player in AD; likewise for brain IFN-γ in PD. IFN-γ is directly linked to a "leaky brain" via angiotensin II type one receptors (ATR1s) blocked by losartan. TGF-β is indirectly linked through BKN and the KKS. TGF-β and IFN-γ are both pleiotropic and the direction of each appears to be determined by the chronic cytokine milieu, including pleiotropic IL-1β, pleiotropic TNF-α, and IL-6. Perhaps chronic inflammation (post viral infection that targets CD4+ T cells, CD8+ T cells, hepatocytes, or pericytes [72]) in those with marginal onboard antioxidants are predisposed to AD and PD."

TGF-β/Smad signaling pathway in renal, hepatic, pulmonary and cardiac fibrosis has been well documented [73]. Recent studies show this to include the brain as well [74-76]. Magnesium possesses the capacity to down regulate this SMAD pathway in the liver and the lungs [77,78]. IFN gamma also appears capable in this regard [79]. Exercise also helps by increasing IFN gamma [80]. This is because exercise upregulates angiotensin II and angiotensin II upregulates IFN gamma [81,82].

ACE and BKN

Angiotensin converting enzyme (ACE) produces angiotensin II and degrades BKN. Estrogen downregulates ACE, up regulating BKN. Bradykinin upregulates tyrosine hydroxylase, the rate limiting step in dopamine synthesis [83]. This might help explain the protective effects of estrogen in avoiding PD. The frequency of the ACE II genotype in AD is 1.4x higher than that in controls v 0.4x for the ACE DD genotype [84]. ACE levels are up to 70% higher in the DD genotype [85]. Endothelial cell junctions are tighter and less permeable in the DD ACE genotype [86]. However, after menopause tight junction permeability due to endothelial dysfunction initiated by oxidative stress, microthrombosis (loss of RBC deformability), immune complexes (endothelial CD147 and perhaps ACE2 receptors linking to spike S epitopes), increases. The ACE DD genotype is protective against AD not only due to tighter endothelial junctions but also to increased ACE and less BKN [87,88]. BKN induced endothelial permeability not only produces perivascular angioedema but also leads to increased fibrosis [89]. Either mechanism may contribute to the brain fog, dyspnea, and post exertional malaise of LC.

Because ACE is higher and bradykinin levels are commensurately lower in those with the ACE DD genotype, African American females should be less likely to develop LC versus their Caucasian counterparts. Furthermore, in African American but not in Caucasian females estrogen levels decreased with increasing premenopausal age and BMI, theoretically minimizing their susceptibility to LC. Yet the incidence of AD is higher in African American females than that in African American men, Caucasian men, or Caucasian females. A 2017-18 NHANES survey indicate that the incidence of obesity in African-American females was almost 50% greater than that in their Caucasian counterparts.

Perhaps the AD inducing properties of postmenopausal obesity (and diabetes) overwhelm the protective properties of the ACE DD genotype. Some studies purport to show a decreased incidence of cancer in those with Alzheimer's disease. However, African-American females [90]. are 40% more likely to die of breast cancer than Caucasian females. African-Americans have the highest death rate and shortest survival of any racial/ethnic group in the US for most cancers and have a greater incidence of Alzheimer's disease than any other racial group in America [91]. On the other hand, overall cancer risk is lower in people with PD, compared to the general population. This difference in cancer risk between AD and PD speaks to further linkage between TGF beta in cancer causation and IFN gamma in cancer avoidance [92].

Estrogen and HRT for more than 10 years have been linked to a slight increase in cancer risk [93]. Estrogen downregulates ACE and is an ACE inhibitor of sorts. ACE inhibitors have been linked to an increase in lung cancer [94]. Not surprisingly, bradykinin has been linked to aggressive prostate cancer [95].

Homocysteine and B Vitamins

Homocysteine plays a prominent role in all forms of dementia [96]. Asians have a lower Ca:Mg diet and a lower incidence of AD [97]. P5P figures prominently in homocysteine recycling and is a required cofactor for aromatic amino acid decarboxylase (AADC)(see figure 5). PD patients are frequently B6 deficient [98]. and exhibit abnormalities in both dopamine and serotonin synthesis [99].

Dopamine synthesis shortfall in PD appears to be primarily driven by IFN gamma and its effect on tryptophan metabolism (see figure 4).

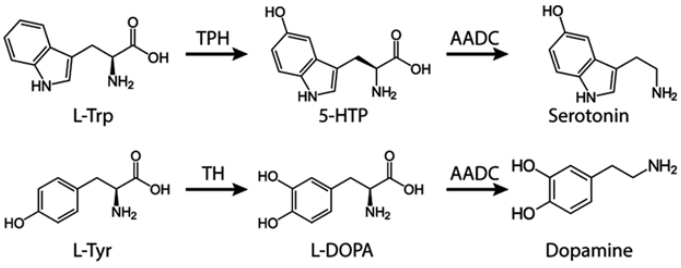


Figure 5: AADC requires the cofactor P5P

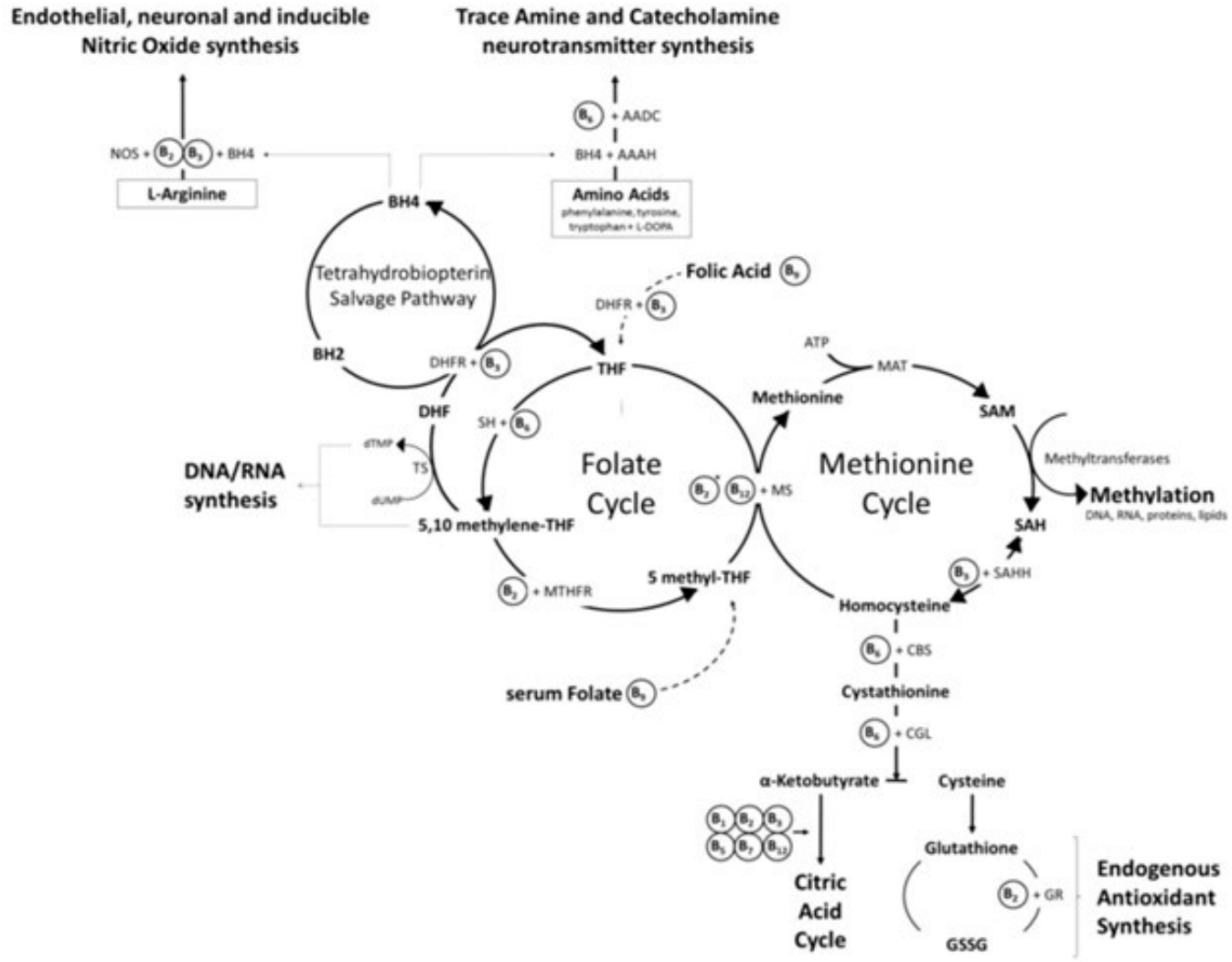


Figure 6: Vitamins B2, B3, B6, B9, and B12 are all heavily involved in both the folate cycle and the methionine cycle. B6 is also required as a cofactor to recycle homocysteine [100].

Homocysteine induces oxidative stress and is a marker for COVID-19 severity, LC, and demential [101-105]. As shown in figure 6, vitamins B2,3,6,9,12 are prominent cofactors in both the folate and methionine cycles, which are integral in the metabolism of homocysteine [106]. ATP and methylation both require Mg++. These B vitamin deficiencies are precisely those associated with cognitive impairment and AD [107]. B complex supplements usually provide methylated B12, but pyridoxine (B6), and folate (B9) are not their active forms. Indeed, the active forms of B1,2,3,9,12 all require magnesium and some require activated B6 as a cofactor [100]. B1,3, and 6 must be phosphorylated (ATP and magnesium as chelate); B2,9,12 must be methylated magnesium as cofactor [108]. The active form of B6 requires ATP and chelated Mg (phosphorylation) and its activated form (P-5-P) as a cofactor, creating a catch 22 situation. Most B6 supplements contain pyridoxine (PNP), which in excess can lead to peripheral neuropathy [109]. This can be avoided by substituting pyridoxal-5-phosphate. Rxn 2 (PNPO) in figure 7 mediated by P5P oxidase is the rate limiting step

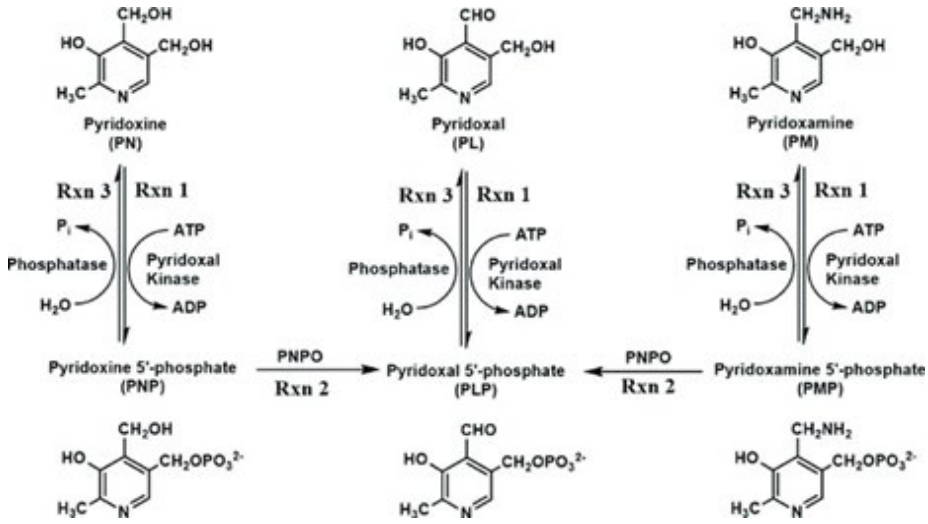


Figure 7: Note the need for ATP (and Mg++) to convert pyridoxal (and PNP, PMP) to P5P. PNPO requires P-5-P as cofactor.

P-5-P is critical to its own synthesis, to that of the active forms of other B vitamins, and to the recycling of homocysteine to glutathione (see figure 8). Its critical role in cognition is well known. Magnesium is also critical to the synthesis of all endogenous and most exogenous antioxidants [110-112].

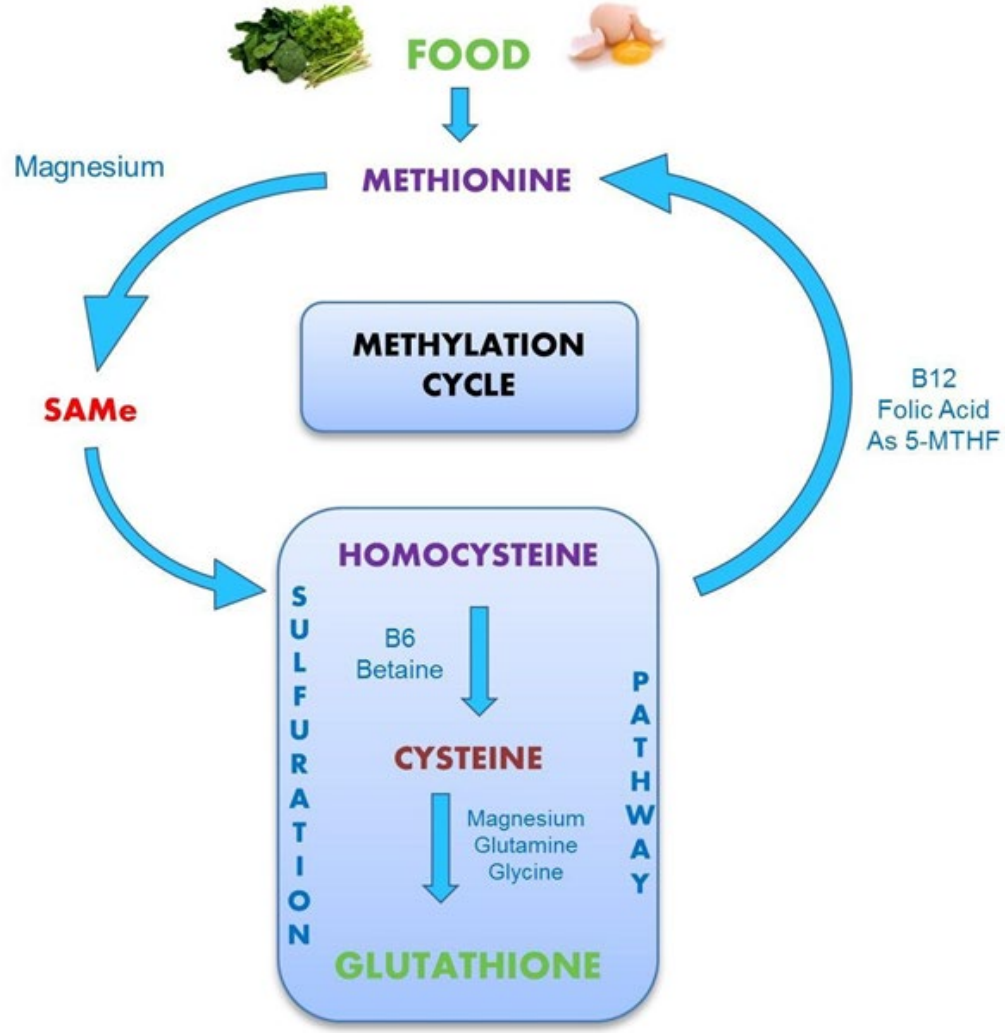


Figure 8: Magnesium and P5P are required to recycle homocysteine.

Vitamin B5 (pantothenate) deficiency is also associated with both AD band PD. In order for pantothenate to reach its active form, three phosphorylation's must occur. Each requires ATP and magnesium [113-115].

Vitamin D and Ca:Mg

An elevated Ca^{++} and a depressed Mg^{++} (high Ca:Mg) are linked to AD [16,17]. and PD [18,19]. A recent 2023 article reported that vitamin D, folic acid and vitamin B12 could reverse the cognitive decline leading to AD. Total benefit exceeded that from any single supplement [120]. Adding magnesium and P5P to this regimen would improve the results immeasurably. As Ca:Mg increases, Vitamin D loses its efficacy for colorectal cancer, prostate cancer, esophageal cancer, cardiovascular disease, metabolic syndrome, total mortality, and cognitive function [121]. The Western diet is high in processed foods with high monosodium glutamate (MSG)/calcium and low fiber/magnesium. The typical Asian diet offers more magnesium but less calcium. The target Ca:Mg for both is 2.0. A fiber rich diet that includes fermented vegetables is inversely proportional to Covid-19 mortality in Europe [122,123]. as demonstrated in Germany (sauerkraut) and South Korea ((kimchi) Ionized serum Ca:Mg and 25(OH)D_3 are measures of general health that reflect CRP and HRV [124-126]. Serum magnesium also reflects diversity of gut microbiota and gut health [127,128]. The correlation between the serum magnesium and dementia depends on the Ca:Mg. On a Western diet the healthy upper limit is 2.6. On an Eastern diet the lower limit is 1.7 [129].

APOE and Methylation

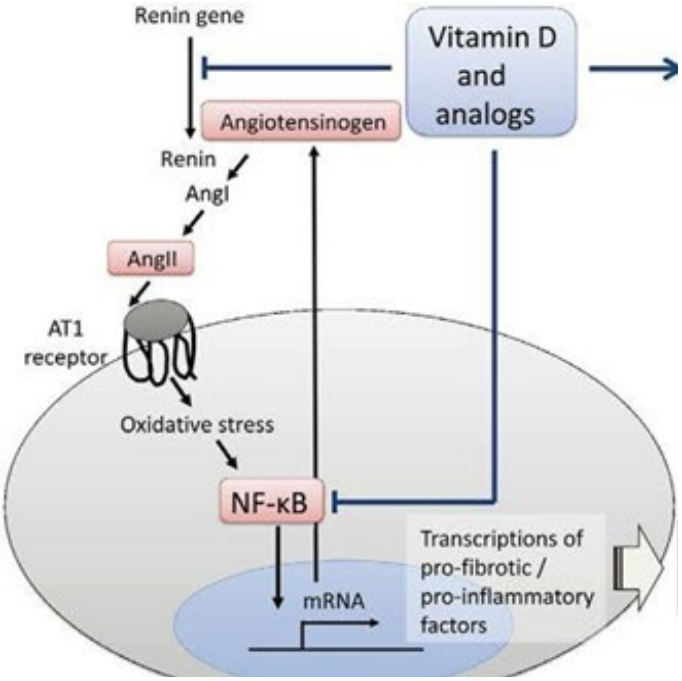
Reducing the Ca:Mg ratio reduces the risk of dementia [130]. Methylation of DNA for stability retards the onset of both neurodegenerative diseases, e.g., the APOE gene, and cancer, e.g., basigin (CD147) gene [131-133]. Hypomethylation increases with age and leads to an unstable genome, with activation of some tumor promoter genes [134,135]. Hypomethylation of CpG islands (cytosine-guanine pairs) promotes AD, LBD, and PD [136-139]. There are three alleles for APOE and APOE4 is the major risk factor for Alzheimer's disease [140]. Hypomethylation of APOE4 is a major determinant in this.

15% of the US population is heterozygous for this and 5% are homozygous. Chris Hemsworth recently announced a pullback in his schedule to spend more time with family. It was also reported that while working on a nature film he learned that he was homozygous for APOE4. But as worrisome as that might seem, AD appears to be less genetic and more epigenetic. The native American Indian population presents plenty of APOE4 but very little Alzheimer's disease [141]. The Paleolithic diet provides an excellent Ca:Mg balance. Dairy is not included (eggs 5.4, milk 10). Perhaps this dementia gene (APOE4) itself is not the problem but an elevated Ca:Mg, crowding out the Mg^{++}. Ca^{++} and Mg^{++} share the same receptor - CaSR (Calcium sensing receptor). DNA methylation occurs via SAMe and magnesium (see figure 8).

Treatment

1. Magnesium and vitamin D (50 ng/L target) are at the top of the list for both prevention and treatment. Magnesium is a critical mineral in the human body and is involved in ~80% of known metabolic functions [142]. Vitamin D possesses invaluable antioxidant and anti-inflammatory properties (see figure 9). Approximately 75% of human immune system functions depend on maintaining a healthy, physiological serum 25(OH)D concentration [143]

Figure 9. Vitamin D provides anti-inflammatory protection upstream and downstream of the AT1R [144].



2. The target Ca:Mg is 2.0, but any ratio greater than 2.6 compromises the efficacy of vitamin D [121]. Covid-19 makes AD worse [145]. Ca^{++} dysregulation plays a prominent role in both AD and amyloid beta deposition [130].

3. Antioxidants are vital in the defense of COVID-19 infection. However, if the onboard supply is suboptimal, the vast numbers of ROS generated may overwhelm mitochondria and markedly compromise ATP production. Most endogenously produced and some exogenous antioxidants require ATP (and magnesium) to attain activated status. Vitamin C (water-soluble), vitamins A, D3, E, K (fat-soluble), Zn, D-ribose, selenium, and many others require no processing [112]. Furthermore, hydroxylation of C1 of 25(OH)D in the synthesis of active vitamin D occurs in the mitochondria and is suppressed by calcium [146]. Loss of mitochondria due to oxidative stress compromises vitamin D efficacy in addition to the elevated Ca:Mg.

4. P5P aka PLP is the active form of B6, which is required for activation of many of the B vitamins associated with homocysteine metabolism.

5. A sedentary lifestyle risks eventual obesity and diabetes. Exercise also facilitates a better IFN gamma:TGF beta balance by increasing IFN gamma levels [80].

6. Probiotics, especially after antibiotic therapy, improves the diversity of the gut microbiome [147-149].

7. Dehydration triggers the renal resorption of Na^{+} and water. This also means loss of Mg^{++} (and K^{+}) to maintain electroneutrality. Also, the thirst reflex diminishes with age. What good is

increased dietary/supplemental Mg^{++} in the face of a magnesuric drain. Hydration maintenance, easily overlooked, potentially trumps all the other suggestions.

Conclusion

"The most recent research presented here suggests that AD, PD, LBD, and T2D might all be secondary to an imbalanced TGF-β/IFN-γ perhaps induced by some previous viral infection that preferentially targeted CD4+ and/or CD8+ T cells These T cells secrete IFN-γ with the lion's share coming from CD8+ T cells. HIV preferentially attacks CD4+ T cells, leaving the heavy IFN-γ producing CD8+ T cells. HIV mimics PD in many ways, including susceptibility to de novo T2D. TGF-β/IFN-γ is elevated in AD (and VZV), at least in the brain, and depressed in PD, LBD, HIV, and T2D."

Estrogen protects against and delays PD, but predisposes to LC and postmenopausal AD, especially if on HRT. Increased BKN mediates LC and AD. The ACE DD genotype is protective against LC and AD. Estrogen down regulates ACE, causing an increase in BKN. Obesity and diabetes predispose to AD, LBD, and PD. Magnesium and P5P, the active form of vitamin B6, are deficient in most with AD, LBD, and PD.

CD147 and BKN in the proposed model play vital roles both in the development of LC and in its long-term consequences. But an imbalance between TGF beta and IFN gamma due to SARS CoV2 induced lymphopenia supercharges the roles of CD147 and BKN. The implications of the proposed hypothesis with respect to LC and its possible long-term consequences extend not only to the unvaccinated but also to the vaccinated, who might be even more susceptible to recurrent SARS CoV2 (see figure 10), unless preventative measures are taken.

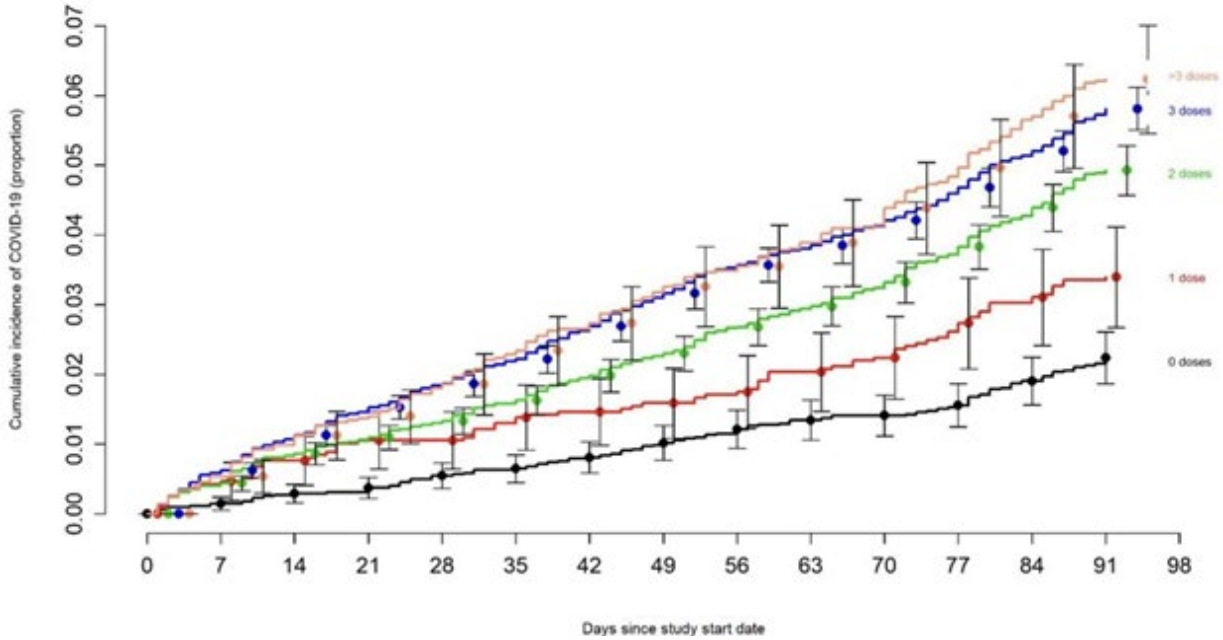


Figure 10: Recurrent COVID-19 is directly related to the number of boosters [150].

Vaccine efficacy or not is irrelevant. ACE2 receptors are not present on immune cells ($CD4^+$, $CD8^+$ T cells, NK cells), the primary combatants against SARS CoV2. The presence of the ACE2 receptor on endothelial cells is controversial [152]. Indeed the pathogenesis of microvascular thrombosis, lymphopenia, and TGF beta predominance in Covid-19 cannot be explained without acknowledging the presence of the CD147 epitope on the spike protein S, first reported in a Chinese study [1]. This finding was quickly challenged, but those challenges were later debunked [2]. However, the worrisome implications of this model are not irreversible.

These preventative measures include serum Ca:Mg near 2.0, serum $25(OH)D_3$ near 50 ng/L, and an abundance of micronutrient antioxidants, especially P-5-P [153]. The efficacy of vitamin D is compromised in the face of an elevated Ca:Mg [121]. But D_3 may be even better for endothelial health [154]. Endothelial competence is not only at the center of LC, AD, LBD, PD, and many cancers but also in the progression of cardiovascular disease, arthritis, multiple sclerosis, and sepsis [154]. So, D3 may be of benefit even in those with an elevated Ca:Mg.

Vitamin D $(1,25(OH)_2D$, the active form, is much more reliant on Mg^{++} for its efficacy. It requires Mg^{++} as a cofactor for three steps in its synthesis. Even parathormone synthesis requires Mg^{++}. Ultimately exercise, diet including some supplementation, and hydration are the primary determinants of epigenetically determined health over and above those associated with LC. HRV, the fifth vital sign, connects all the vital players - gut microbiome diversity155, dietary micronutrients, e.g., magnesium156, balanced Ca:Mg125, balanced TGF-beta157 and TNF-α158, and D3125. It's all about balance[125,155-158].

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