ISSN: 2577 - 8005

Mini Review

Medical & Clinical Research

Vitamin B6, Magnesium, and Vitamin D: The Triple Play

Patrick Chambers*

Torrance Memorial Medical Center, Department of Pathology, 3330 Lomita Boulevard, Torrance, CA 90505, USA.

***Corresponding Author**
Patrick Chambers, Torrance Memorial Medical Center, Department of Pathology, 3330 Lomita Boulevard, Torrance, CA 90505, USA.

Submitted: 30 Sep 2023; **Accepted**: 06 Oct 2023; **Published**: 15 Oct 2023

Citation: *Chambers P (2023) Vitamin B6, Magnesium, and Vitamin D: The Triple Play. Medical & Clinical Research, 8(10), 01-07.*

Abstract

Vitamin B6, magnesium, and vitamin D are important antioxidants. Mg is a required cofactor for the synthesis of vitamin D and the active forms of vitamins B1,2,3,5,6,9,12 (seven of the eight B vitamins). Five of the seven (and magnesium) are critical to the methylation cycle, compromised by MTHFR (methylene tetrahydrofolate reductase) variants, present in the majority of Caucasians and Asians. Homocysteine (Hcy), a powerful pro-oxidant, is upregulated in these variants. Oxidative stress compromises mitochondrial function, required for the synthesis of the active form of vitamin D. Pyridoxal phosphate (P5P or PLP), the active form of B6, enhances the intracellular entry of magnesium and is required for the synthesis of the antioxidants melatonin and glutathione, oft called the "mother" of all antioxidants. Deficiencies of P5P and vitamin D are associated with decreased gut microbiota diversity and short chain fatty acids, e.g., butyrate, as seen in Long Covid (LC) and Chronic Fatigue Syndrome (CFS). This suboptimal gut microbiome reflects the continuing decline in the nutritional value of the Western diet. The interdependencies of and associations between P5P, magnesium, and 1,25(OH)2D, the active form of vitamin D, are explored.

Keywords: Microbiome, Oxidative Stress, Homocysteine, Glutathione, Mthfr, Long Covid, Pyridoxine

Introduction

Magnesium is a critical mineral in the human body and is involved in ~80% of known metabolic functions [1]. Vitamin D possesses invaluable antioxidant and anti-inflammatory properties. Approximately 75% of human immune system functions depend on maintaining a healthy, physiological serum 25(OH)D concentration [2]. P5P participates in over 4% of all known catalytic activities [3].

Vitamin C is probably the most widely discussed and touted of all vitamins, followed by vitamins D, B9 (folate), and B12. After magnesium and vitamins C/D, P5P is arguably the most important micronutrient but Vitamin B6 has languished in obscurity. The Western diet has not only seen a decline in nutritional value but it has also become imbalanced, as indicated by the ever increasing Ca:Mg. Deficiencies of P5P, Mg, and D have been primary victims of the deteriorating gut microbiome. The linkage between P5P, magnesium, 1,25(OH)2 D, and all of the B vitamins has also largely remained unexamined and has obscured the impact of the highly prevalent MTHFR variants.

The interrelationships between some nutrients can be leveraged to obtain synergistic effects using combinations [4]. P5P, magnesium, and 1,25(OH)2D3 are excellent examples of this.

P5P and Magnesium

P5P acts as cofactor for over 160 different enzymes, including many involved in the synthesis of neurotransmitters and collaborates with magnesium in many other enzymatic reactions [5]. All three forms of B6-pyridoxine (most common form in supplements), pyridoxal, pyridoxamine-are inactive and must be phosphorylated (ATP-Mg complex required) for activation. PNPO (pyridoxine phosphate oxidase) is the rate limiting step to reach the active form-P5P (see figure 1).

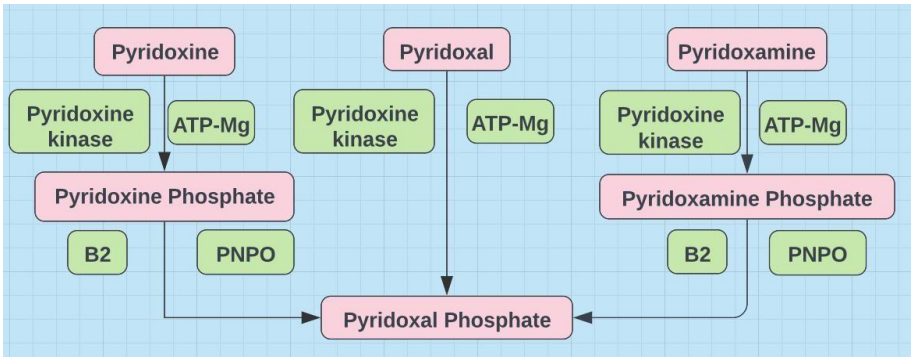

Figure 1: Most B vitamin supplements contain B6 as pyridoxine that ironically competes with P5P for receptor sites and can lead to symptoms of B6 deficiency.

According to a 2003-4 NHANES study by the NIH [6], 24% of Americans who do not supplement with B6 and 11% of those that do have deficient blood levels of P5P. This conforms to a report that pyridoxine, the inactive form and the most common form in B supplements, competitively inhibits P5P and causes a peripheral neuropathy [7]. B2 is a required cofactor for the synthesis of P5P (Figure 1). This means that if B2 is deficient without P5P supplementation, then B6 supplementation as pyridoxine can cause symptoms of B6 deficiency.

Decreased gamma-amino-butyric acid (GABA) appears to mediate the peripheral neuropathy [8]. Conversion of glutamate to GABA requires a P5P-dependent decarboxylase. Magnesium bioavailability is increased by the concomitant intake of vitamin P5P [9]. Pyridoxal phosphate but not pyridoxine, appears to form a complex with magnesium and hence may enhance the transport or accumulation of magnesium in cells [10].

Several recent articles have challenged this beneficial effect of B6 on magnesium absorption [11,12]. But both employed Magne, which is 300 mg Mg and 30 mg pyridoxine. Another article claimed that B6 enhances erythrocytic Mg but only at high doses and that high doses risk peripheral neuropathy. This study also used Magne [13]. Even the NIH in its Aug 2023 update on B6 failed to acknowledge the efficacy differential between pyridoxine and P5P. Furthermore, taking P5P concomitantly with magnesium can potentially double [14] or triple [10] the absorption of magnesium.

Not only does P5P enhance cellular uptake of magnesium but magnesium enhances that of P5P [15]. This impacts the P5P decarboxylases that produce serotonin, dopamine, and GABA. P5P even enhances libido in both sexes by inhibiting prolactin. In addition to these neurotransmitters, melatonin and glutathione synthesis also requires P5P.

The combination of P5P and magnesium supersedes magnesium alone in alleviating PMS [16]. Additionally several studies have shown P5P to be more efficacious than pyridoxine in treating microcytic anemias [17,18]. In one [18] researchers found that a 50 mg/day dose of P5P was much more effective than a 300 mg/day dose of pyridoxine. Oral contraceptives and pregnancy can deplete P5P [19]. Estrogens compete with other P5P dependent enzymes for P5P [20]. This suggests that females in their reproductive years might be more susceptible to P5P deficiency. Magnesium deficiency in females is also more common during these years (Figure 2). Are these concomitant deficiencies linked? This raises a provocative question about the predilection for LC in this same gender and age range.

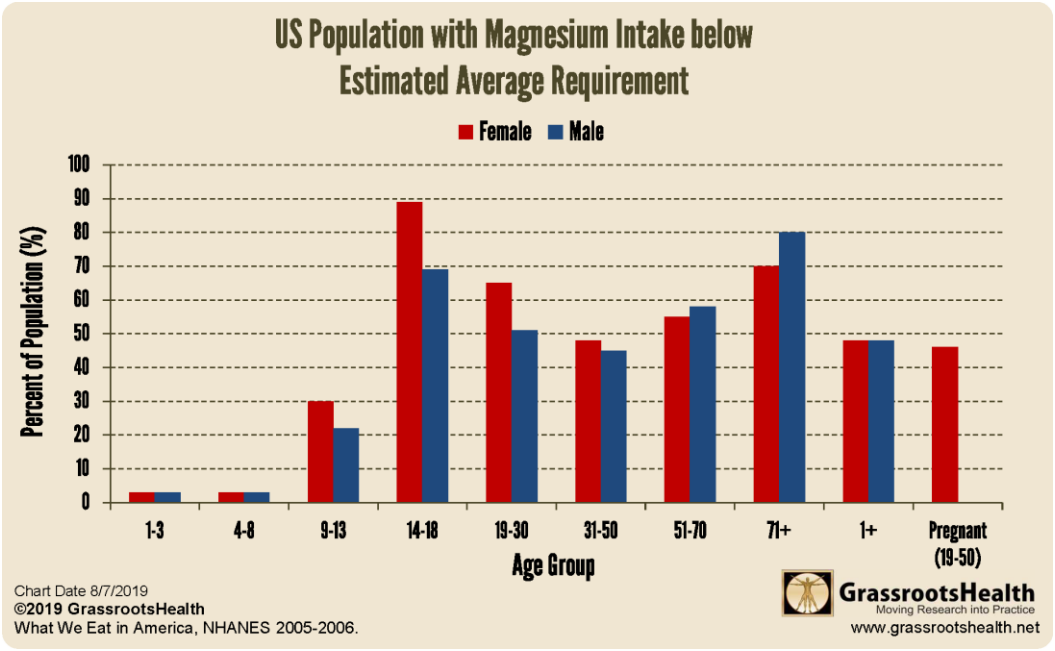

Figure 2: The lower intake in females during their reproductive years suggests a possible correlation with LC in this same age range.

P5P and MTHFR

Magnesium is a required cofactor for eight steps in the synthesis of active D (Figure 3). 1-alpha hydroxylase aka CYP27B1 activity, responsible for synthesis of 1,25(OH)2D3, is B2 and mitochondrial dependent [21,22].

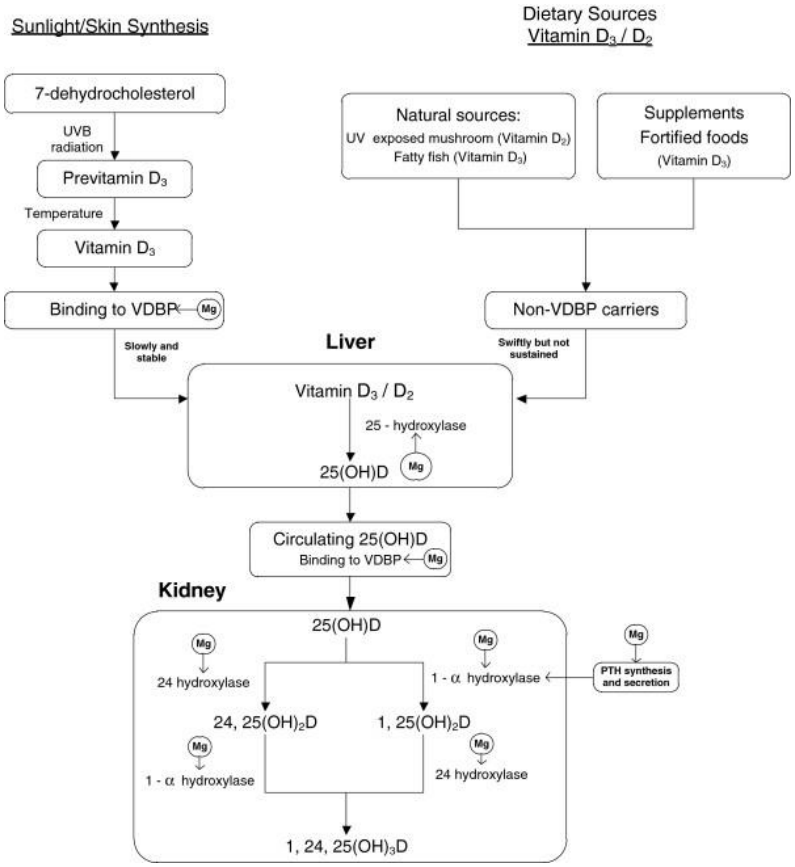

Figure 3: Mg^{++} is a required cofactor for numerous enzymes in the synthesis of the active form of vitamin D as well as parathormone, integral to maintaining adequate serum calcium.

The B2,3,6,9,12 vitamins are vital to the methylation cycle (Figure 4), critical in those with MTHFR variants. The active forms of all of these B vitamins require magnesium for either phosphorylation (B2,3,6) or methylation (B9,12).

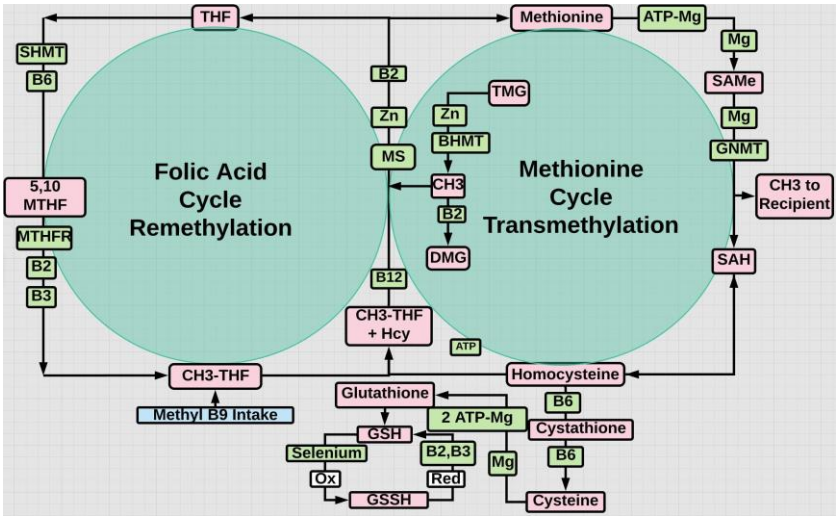

Figure 4: Vitamins B2,3,6,9 (folate),12 are all required for proper function of the methylation cycle.

P5P (and magnesium) is a required cofactor for the synthesis of glutathione (Figure 4) and melatonin (Figure 5), both of which are powerful antioxidants, often deficient in those with Covid-19 [23]. In their absence the resultant oxidative stress induces mitochondrial dysfunction. This restricts mitochondrial dependent CYP27B1 and 1,25(OH)2D synthesis. LC and CFS further aggravate oxidative stress, trigger tryptophan steal with B2 and B6 consumption (Figure 5). This compromises the methylation cycle and energizes MTHFR related difficulties, especially elevated Hcy. Hyperhomocysteinemia is associated with P5P deficiency independent of vitamins B1,2,9,12 or antioxidant status [24].

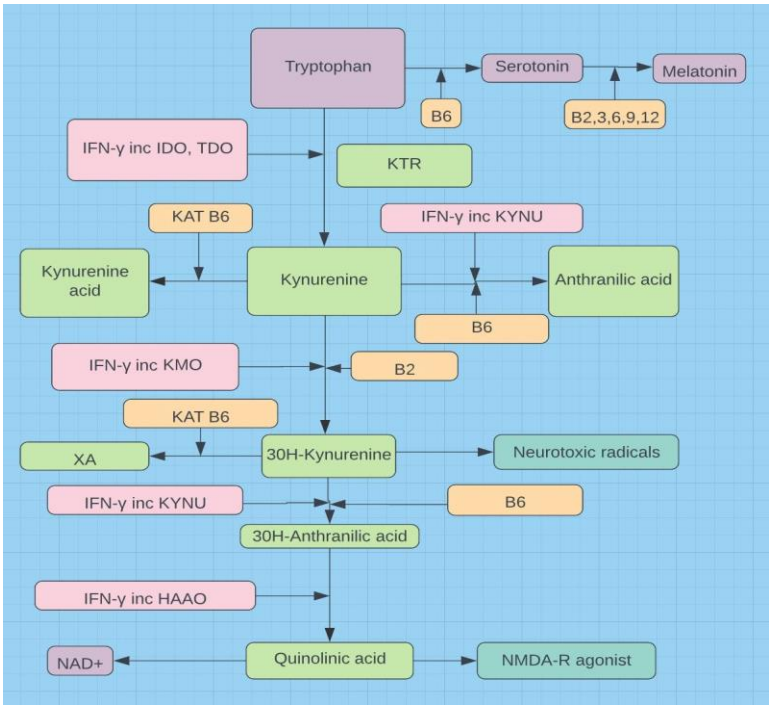

Figure 5: As oxidative stress mounts, tryptophan pivots from the serotonin pathway to the kynurenine pathway (tryptophan steal). Production of ATP reverts from mitochondrial based to fermentation, which utilizes NAD+ (B3).

This underscores the significance of P5P sufficiency in Caucasians and Asians ⅓ of whom have the 677T allele and another ⅓ of which have the 1298C allele. Heterozygosity of 677T or homozygosity of 1298C is associated with a 35% reduction in MTHFR activity, predisposing them to elevated homocysteine. Furthermore magnesium and P5P are required to convert excess Hcy into glutathione, the master antioxidant (Figure 4).

P5P also improves the immune response and increases CD4 and CD8 T cells [25]. The stimulation of CD8 T cells by P5P supports its reported anti-tumor properties [26]. This increase in CD8 T cells suggests that P5P might prove beneficial in Covid-19, which targets CD8 cells and increases CD4:CD8. In contrast HIV targeted CD4 cells and lowered this ratio. P5P decreases inflammatory cytokines, including Tumor Necrosis Factor Alpha (TNF-α) and Interleukin 6 (IL-6) [27].

P5P and Vitamin D, the Gut Microbiome Connection

Gut microbiome studies of both LC [28] and CFS [29] report deficiencies in butyrate and GABA producing bacteria, e.g., Bacteroides [30], Bifidobacterium dentium [31], and Lactobacillus brevium [32]. Bacteroides not only drives gut microbiota diversity but also is one of only six known species that produces P5P. P5P deficiency alone reduces the relative abundance of Bacteroides in the microbiota and directly reflects microbiota diversity (depressed) [33].

Men with the highest compared to lowest 1,25(OH)2D and activation ratios, i.e., active form/storage form (1,25(OH)2D/25(OH)D), are more likely to possess butyrate-producing bacteria associated with favorable gut microbial health [34].

Vitamin D and Magnesium

Vitamin D efficacy diminishes as Ca:Mg exceeds 2.6 (mean from 1977 NHANES II) for colorectal cancer [35], prostate cancer [36], esophageal cancer [37], cardiovascular disease [37], metabolic syndrome[37], total mortality [37], and cognitive function [38]. An elevated Ca++ and a depressed Mg++ (high Ca:Mg) are directly linked to Alzheimer's Disease (AD) [39,40].

In the West as the wave of AD cases builds, it is important to note that Ca++ dysregulation plays a prominent role in both AD and amyloid β deposition [41]. AD predisposition is associated not only with an elevated Ca:Mg but also with an elevated homocysteine [42] and depressed Vitamin D[43]. Mitochondrial dysfunction due to oxidative stress triggers the tryptophan steal, leading to additional consumption of B2 and P5P (Figure 5).

Whether depending on solar exposure (10am to 2pm) or D3 supplements, the benefits of vitamin D are increasingly marginalized in the face of a magnesium deficiency (Figure 6). Magnesium is required for synthesis of the active form of B2.

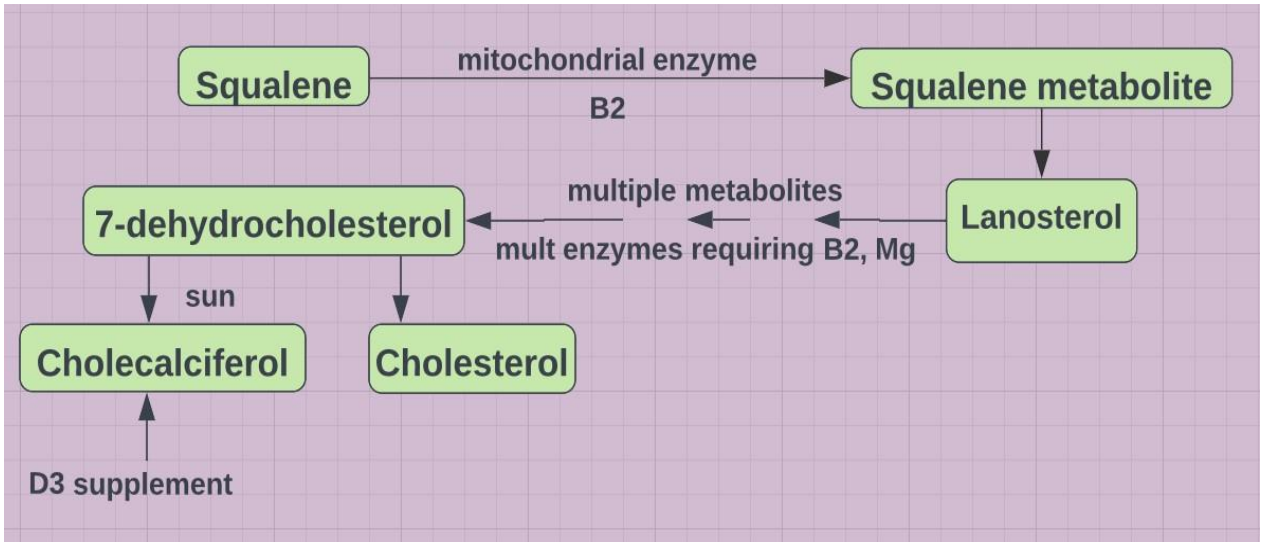

Figure 6: In the absence of adequate magnesium (and B2) the benefits of solar exposure diminish. Chronic inflammation and the induced tryptophan steal aggravate this (see figure 5).

Summary

Thus, deficiencies in P5P, magnesium, and vitamin D are inextricably linked to chronic inflammation and exacerbated by MTHFR variants. Depressed P5P and vitamin D further reflect the same gut microbiome seen in LC and CFS.

In chronic disease, e.g., LC, CFS, autoimmune disease, ROS accumulate due to the antioxidant shortfall, especially P5P dependent melatonin (see figure 5) and glutathione (Figure 3). The resultant oxidative stress overloads mitochondria, depressing 1,25(OH)2D synthesis, consuming B2 and B6 (Figure 4), and further aggravating MTHFR related hypomethylation (see figure 3). P5P directly reflects diverse gut microbiota, lacking in both LC and CFS.

Almost all B vitamins require magnesium for activation, either

phosphorylation or methylation. MTHFR variants dictate predominantly hypomethylation and increased Hcy. Hcy is highly influenced by B vitamin status, specifically status of B2,3,6,9,12 (Figure 4). P5P deficiency restricts not only methylation and recycling of Hcy but also limits the synthesis of glutathione from Hcy in the trans-sulfuration pathway (Figure 4).

Conclusion

As described, many studies have challenged the enhanced efficacy of magnesium in combination with B6. But these are all seriously flawed, as detailed. Reports challenging the efficacy of vitamin D and magnesium. have also appeared on occasion [44] and multiple flaws revealed [45]. The RDA for many micronutrients are out of date or demonstrably in error, e.g., 25(OH)D3 [45].

Confounding factors in many of these challenging studies are insufficiently evaluated. Declining dietary nutrition, escalating oxidative stress, be it infectious or lifestyle related, and suboptimal gut microbiota make this triple play imperative. P5P appears to enhance cellular entry of magnesium (and vice versa), be they enterocytes, erythrocytes, or neurons. Vitamin, magnesium are the superstars, but P5P plays a strong supporting role. The domino effect of P5P on increasing intracellular magnesium, which then enables synthesis of vitamin D, cannot be overemphasized. But the distinction between P5P and its pretenders (pyridoxine, pyridoxamine) must not be overlooked.

References

1. Workinger JL, Doyle RP, Bortz J (2018) Challenges in the Diagnosis of Magnesium Status. Nutrients 10(9):1202.
2. Wimalawansa SJ (2022) Rapidly Increasing Serum 25(OH) D Boosts the Immune System, against Infections-Sepsis and COVID-19. Nutrients 14(14):2997.
3. Percudani R, Peracchi A (2020) A genomic overview of pyridoxal-phosphate-dependent enzymes. EMBO Rep 4:850-854.
4. Indika NR, Frye RE, Rossignol DA, Owens SC, Senarathne UD, et al. (2023) The Rationale for Vitamin, Mineral, and Cofactor Treatment in the Precision Medical Care of Autism Spectrum Disorder. J Pers Med Jan 13(2):252.
5. Bjørke-Monsen AL, Varsi K, Sakkestad ST. et al. (2023) Assessment of vitamin B6 status in never-pregnant, pregnant and postpartum women and their infants. Eur J Nutr 62:867-878.
6. NIH Vitamin B6 Fact Sheet for Health Professionals. https://ods.od.nih.gov/factsheets/VitaminB6-HealthProfessional/
7. Vrolijk MF, Opperhuizen A, Jansen EHJM, Hageman GJ, Bast A, et al. (2017) The vitamin B6 paradox: Supplementation with high concentrations of pyridoxine leads to decreased vitamin B6 function. Toxicol In Vitro 44:206-212.
8. Hadtstein F, Vrolijk M (2021) Vitamin B-6-Induced Neuropathy: Exploring the Mechanisms of Pyridoxine Toxicity. Adv Nutr 12(5):1911-1929.
9. Abraham GE, Schwartz UD, Lubran MM (1981) Effect of vitamin B-6 on plasma and red blood cell magnesium levels in premenopausal women. Ann Clin Lab Sci 11:333-336.
10. Boylan LM, Spallholz JE (1990) In vitro evidence for a relationship between magnesium and vitamin B-6. Magnes Res 3:79-85.
11. Noah L, Pickering G, Dubray C, Mazur A, Hitier S, et al. (2020) Effect of vitamin B6 supplementation, in combination with magnesium, on severe stress and magnesium status: Secondary analysis from an RCT. Proceedings of the Nutrition Society 79(OCE2), E491.
12. Pouteau E, Kabir-Ahmadi M, Noah L, Mazur A, Dye L, et al. (2018) Superiority of magnesium and vitamin B6 over magnesium alone on severe stress in healthy adults with low magnesemia: A randomized, single-blind clinical trial. PLoS One 13(12):e0208454.
13. Eisinger J, Dagorn J (1986) Vitamin B6 and magnesium. Magnesium 5(1):27-32.
14. Abraham GE, Schwartz UD, Lubran MM (1981) Effect of vitamin B-6 on plasma and red blood cell magnesium levels in premenopausal women. Ann Clin Lab Sci 11(4):333-336.
15. Planells E, Lerma A, Sánchez-Morito N, Aranda P, LLopis J (1997) Effect of magnesium deficiency on vitamin B2 and B6 status in the rat. J Am Coll Nutr 16(4):352-356.
16. Fathizadeh N, Ebrahimi E, Valiani M, Tavakoli N, Yar MH (2010) Evaluating the effect of magnesium and magnesium plus vitamin B6 supplement on the severity of premenstrual syndrome. Iran J Nurs Midwifery Res 15(Suppl 1):401-405.
17. Mason DY, Emerson PM (1973) Primary acquired sideroblastic anaemia: response to treatment with pyridoxal-5-phosphate. Br Med J 1(5850):389-390.
18. Gehrmann G (1965) Pyridoxine-Responsive Anaemias. Br J Haematol 11:86-91.
19. Rose D (1966) Excretion of Xanthurenic Acid in the Urine of Women taking Progestogen-Oestrogen Preparations. Nature 210:196-197.
20. Rose DP (1978) The interactions between vitamin B6 and hormones. Vitam Horm 36:53-99.
21. Pinto JT, Cooper AJ (2014) From cholesterogenesis to steroidogenesis: role of riboflavin and flavoenzymes in the biosynthesis of vitamin D. Adv Nutr 5(2):144-163.
22. Bikle DD (2014) Vitamin D metabolism, mechanism of action, and clinical applications. Chem Biol 21(3):319-329.
23. Silvagno F, Vernone A, Pescarmona GP (2020) The Role of Glutathione in Protecting against the Severe Inflammatory Response Triggered by COVID-19. Antioxidants (Basel) 9(7):624.
24. Molina-López J, Florea D, Quintero-Osso B, de la Cruz AP, Rodríguez-Elvira M, et al. (2016) Pyridoxal-5'-phosphate deficiency is associated with hyperhomocysteinemia regardless of antioxidant, thiamine, riboflavin, cobalamin, and folate status in critically ill patients. Clin Nutr 35(3):706-712.
25. Cheng CH, Chang SJ, Lee BJ, Lin KL, Huang YC (2006) Vitamin B6 supplementation increases immune responses in critically ill patients. Eur J Clin Nutr 60(10):1207-1213.
26. Bargiela D, Cunha PP, Veliça P, Foskolou IP, Barbieri L, et al. (2022) Vitamin B6 Metabolism Determines T Cell Anti-

Tumor Responses. Front Immunol 13:837669.
27. Huang SC, Wei JC, Wu DJ, Huang YC (2010) Vitamin B(6) supplementation improves pro-inflammatory responses in patients with rheumatoid arthritis. Eur J Clin Nutr 64(9):1007-1013.
28. Yeoh YK, Zuo T, Lui GC, Zhang F, Liu Q, et al. (2021) Gut microbiota composition reflects disease severity and dysfunctional immune responses in patients with COVID-19. Gut 70:698-706.
29. König RS, Albrich WC, Kahlert CR, Bahr LS, Löber U, et al. (2022) The Gut Microbiome in Myalgic Encephalomyelitis (ME)/Chronic Fatigue Syndrome (CFS). Front Immunol 12:628741.
30. Strandwitz P, Kim KH, Terekhova D, Liu JK, Sharma A, et al. (2019) GABA-modulating bacteria of the human gut microbiota. Nat Microbiol 3:396-403.
31. Pokusaeva K, Johnson C, Luk B, Uribe G, Fu Y, et al. (2017) GABA-producing Bifidobacterium dentium modulates visceral sensitivity in the intestine. Neurogastroenterol Motil 1:e12904.
32. Ko et al., (2013) Gamma-aminobutyric acid production in black soybean milk by Lactobacillus brevis FPA 3709 and the antidepressant effect of the fermented product on a forced swimming rat model. Process Biochem 48 (2013): 559-568.
33. Mayengbam S, Chleilat F, Reimer RA (2020) Dietary Vitamin B6 Deficiency Impairs Gut Microbiota and Host and Microbial Metabolites in Rats. Biomedicines 11 (2020): 469.
34. Thomas RL, Jiang L, Adams JS, Xu ZZ, Shen J, et al. (2020) Vitamin D metabolites and the gut microbiome in older men. Nat Commun 11(1):5997.
35. Dai Q, Sandler R, Barry E, Summers R, Grau M, Baron J, et al. (2012) Calcium, magnesium, and colorectal cancer. Epidemiology 23(3):504-505.
36. Dai Q, Motley SS, Smith JA Jr, Concepcion R, Barocas D, et al. (2011) Blood magnesium, and the interaction with calcium, on the risk of high-grade prostate cancer. PLoS One 6(4):e18237.
37. Costello RB, Rosanoff A, Dai Q, Saldanha LG, Potischman NA (2021) Perspective: Characterization of Dietary Supplements Containing Calcium and Magnesium and Their Respective Ratio-Is a Rising Ratio a Cause for Concern? Adv Nutr 12(2):291-297.
38. Zhu X, Borenstein AR, Zheng Y, Zhang W, Seidner DL, et al. (2020) Ca:Mg Ratio, APOE Cytosine Modifications, and Cognitive Function: Results from a Randomized Trial. J Alzheimers Dis 75(1):85-98.
39. Zhu X, Borenstein AR, Zheng Y, Zhang W, Seidner DL, et al. (2020) Ca:Mg Ratio, APOE Cytosine Modifications, and Cognitive Function: Results from a Randomized Trial. J Alzheimers Dis 75(1):85-98.
40. Du K, Zheng X, Ma ZT, Lv JY, Jiang WJ, et al. (2022) Association of Circulating Magnesium Levels in Patients With Alzheimer's Disease From 1991 to 2021: A Systematic Review and Meta-Analysis. Front Aging Neurosci 13:799824.
41. Foraker J, Millard SP, Leong L, Thomson Z, Chen S, et al. (2015) The APOE Gene is Differentially Methylated in Alzheimer's Disease. J Alzheimers Dis 48(3):745-755.
42. Smith AD, Refsum H, Bottiglieri T, Fenech M, Hooshmand B, et al. (2018) Homocysteine and Dementia: An International Consensus Statement. J Alzheimers Dis 62(2):561-570.
43. Shen L, Ji HF (2015) Vitamin D deficiency is associated with increased risk of Alzheimer's disease and dementia: evidence from meta-analysis. Nutr 14:76.
44. Huțanu A, Georgescu AM, Voidăzan S, Andrejkovits AV, Negrea V, et al. (2022) Low Serum Vitamin D in COVID-19 Patients Is Not Related to Inflammatory Markers and Patients' Outcomes-A Single-Center Experience and a Brief Review of the Literature. Nutrients 14(10):1998.
45. Chambers P, Comment on Hutanu et al. (2022) Low Serum Vitamin D in COVID-19 Patients Is Not Related to Inflammatory Markers and Patients' Outcomes-A Single-Center Experience and a Brief Review of the Literature. Nutrients 14:3387.