EXPLORING THE VITAMIN D-MULTIPLE SCLEROSIS AXIS

Yazar
UFUK ÇINKIR

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Introduction

Multiple sclerosis (MS) is a chronic, progressive neurodegenerative disorder of the central nervous system (CNS), primarily characterised by demyelination and influenced by a complex interplay of genetic and environmental factors. This condition predominantly impacts younger adults, with a higher incidence in females, who are affected at a ratio of approximately 1:3 compared to males (Compston & Coles, 2002: 1221–1231, Reich, Lucchinetti & Calabresi, 2018: 169-180). MS begins with the loss of myelin; as the disease progresses, axonal degeneration also contributes to long-term neurological impairment. MS is a leading cause of disability in young and middle-aged individuals, significantly affecting quality of life. It is notably more prevalent among Caucasians and is recognised as a significant health concern worldwide, with an estimated 2 million people currently affected (Koch-Henriksen & Sørensen, 2010: 520-532, GBD 2016 Multiple Sclerosis Collaborators, 2019: 269-285). The lesions resulting from MS can appear in the CNS's white and grey matter, contributing to a wide array of neurological symptoms. These can include motor and sensory disturbances such as dizziness, imbalance, sensory loss, reduced motor strength, vision impairment, and cognitive and urinary problems. Common visual disturbances include diplopia (double vision), while other systemic issues, such as urinary incontinence, can also occur (Milo & Kahana, 2010: 387-394, Fox, Rae-Grant & Béthoux, 2018: 15-16, 45-51). In addition to these classic symptoms, fatigue, a hallmark of MS, and sleep disturbances are frequently reported, significantly affecting daily functioning and overall health (Fox, Rae-Grant & Béthoux, 2018: 45-51, Weerasinghe-Mudiyanselage et al., 2024: 84-91).

Vitamin D (VitD) deficiency during childhood and adolescence represents a significant risk factor for the development

of MS. VitD is predominantly synthesised through cutaneous exposure to ultraviolet B (UVB) radiation or obtained via supplementation, with dietary sources playing a minimal role in most populations. Epidemiological data reveal a strong association between higher MS prevalence and earlier disease onset in regions with increased latitude and reduced sunlight exposure, while a diet rich in fatty fish—a primary natural source of VitD —may attenuate this latitude-associated risk. Human leukocyte antigen (HLA)-DRB1*1501, the most robust genetic risk factor for MS, is directly regulated by 1,25-dihydroxyvitamin D3, underscoring the immunomodulatory role of VitD in MS pathogenesis. (Dobson & Giovannoni, 2019: 27-28, Bäärnhielm, Olsson & Alfredsson, 2014: 726, Kampman & Brustad, 2008: 140, Marck & van der Meer, 2013: 792-799, Ramagopalan et al., 2009: 1- 5, Cocco et al., 2012: 1-4, Kular et al., 2018: 1-13)

Compelling longitudinal studies demonstrate that elevated serum 25-hydroxyvitamin D3 levels are associated with a 30–60% reduction in MS risk, with data from large U.S. and Scandinavian cohorts reinforcing the critical role of VitD as a modifiable determinant of MS susceptibility. (Munger et al., 2004: 60-65, Munger et al., 2006: 2832- 2837, Nielsen et al., 2017: 44-51, Munger et al., 2017: 1578- 1582).

In the context of modulating disease activity following a diagnosis of MS, an expanding body of evidence suggests that VitD supplementation may reduce relapse rates and attenuate magnetic resonance imaging (MRI)-detected lesion activity in individuals with MS (pwMS) (Burton et al., 2010: 1852, Laursen et al., 2016: 169-173, Goldberg, Fleming & Picard, 1986: 193-200, Achiron et al., 2015: 767-768, Ascherio et al., 2014: 306-313, Mowry et al., 2012: 234-239).

However, conducting randomised controlled trials (RCTs) in this domain has considerable methodological and logistical challenges. These include the need for extensive sample sizes and prolonged follow-up periods, the inherent heterogeneity of disease expression, limited sensitivity to detect subtle clinical changes, participant attrition, and confounding factors such as environmental sun exposure and baseline VitD supplementation in control groups. Although several studies have demonstrated promising outcomes with high-dose VitD supplementation compared to placebo, consistent evidence supporting long-term clinical benefits remains elusive (Soilu-Hänninen et al., 2012: 565-571, Hupperts et al., 2019: 1906-1914, Camu et al., 2019: 1-6, Kampman et al., 2012: 1144-1150, Golan et al., 2013: 1-8). Ethical considerations further compound these challenges, as withholding VitD supplementation in control groups is considered ethically untenable. As a result, a definitive assessment of VitD's therapeutic efficacy in MS may remain constrained by these enduring ethical and methodological obstacles (Scragg, 2018: 6-8).

Both the circulating and biologically active forms of VitD — 25-hydroxyvitamin D3 (25(OH)D3) and 1,25-dihydroxyvitamin D3 (1,25(OH)2D3), respectively, can cross the blood-brain barrier (BBB) and exert their effects within the CNS. Once inside the CNS, these compounds influence various neuronal and glial cells (Pardridge, Sakiyama & Coty, 1985: 1138-1140, Yu et al., 2011: 295-306). Notably, neurons, microglia, and astrocytes express the enzyme 1α-hydroxylase (CYP27B1), which catalyses the conversion of 25(OH)D3 into its active form, 1,25(OH)2D3 (Smolders et al., 2013: 91-104, Eyles et al., 2005: 21-28, Boontanrart et al., 2016: 126-135, Jiao et al., 2017: 492–495). In addition to these cell types, oligodendrocytes also express the vitamin D receptor (VDR), making them responsive to VitD signalling. (Smolders et al., 2013: 91-104, Eyles et al., 2005: 21-28, Boontanrart et al., 2016:

126-135, Jiao et al., 2017: 492–495, de la Fuente et al., 2015: 975–980, Sloka et al., 2015: 1, 5-9, Lee et al., 2010: 1-2, 4-7). The active form 1,25(OH)2D3 may either be synthesised intracellularly or passively diffuse through the plasma membrane to bind to cytoplasmic VDR (Nurminen, Seuter & Carlberg, 2019: 1-11). Upon ligand binding, the VDR-1,25(OH)2D3 complex translocates to the nucleus, where it dimerises with the retinoid X receptor (RXR) and binds to vitamin D response elements (VDREs) on target genes (Nurminen, Seuter & Carlberg, 2019: 1-11). This binding modulates the transcription of numerous genes involved in processes ranging from bone health to CNS development and immunomodulation (Sangha et al., 2023: 2).

MS is characterised by a complex pathophysiology involving inflammatory demyelination and progressive neurodegeneration. The autoimmune component of MS stems from T-cell-mediated attacks on the myelin sheath, impairing efficient impulse transmission and producing neurological deficits. This immune-driven demyelination leads to focal inflammatory lesions in the CNS, chronic myelin destruction, axonal damage, and, ultimately, neuronal loss. While remyelination plays a critical role in mitigating permanent disability, its effectiveness diminishes as MS progresses. Unfortunately, neuroprotective strategies to preserve neural integrity or promote remyelination remain elusive (Van Schependom et al., 2019: 1-13, Goverman, 2009: 393-405, Høglund & Maghazachi, 2014: 27-33, Coggan et al., 2015: 21216-21230, Allanach et al., 2022: 29-44, Klotz, Antel & Kuhlmann, 2023: 305-319, Stangel et al., 2017: 742-754, Sangha et al., 2023: 2).

Understanding the interplay between VitD deficiency and its potential influence on immune regulation, myelination, and neurodegeneration is essential for identifying novel approaches to mitigate MS risk and modulate disease activity. Although the immunomodulatory role of VitD —particularly its capacity to

reduce inflammation—is well-established, evidence for its neuroprotective effects remains relatively limited. Nonetheless, emerging studies are beginning to elucidate the mechanisms by which VitD may protect against axonal degeneration and glial and neuronal loss (Cadden, Koven & Ross, 2011: 198-204, Gandhi et al., 2021: 1-8, Gombash et al., 2022: 1-9).

This book presents an in-depth analysis of the metabolism of VitD, its biological and immunological effects, its relationship with MS, and its emerging role in the therapeutic management of the disease.

Sources and Metabolic Dynamics of Vitamin D

Since the seminal elucidation of the chemical structure of VitD in 1930 by Nobel laureate Adolf Otto Reinhold Windaus, building upon the foundational contributions of preceding researchers (Wolf, 2004: 1299-1302), the field of VitD research has witnessed remarkable strides. Initially, investigations were centred on its metabolic effects on bone, thereby underscoring the indispensable role of VitD and its metabolites in maintaining calcium homeostasis and regulating bone metabolism. However, with the discovery of 25(OH)D in 1968 (Blunt, Tanaka & DeLuca, 1968: 1503-1506, Ponchon, Kennan & DeLuca, 1969: 2032-2036), followed by the identification of 1,25-hydroxyvitamin D3 (Norman et al., 1971: 51-54, Holick, Schnoes & DeLuca, 1968: 803-804), the scope of research expanded to encompass a diverse array of physiological and pathological contexts, including immune-mediated diseases, infections, oncogenesis, and cardiovascular disorders (DeLuca, 2004: 1689-1695). VitD exerts a multifaceted influence on immune system regulation, modulating the activity of suppressor T lymphocytes, cytokine synthesis, and apoptosis pathways at the cellular level (Dattola et al., 2020: 226–235). Furthermore, it plays a critical role in enhancing intestinal phosphate

absorption while concurrently preventing its renal excretion. Hence, while the established role of VitD in bone health remains indisputable, this constitutes merely one facet of its extensive pleiotropic functional repertoire (Dominguez et al., 2021: 1-2).

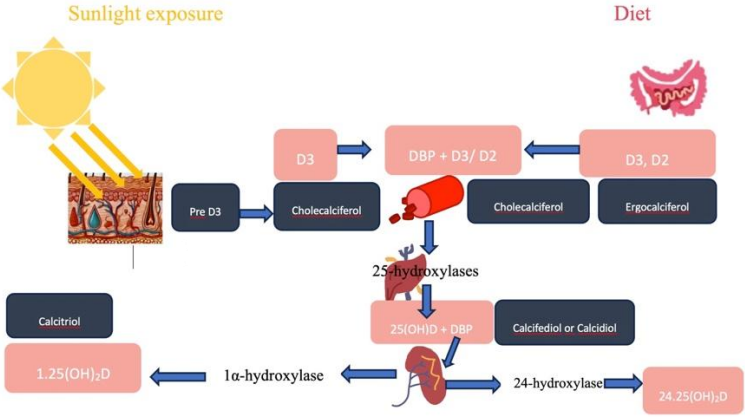
Previtamin D3 is synthesised in the skin from 7-dehydrocholesterol (provitamin D) through exposure to UV radiation within the 290–320 nm wavelength range. Due to its thermodynamic instability, pre-vitamin D3 undergoes photochemical isomerisation, resulting in a structural rearrangement of its triene system, forming vitamin D3 (cholecalciferol). The biosynthesis of vitamin D3 represents a complex physiological process integral to calcium and phosphate homeostasis and various immunomodulatory functions. This synthesis begins in the skin, where exposure to UVB radiation catalyses the conversion of provitamin D3 (7-dehydrocholesterol) within the epidermal basal layers into pre-vitamin D3. Subsequently, a thermally dependent isomerisation transforms pre-vitamin D3 into cholecalciferol.

In addition to dermal synthesis, vitamin D3 can be sourced exogenously through dietary intake of natural and fortified foods and supplements containing either ergocalciferol (D2) or cholecalciferol. Upon absorption in the gastrointestinal tract, vitamin D3 associates with vitamin D-binding protein (DBP) for transport within the circulatory system. The liver plays a pivotal role in the initial metabolic activation of VitD. Both vitamin D2 and D3 undergo hydroxylation via hepatic 25-hydroxylases, forming 25(OH)D, also known as calcifediol or calcidiol (Dominguez et al., 2021: 3).

The second critical hydroxylation occurs in the kidney under the enzymatic activity of 1α-hydroxylase, yielding the hormonally active secosteroid, 1,25(OH)2D, also termed calcitriol. The production of calcitriol is tightly regulated: it is stimulated by parathyroid hormone (PTH) in response to hypocalcemia and

modulated by feedback inhibition from elevated levels of calcium, phosphate, and calcitriol itself (Dominguez et al., 2021: 3) (Figure 1).

Figure 1: The synthesis of vitamin D3



The extent and nature of UV exposure are critical determinants of VitD synthesis. Exposure to 25% of the minimum erythema dose (MED) over approximately 25% of the body surface area, typically involving the face, hands, and arms, yields an estimated 1000 IU of VitD (Webb & Engelsen, 2006: 1697-1703). Comprehensive whole-body exposure at midday during the summer for approximately 15 minutes, corresponding to 1 MED, can synthesise up to 10,000 IU (250 µg) of cholecalciferol (Holick, 2004: 362-371, Dominguez et al., 2021: 3). Partial exposure limited to the face, hands, and arms, at one-third or one-sixth of the MED, generates the equivalent of 200 to 600 IU (Vieth, 1999: 842-856).

Several intrinsic and extrinsic factors influence the efficiency of this endogenous synthesis process. Key determinants include age, skin pigmentation (melanin content), seasonal variability, weather conditions, geographic latitude, altitude, time of day, extent of clothing coverage, body surface area exposed,

recreational behaviours, sunscreen application, and individual skin characteristics. Of particular importance, ageing is associated with a marked reduction in the skin's capacity to produce VitD (Dominguez et al., 2021: 3, Haddad, 1992: 1213–1215, Binkley et al., 2007: 2130-2135, Neville, Palmieri & Young, 2021: 1).

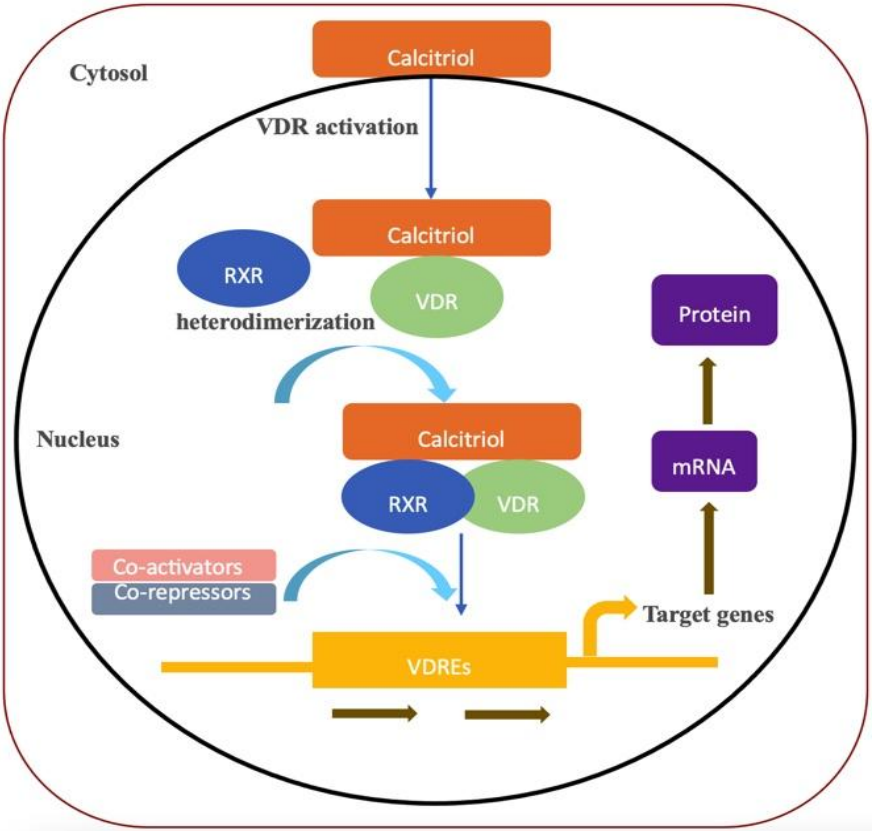
VitD refers to a group of fat-soluble compounds with a structural backbone based on cholesterol rings. The primary circulating form, 25(OH)D, has a two to three-week half-life. In contrast, the active form, 1,25(OH)2D, has a much shorter half-life, ranging from four to eight hours. This active compound binds to the VDR, triggering its physiological effects and regulating its levels via a negative feedback loop (Christakos et al., 2016: 365-394).

VitD production has been essential to life on Earth for millennia. Both plants and animals have evolved mechanisms for synthesising and metabolising VitD as life forms became increasingly complex. The capacity to convert VitD into more bioactive metabolites coincided with the rise of more specialised cellular functions. In more complex organisms, the VDR is found in virtually every cell, and the cells of these organisms are also capable of producing 1,25(OH)2D in response to various physiological needs (Binkley et al., 2007: 2130-2135, Bikle, 2011: 7-12).

The VDR belongs to a broader family of receptors that also includes those for steroid hormones, thyroid hormones, the retinoid family (vitamin A derivatives), and a diverse group of compounds such as bile acids, fatty acids, isoprenoids, eicosanoids, and cholesterol metabolites. The receptor was first described in 1969 (Haussler & Norman, 1969: 160-162) as a binding protein for a previously unidentified VitD metabolite, which was later determined to be 1,25(OH)2D. In 1987, the VDR was cloned and sequenced, revealing further insights into its role (McDonnell et al., 1987: 1214). Experimental models with VDR knockout mutations

exhibited the complete range of symptoms associated with severe VitD deficiency, confirming that the VDR is the key mediator of VitD action (Sekine et al., 1997: 391-396). Although its expression is not universal, the VDR is widely distributed throughout various tissues in the human body (Bikle, 2011: 7-12, Walters, 1992: 719-764). Upon binding to 1,25(OH)2D, the VDR dimerises with the RXR and this heterodimer then translocates to the nucleus. There, it binds to VDREs, modulating the transcription of specific genes (Bikle, 2011: 7-12) (Figure 2).

Figure 2: Mechanistic Insights into Vitamin D Receptor Activation at Target Cells



Upon entering the bloodstream, VitD (D2 and D3) is weakly bound to the DBP, facilitating its transport and storage in adipose tissue. Subsequently, it undergoes hydroxylation in the liver to form 25(OH)D, a process mediated by various enzymes, particularly cytochrome P450 isoforms such as CYP2R1 and CYP27A1. This hydroxylation can also occur in multiple tissues via an autocrine or paracrine mechanism (Christakos et al., 2016: 365-394). Notably, the conversion rate to 25(OH)D may be reduced in individuals receiving high doses of VitD (Smith & Goodman, 1971: 2159-2166).

The next step involves further hydroxylation in the renal tubule, yielding the biologically active 1,25-dihydroxyvitamin D (Christakos et al., 2016: 365-394, Brown, 1999: 11-16). The entry of the DBP-25(OH)D complex into renal tubular cells is facilitated by the receptor-mediated action of proteins such as cubilin and megalin, which are essential for VitD metabolism. A reduction in the expression of these proteins leads to a loss of 25(OH)D in the urine, thereby contributing to VitD deficiency. In renal tubular cells, two hydroxylases from the cytochrome P450 family, 1-alpha-hydroxylase (CYP27B1) and 24-alpha-hydroxylase (CYP24A1) mediate the conversion of 25(OH)D into either the active 1,25(OH)2D or the inactive 24,25(OH)2D (van Driel et al., 2006: 922-923, 929-932, Takeyama et al., 1997: 1827-1829).

It is crucial to note that several key steps in VitD metabolism—such as the binding of vitamin D3, D2, and 25(OH)D to DBP, as well as the hepatic and renal hydroxylations that produce 25(OH)D and 1,25(OH)2D—require magnesium as a cofactor. A magnesium deficiency impairs these processes, thereby hindering the transport and activation of VitD (Dominguez et al., 2021: 6-9). Magnesium is also involved in the synthesis and secretion of parathyroid hormone (PTH), and its deficiency can suppress PTH function (Anast et al., 1972: 606-608, Medalle, Waterhouse & Hahn,

1976: 854-858, Rude et al., 1978: 800-806, Mutnuri, Fernandez & Kochar, 2016: 1-3). In addition, insufficient dietary magnesium intake may alter the PTH response to 25(OH)D, establishing a feedback loop where the deficits of magnesium and VitD exacerbate each other, potentially leading to a vicious cycle of nutritional insufficiencies (Cheung et al., 2019: 82-93). This interplay between magnesium and VitD deficiencies can have significant clinical consequences, including an increased risk of fragility fractures, particularly among women (Veronese et al., 2017: 1570–1575). A substantial study by Deng et al. delved into the potential interplay between VitD levels, magnesium intake, and mortality. The findings revealed that increased magnesium intake was independently linked to a lower risk of 25(OH)D deficiency (<12 ng/mL) or insufficiency (12–20 ng/mL). Moreover, the inverse relationship between serum 25(OH)D levels and mortality—especially in cases of cardiovascular disease and colorectal cancer—was significantly modified by magnesium intake, with the strongest inverse correlation observed among individuals with magnesium consumption above the median level (Deng et al., 2013: 1-12). A recent randomised controlled trial nested within the Personalised Prevention of Colorectal Cancer Trial further corroborated these findings, demonstrating that optimal magnesium enhances 25(OH)D levels (Dai et al., 2018: 1249–1257).

Recent investigations into human kidney function have revealed that, contrary to experimental models, the distal nephron is the principal site of 1-alpha-hydroxylase expression (Zehnder et al., 1999: 2465–2473). The circulating concentration of 1,25(OH)2D is determined not only by the availability of 25(OH)D but also by the activities of the enzymes 1-alpha-hydroxylase and 24-alpha-hydroxylase. The regulation of 1-alpha-hydroxylase activity is primarily governed by the concentrations of PTH, calcium, phosphorus, and fibroblast growth factor 23 (FGF23) (Christakos et

al., 2016: 365-408, Smith & Goodman, 1971: 2159-2166, Prié & Friedlander, 2010: 1717–1721). FGF23 acts to suppress 1-alpha-hydroxylase (CYP27B1) activity, thereby inhibiting the renal synthesis of 1,25(OH)2D while simultaneously promoting the activity of 24-alpha-hydroxylase and the formation of 24,25(OH)2D (Prié & Friedlander, 2010: 1717–1721, Liu et al., 2006: 1305–1315). Additionally, 1,25(OH)2D stimulates FGF23, which decreases renal phosphate reabsorption, counteracting the enhanced intestinal absorption of phosphate induced by 1,25(OH)2D (Liu et al., 2006: 1305–1315). Both the active form, 1,25(OH)2D, and its precursor, 25(OH)D, are partially degraded by 24-hydroxylase, whose activity is modulated by 1,25(OH)2D and suppressed by elevated levels of PTH (Christakos et al., 2016: 365-408, Negri, 2006: 510–514).

As previously noted, 1-alpha-hydroxylase is also expressed in various tissues outside the kidneys, including the gastrointestinal tract, vascular tissue, breast tissue, skin, osteoblasts, and osteoclasts (Hewison et al., 2007: 316-320). This broad tissue distribution accounts for the diverse clinical manifestations of certain diseases. For instance, in conditions like sarcoidosis, there is an increased production of 1,25(OH)2D by pulmonary macrophages and lymph nodes, which can lead to hypercalcemia (Zhou & Lower, 2020: 618–625).

Vitamin D as a Key Regulator of Innate and Adaptive Immunity

The accumulating body of evidence emphasising the multifaceted role of VitD as both a regulator of calcium homeostasis and a key immunomodulatory agent calls for a deeper understanding of its immunological influence. The connection between VitD deficiency and the onset of various autoimmune disorders suggests that VitD’s involvement in immune regulation is far more intricate than previously acknowledged (Miclea et al., 2020: 2-4).

As the biologically active form, $1,25(OH)_2D_3$ plays a central role in modulating innate and adaptive immune responses. It influences critical immune cell types, such as dendritic cells and macrophages, essential for orchestrating inflammatory responses. Through its regulation of cytokine production, $1,25(OH)_2D_3$ serves to temper inflammatory cascades, thus mitigating the aberrant immune activation that characterises autoimmune conditions (White, 2012: 21-29, Barragan, Good & Kolls, 2015: 8127-8140, Piemonti et al., 2000: 4443-4450). Additionally, its modulation of T-cell differentiation—encouraging the development of regulatory T cells (Tregs) while suppressing helper T (Th)1 and Th17 responses—emphasises its importance in preventing excessive immune reactions, which are frequently implicated in autoimmune pathologies (Cantorna, 2010: 286-288, Baeke et al., 2011: 132-141, Lemire et al., 1995: 1704-1708, Colotta, Jansson & Bonelli, 2017: 78-97).

The dual immunoregulatory capacities of VitD are critical in maintaining immune homeostasis and preventing chronic inflammation or autoimmunity. Given its profound immunomodulatory effects, VitD deficiency likely functions as a permissive factor in developing autoimmune diseases rather than merely being a consequence of the disease process itself. However, despite the growing body of evidence, the precise molecular and mechanistic pathways through which VitD exerts its protective effects remain incompletely understood (White, 2012: 21-29, Holick, Schnoes & DeLuca, 1971: 803-804, Colotta, Jansson & Bonelli, 2017: 78-97).

The complex interplay between VitD and immune modulation underscores the necessity of elucidating the specific receptors, signalling pathways, and genetic factors that govern its immunological effects. Beyond that, the marked interindividual variability in VitD metabolism, along with the influence of genetic

and environmental determinants, offers potential explanations for the differential susceptibility to autoimmune diseases across diverse populations. The therapeutic implications of these insights are significant. Given VitD's critical role in maintaining immune equilibrium, targeted supplementation or modulation of VitD signalling pathways holds the potential to revolutionise the management of autoimmune disorders. Nevertheless, the challenges associated with defining optimal dosing regimens, establishing robust monitoring protocols, and assessing long-term effects remain, particularly in immune-mediated conditions where precision in immune regulation is paramount. Addressing these complexities is essential for refining clinical strategies to prevent and treat autoimmune diseases.

Vitamin D and Innate Immunity

Upon engulfment of microbial invaders by macrophages, a cascade of immunological events is initiated, wherein Toll-like receptors (TLRs) are stimulated, thereby orchestrating a heightened expression of the VDR alongside 1-alpha-hydroxylase in both macrophagic and monocytic populations (Liu et al., 2006: 1770–1773). Upon activation of TLRs, macrophages and dendritic cells elevate the expression of critical molecules such as major histocompatibility complex class II (MHC II), cluster of difference (CD)80/CD86, CD40, and various cytokines, all of which are indispensable for effective antigen presentation to T cells. VitD suppresses these molecules, fostering a state in which macrophages and dendritic cells adopt a more immature and tolerogenic phenotype (Piemonti et al., 2000: 4443-4450, Széles et al., 2009: 1-10). The suppression of macrophage and dendritic cell activity may be attributed to the downregulation of TLRs (Liu et al., 2006: 1770–1773, Li et al., 2014: 1-11, Martinez-Moreno, Hernandez & Urcuqui-Inchima, 2010: 169-180) or the inhibition of interleukin

(IL)-12 production through nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) signalling pathways (D'Ambrosio et al., 2020: 252-260), both of which are modulated by VitD.

The active metabolite 1,25(OH)2D3, in conjunction with the VDR–RXR complex, facilitates the transcriptional activation of antimicrobial peptides, such as defensins and cathelicidins. Cathelicidin is crucial in combating infections by destabilising microbial membranes and disrupting viral envelopes. (Barlow et al., 2011: 1-7, Shahmiri et al., 2016: 1-7, Sousa et al., 2017: 76–82, White, 2012: 21-29). Moreover, calcitriol exerts additional anti-inflammatory effects through glucocorticoid-mediated pathways. Specifically, glucocorticoids stimulate monocytes to produce mitogen-activated kinase phosphatase-1 (MPK-1), an enzyme that attenuates the activity of pro-inflammatory mitogen-activated protein kinases (MAPKs) (Zhang, Leung & Goleva, 2013: 14544-14549). These observations highlight the extensive immunoregulatory capacity of VitD signalling, which transcends its conventional endocrine functions. The interplay between VitD and glucocorticoid pathways implies a convergent, synergistic framework that meticulously modulates inflammatory cascades while safeguarding antimicrobial competence.

Beyond its intrinsic antimicrobial properties, calcitriol profoundly influences immune homeostasis by orchestrating immune cell populations' maturation and functional specialisation across multiple regulatory axes. Of particular significance is its capacity to drive the differentiation of hematopoietic stem cells toward the natural killer cell lineage, thereby augmenting innate immune surveillance. Simultaneously, calcitriol imposes a regulatory constraint on antigen-presenting cell dynamics by inhibiting monocyte-to-dendritic cell transition, impairing dendritic cell maturation, and attenuating the secretion of the pro-

inflammatory cytokine IL-12. Furthermore, calcitriol modulates antigen presentation by downregulating the expression of MHC-II molecules, thus tempering excessive immune activation. In parallel, its pro-apoptotic effects on dendritic cells serve as an additional mechanism reinforcing immune tolerance and homeostatic equilibrium (Barragan, Good & Kolls, 2015: 8127-8140, Piemonti et al., 2000: 4443-4450, D'Ambrosio et al., 2020: 252-260).

VitD is essential in regulating microglial function, modulating the inflammatory milieu and contributing to myelin damage during CNS autoimmunity. VitD has been shown to regulate microglial phenotype and oxidative stress across various models of CNS diseases and injury. In experimental autoimmune encephalomyelitis (EAE) models, calcitriol administration immediately following disease induction mitigates microglial activation, reduces oxidative stress, and decreases BBB permeability. Similarly, a reduction in neuronal VDR expression during early developmental stages rendered mice more susceptible to EAE, suggesting that neuronal VDR signalling exerts a protective role against CNS autoimmunity. Emerging evidence suggests that VitD effectively shifts microglia from a pro-inflammatory M1 phenotype to a reparative M2 phenotype, thereby dampening inflammation and limiting demyelination (De Oliveria et al., 2020: 1-2, Lee et al., 2020: 1-7, Evans et al., 2018: 147-156, Calvello et al., 2017: 327-328, Cui et al., 2019: 1-10, He et al., 2019: 1-8)

VitD's role in innate immunity extends far beyond its classical function in calcium homeostasis, positioning calcitriol as a pivotal immunoregulatory molecule with multifaceted biological effects. The convergence of TLR activation, VDR signalling, and antimicrobial peptide induction underscores a highly coordinated immune defence mechanism. Additionally, calcitriol's capacity to fine-tune antigen presentation, modulate dendritic cell maturation, and orchestrate monocyte differentiation into immunologically

distinct phenotypes reflects its profound influence on the innate immune landscape. The intricate crosstalk between calcitriol and glucocorticoid-mediated pathways further reinforces its role in tempering excessive inflammatory responses while preserving host defence.

Vitamin D and Adaptive Immunity

The expression of the nuclear VDR in both T and B lymphocytes is a pivotal component of the immune system's regulatory mechanisms. Although the basal expression of VDR is relatively low in these cells during their resting state, its induction upon immune activation underscores the dynamic role of VitD in immune modulation (Provvedini et al., 1983: 1181–1183).

Calcitriol has been demonstrated to exert direct regulatory effects on B-cell homeostasis, encompassing the inhibition of memory and plasma cells as well as the induction of apoptosis in immunoglobulin B-producing cells. This mechanism is postulated to represent a pivotal pathophysiological link between VitD and autoimmunity, potentially influencing disease susceptibility and progression (Chen et al., 2007: 1634-1646).

Calcitriol exerts a critical regulatory influence on T-cell responses by modulating the proliferation and differentiation of Th cells and orchestrating a nuanced cytokine production profile. It suppresses pro-inflammatory Th1 cytokines, including IL-2, interferon-γ (IFN-γ), and tumour necrosis factor (TNF), along with Th19 cytokines like IL-19 and Th22 cytokines such as IL-22. In contrast, calcitriol enhances the production of anti-inflammatory Th2 cytokines, notably IL-3, IL-4, IL-5, and IL-10. Additionally, calcitriol inhibits IL-17 production in Th17 cells, further cementing its role in immune modulation. While specific T-cell subsets directly respond to circulating calcitriol, others possess the enzymatic machinery to locally convert inactive VitD into its active form,

allowing for context-dependent immune regulation. (Cantorna, 2010: 286-288, Baeke et al., 2011: 132-141, Lemire et al., 1995: 1704-1708).

Optimal VitD levels may attenuate the capacity of B cells to function as antigen-presenting cells. B-cell depletion therapies have demonstrated remarkable efficacy in treating MS, and the therapeutic benefits observed appear to be largely independent of antibody production. This observation, coupled with emerging evidence, suggests that B cells play a critical role as antigen-presenting cells in the immunopathogenesis of MS (Cross et al., 2006: 63-70, Lovett-Racke et al., 2019: 187-196, Lovett-Racke et al., 2021: 1-8). Immune profiling studies of MS patients receiving B cell depletion therapy have shown a favourable modulation of the T cell compartment, characterised by a reduction in memory T cells and an increase in Tregs (Lovett-Racke et al., 2019: 187-196, Lovett-Racke et al., 2021: 1-8), further supporting the role of B cells in T cell activation. In this context, VitD deficiency may enhance the antigen-presenting capacity of B cells, thereby promoting T cell activation and differentiation and ultimately increasing the susceptibility to MS.

This dual mechanism underscores the complexity of VitD's role in shaping immune responses, suggesting that its effects are not only systemic but also finely tuned to local immune environments.

Vitamin D and the Central Nervous System

An expanding body of evidence indicates that VitD functions as a neurosteroid. The extensive expression of the VDR across both the developing and mature brain—including key regions such as the hippocampus, amygdala, hypothalamus, cortex, and cerebellum (Eyles et al., 2005: 21-28, Stumpf et al., 1982: 1403-1405, McGrath et al., 2004: 557–560)—emphasises its fundamental role in regulating gene expression within the CNS. Moreover, the presence

of 1α-hydroxylase and 25-hydroxylase enzymes in the brain enables the local biosynthesis of active VitD, thereby reinforcing its neurobiological significance (Eyles et al., 2005: 21-28, Zehnder et al., 2001: 888-889). While gene regulation constitutes a primary function of VitD, it also mediates non-genomic effects, most notably through the modulation of calcium signalling—an indispensable mechanism for preserving normal cellular physiology.

VitD promotes cell differentiation and apoptosis, which are critical for embryonic development. When VitD is removed during gestation in model systems, multiple regions of the brain have increased cell proliferation and decreased apoptosis, as well as enhanced cell proliferation, leading to CNS anomalies (Eyles et al., 2003: 641-653, Brown et al., 2003: 139-143, Ko et al., 2004: 61-68). The increased proliferation was mediated by increased expression of cyclin genes, which were regulated by VDR signalling (Sinkkonen et al., 2005: 2440-2450), while the reduction in apoptosis may have been due to increased levels of B-cell lymphoma (Bcl)-2 and Bcl -2-associated X protein (BAX) (Ko et al., 2004: 61-68). Low VitD also leads to more neural stem cells, possibly due to a loss of regulation of cell proliferation or a failure in neural stems to efficiently differentiate into neural cell progenitors (Cui et al., 2007: 227–232). Changes in brain morphology have been observed in rodents with VitD deficiency (Eyles et al., 2003: 641-653, Al-Amin et al., 2019: 1315–1329).

Accumulating evidence underscores the critical role of VitD in modulating brain structure and cellular differentiation. In humans, VitD deficiency has been associated with decreased brain volume and enlarged ventricles in older adults, highlighting its potential influence on neuroanatomical integrity (Annweiler et al., 2015: 41-47). It has also been demonstrated that VitD suppresses the proliferation of hippocampal neurons while simultaneously promoting neurite outgrowth, suggesting a nuanced regulatory

function in neuronal development (Brown et al., 2003: 139-143). Of particular significance, studies on dopaminergic neurons indicate that VitD deficiency during embryogenesis reduces the expression of Nurr1 and P57kip2—genes indispensable for the development and homeostasis of dopaminergic systems (Cui et al., 2010: 220-223). Additionally, VitD has been shown to regulate the transcription of genes vital to the proper functioning of dopaminergic neurons, further reinforcing its role in maintaining neuronal integrity (Orme, Bhangal & Fricker, 2013: 1-7, Pertile, Cui & Eyles, 2015: 193-194).

Intriguingly, while VitD promotes neuronal differentiation, its influence on astrocyte development appears to be inhibitory under certain conditions; when adult neural stem cells are exposed to VitD, astrocyte differentiation is impaired (Shirazi et al., 2015: 240). In contrast, VitD facilitates the differentiation of neural stem cells into oligodendrocytes—the myelinating cells of the CNS—a process that is disrupted when VDR signalling is inhibited, preventing the maturation of oligodendrocyte precursor cells (Shirazi et al., 2015: 240-245, De la Fuenta et al., 2015: 975-977). These findings collectively identify VitD as a pivotal neuronal and oligodendrocyte lineage commitment regulator. Given the essential bidirectional signalling between neurons and oligodendrocytes, this regulatory function of VitD is indispensable not only for the proper myelination of the CNS during early development but also for facilitating remyelination following CNS injury.

Vitamin D: A Key Player in Neuroprotection

VitD exerts its neuroprotective effects through multifaceted and interconnected mechanisms. Central to these actions are the regulation of neurotrophic factors and the mitigation of oxidative stress, which are fundamental to neuronal resilience and homeostasis. Neurotrophic factors are indispensable for neuronal

and glial populations' differentiation, survival, and functional preservation. Notably, VitD enhances the expression of several pivotal neurotrophic factors, including nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), glial cell line-derived neurotrophic factor (GDNF), and neurotrophin-3 (NT3) (Di Somma, 2017: 1-13). As the endogenous production of these factors diminishes with age, the residual levels become increasingly crucial for sustaining cellular integrity and facilitating neuroprotection. A deficiency in VitD compromises this regulatory axis, potentially diminishing neurotrophic support and rendering neural cells more vulnerable to external insults and neurodegenerative processes.

Neurons are inherently susceptible to oxidative damage due to their elevated metabolic activity, which necessitates high oxygen consumption, the generation of reactive byproducts during neurotransmitter metabolism, susceptibility to excitotoxicity, and a lipid-rich cellular composition (Sivandzade et al., 2019: 1-12).

Additional neuroinflammation will increase the reactive oxygen species (ROS) load. Adequate VitD levels downregulate intracellular oxidative-stress-related activities, while suboptimal levels result in increased oxidative damage and neuronal apoptosis (Wimalawansa, 2019: 1). Increased reactive oxygen production has been implicated in the pathogenesis of multiple neurodegenerative conditions, including Parkinson's disease (Trist, Hare & Double, 2019: 1-2), Alzheimer's disease (Niedzielska et al., 2016: 4094-4116), Huntington's disease (Browne & Beal, 2006: 2061-2062), stroke (Rodrigo et al., 2013: 698-714) and MS (Di Filippo et al., 2010: 369-376), and suboptimal serum VitD levels have been linked to these conditions. VitD is a potent regulator of the nuclear factor erythroid-2-related factor 2 (Nrf2) antioxidant pathway in neurons and glial cells, and intracellular Nrf2 levels are inversely correlated with the accumulation of mitochondrial ROS. Within the CNS, upregulation of Nrf2 target genes superoxide dismutase (SOD),

catalase (CAT), glutathione S-transferase (GST) and heme oxygenase-1 (HMOX1) makes neurons more resistant to oxidative insults (Brandes & Gray, 2020: 1-11). Furthermore, neurotrophic signalling pathways, such as the BDNF-tropomyosin-related kinase B (TrkB) pathway that is essential for mature neuron survival and normal function, also signal Nrf2 activation (Khairy & Attia, 2021: 650-651, Hannan et al., 2020: 1-14). VitD then has double the influence on neuronal survival – first in neurotrophic action by increasing levels of BDNF and second in oxidative defence by direct activation of Nrf2. The neuroprotective properties of VitD centre around its antioxidant function, and in conjunction with neurotrophic factor expression, likely enhance neural defence and repair mechanisms.

Vitamin D as a Guardian of the Nervous System: Unlocking Antioxidant Pathways to Combat Multiple Sclerosis

Oxidative stress and mitochondrial dysfunction are central hallmarks of MS pathophysiology, intricately shaping disease progression. Among the key players, T cells not only generate ROS but are also profoundly modulated by them, creating a sophisticated interplay that amplifies neuroinflammation and neuronal injury in MS (Ohl, Tenbrock & Kipp, 2016: 62). However, the most significant sources of elevated ROS in the disease are activated microglia and macrophages, which unleash a cascade of oxidative radicals—including superoxide, hydrogen peroxide, and nitric oxide (NO)—via potent ROS-generating enzymes such as myeloperoxidase (MPO), nicotinamide adenine dinucleotide phosphate hydrogen (NADPH) oxidase, and nitric oxide synthase (NOS). These oxidative mediators have been directly implicated in driving demyelination, a process consistently observed in MS and its experimental models (Ohl, Tenbrock & Kipp, 2016: 61-64, Genestra, 2007: 1807-1819).

Postmortem analyses of MS brains further underscore the pathogenic role of oxidative stress. MPO expression is markedly upregulated in activated macrophages and microglia adjacent to lesions, revealing a focal contribution to tissue damage. Strikingly, homogenates of demyelinated MS brain regions exhibit significantly higher levels of MPO compared to unaffected areas from the same individual, reinforcing the notion that oxidative injury is not merely a secondary byproduct but a primary force in MS pathology (Gray et al., 2008a: 86, Gray et al., 2008b: 195-196).

Additional hallmarks of oxidative injury further underscore its pathogenic significance in MS. Among these, 4-hydroxy-2-nonenal (4-HNE), a highly reactive byproduct of lipid peroxidation, serves as a key indicator of membrane oxidative damage. Likewise, nitrotyrosine, formed through NO reaction with superoxide, represents a molecular fingerprint of peroxynitrite-mediated nitrative stress. Both markers exhibit a striking accumulation within macrophages and astrocytes in MS lesions, reinforcing the notion that oxidative pathology is not merely a secondary consequence but an integral driver of neuroinflammatory and neurodegenerative processes in the disease (Cross et al., 1998: 45-46, Liu et al., 2001: 2057-2058, van Horssen et al., 2008: 1729-1731, van Horssen et al., 2011: 143).

In the later stages of MS, ROS primarily originate from mitochondrial dysfunction within neurons. Mitochondrial impairment and the consequent ROS production have been implicated in the non-inflammatory axonal degeneration following chronic demyelination. It is postulated that mitochondria become increasingly burdened due to sodium channel redistribution, a compensatory mechanism triggered by demyelination. This redistribution results in substantial sodium influxes, placing significant metabolic demands on the adenosine triphosphate (ATP)-dependent sodium-potassium pump (Craner et al., 2004: 8168–

8172). The heightened ATP demand necessitates mitochondrial proliferation and increased energy production, inadvertently leading to excessive ROS generation. Notably, mitochondrial stress markers such as heat shock protein 70 (HSP70) have been observed at elevated levels in astrocytes and axons within MS lesions (Witte et al., 2009: 193-195, Campbell & Mahad, 2018: 1113,1118). However, a critical point of contention remains regarding whether mitochondrial-derived ROS predominantly arise from ATP upregulation and mitochondrial proliferation following chronic demyelination or whether oxidative mitochondrial damage is incurred during the acute inflammatory phase of MS (Waxman, 2006: 192-195).

The endogenous defence system against ROS within the CNS relies on antioxidant enzymes. Exposure to ROS activates Nrf2, which subsequently translocates to the nucleus and induces antioxidant response element (ARE) promoters, thereby driving the expression of antioxidant enzymes. Hundreds of Nrf2-responsive antioxidant genes have been identified (Hybertson et al., 2011: 236-238). A growing body of evidence implicates Nrf2 dysregulation in MS pathogenesis. In EAE, an established animal model of MS, Nrf2-deficient mice exhibit a more aggressive disease onset, exacerbated clinical symptoms, heightened glial activation, elevated pro-inflammatory cytokine expression, and increased neurodegeneration compared to wild-type controls (Johnson et al., 2010: 239-241, Larabee et al., 2016: 1503-1504, Morales Pantoja et al., 2016: 645-648). Conversely, pharmacological activation of Nrf2 in EAE mice attenuates disease severity (Linker et al., 2011: 678-679). Postmortem analyses of MS-affected brains reveal robust Nrf2 upregulation within active MS lesions, with pronounced expression in degenerating neurons and glial cells, including oligodendrocytes (van Horssen et al., 2010: 1283-1288, Licht-Mayer et al., 2015: 267-273).

Nrf2 activation is already leveraged in MS therapeutics. Both VitD and dimethyl fumarate (DMF) function as potent Nrf2 activators. DMF, an approved oral therapy for relapsing-remitting MS (RRMS), has been demonstrated to attenuate disease activity and slow progression through its immunomodulatory and neuroprotective properties (Bresciani et al., 2023: 1-2). VitD and DMF mediate their antioxidant effects via the Nrf2/Kelch-like ECH-associated protein (KEAP) 1 signalling axis, enhancing glutathione signalling and promoting neuroprotection. Additionally, these agents exert beneficial effects by suppressing pro-inflammatory cytokine expression while upregulating neurotrophic factors (Saha et al., 2020: 1-18, Salehi et al., 2019: 114-120). Notably, VitD and DMF derivatives exhibit a synergistic effect in upregulating VDR expression and enhancing Nrf2 activity, mechanisms that have been implicated in limiting leukaemia progression (Nachliely et al., 2019: 8-9). However, despite their overlapping pathways, DMF presents a safer therapeutic profile, mitigating the risk of calcemic toxicity associated with prolonged high-dose VitD administration. Excessive VitD has been shown to exacerbate EAE, underscoring the necessity of a carefully calibrated approach to VitD-based interventions (Häusler et al., 2019: 2737, 2741-2750). Furthermore, melatonin—produced during the dark phase—demonstrates antioxidant properties akin to those of VitD in EAE models (Long et al., 2018: 2-3, Ghareghani et al., 2018: 233- 241).

Unravelling Pathophysiological Mechanisms and Therapeutic Horizons in the Experimental Autoimmune Encephalitis Model

Neural cells demonstrate the VDR expression, with neurons and microglia synthesising the active metabolite 1,25-dihydroxyvitamin D_3, underscoring its pivotal role in regulating neurophysiological functions. The active form of VitD modulates the secretion of neurotrophic factors. Calcitriol emerges as a

fundamental agent in regulating neurotrophic factors while concurrently serving as a critical modulator of neuronal calcium flux through its interaction with L-type calcium channels. This interaction facilitates the intricate control of cellular homeostasis and is vital in refining synaptic plasticity (Gooch et al., 2019: 1-3, Fernandes de Abreu, Eyles & Féron, 2009: 265-277). By influencing these processes, calcitriol sustains neuronal integrity and underpins adaptive neuronal responses essential for cognitive and functional flexibility.

In addition to its role in neuronal function, calcitriol has demonstrated the capacity to modulate the progression of EAE. This effect is primarily attributed to its ability to regulate T-cell infiltration into the CNS, suppress Th1-mediated inflammatory responses, and enhance the production of IL-10 (Waddell, Zhao & Cantorna, 2015: 237-243, Chauss et al., 2022: 62-74). Calcitriol exerts profound immunoregulatory effects through these mechanisms, thereby modulating the immune response and potentially mitigating the pathological processes underlying autoimmune neuroinflammation.

Via the activation of microglia, 1,25-dihydroxyvitamin D_3 facilitates the efficient clearance of myelin debris and augments the phagocytosis of pathological proteins, including amyloid-β peptides. In parallel, it mitigates the expression of pro-inflammatory NOS, thereby attenuating demyelination. Additionally, calcitriol has been implicated in the promotion of remyelination, a process driven by its ability to enhance the maturation of oligodendrocytes and stimulate astrocyte activation (Nystad et al., 2014: 1178-1186, Mirarchi et al., 2023: 1-14). These actions collectively reinforce its neuroprotective role, contributing to the prevention of neurodegeneration and the restoration of neural integrity in various neuropathological contexts.

Vitamin D and Autoimmunity: A Complex Role in Immune Regulation

Autoimmune diseases result from a dysregulated immune system in which the body fails to recognise its own antigens, leading to the inadvertent destruction of its own tissues. These disorders are inherently multifactorial, arising from the intricate interaction of genetic susceptibility, epidemiological risk factors, and environmental influences. In this context, the role of VitD in autoimmune diseases is of paramount importance. Numerous epidemiological studies have consistently demonstrated a robust association between VitD deficiency and a variety of autoimmune conditions, including autoimmune encephalomyelitis, rheumatoid arthritis, MS, autoimmune thyroiditis, systemic lupus erythematosus (SLE), inflammatory bowel disease (IBD), and type 1 diabetes mellitus. Moreover, experimental animal models have provided compelling evidence that active VitD supplementation can significantly reduce or even prevent the onset of these autoimmune disorders (Bock, Pieber & Prietl, 2012: 1-7, Colotta, Jansson & Bonelli, 2017: 78-97, Cantorna, 2010: 286-288, Fletcher et al., 2022: 1,6-10, Arnson, Amital & Shoenfeld, 2007: 1137, 1139-1140). This growing body of evidence underscores the potential therapeutic value of VitD in modulating immune responses and mitigating autoimmune pathology.

Vitamin D and Multiple Sclerosis Risk: Investigating the Immunological Interplay and Clinical Implications

Over time, a well-documented association has emerged between latitude and the risk of MS, with disease prevalence following a distinct geographical gradient—lowest in equatorial regions and progressively increasing toward higher latitudes (Sabel et al, 2021: 2038-2045, Shi et al., 2024: 1-12, Simpson Jr et al., 2011: 1132, Koch-Henriksen & Sørensen, 2010: 520-532). Moreover,

extensive research has demonstrated a strong inverse correlation between MS prevalence and regional levels of solar radiation, further reinforcing the potential role of environmental factors, particularly sunlight exposure and its influence on VitD synthesis, in modulating disease susceptibility (Sintzel et al., 2018: 59-81, Sloka et al., 2011: 103-104). The impact of outdoor exposure on MS risk has also been a focus of investigation, with findings indicating that individuals who engaged in greater outdoor activities and, consequently, received more UVB exposure are at a significantly reduced risk of developing MS in later life (Ramagopalan et al., 2011: 1411-1412, Orton et al., 2011: 428-429, Kampman, Wilsgaard & Mellgren, 2007: 471-477). Moreover, a growing body of compelling evidence indicates that maternal sun exposure during pregnancy plays a crucial role in shaping the risk of MS in offspring. Epidemiological studies have consistently demonstrated that individuals born to mothers with higher levels of sunlight exposure during gestation exhibit a substantially lower risk of developing MS compared to those whose maternal sun exposure was limited. This association highlights the potential influence of prenatal environmental factors, particularly the regulation of VitD synthesis, on fetal immune system programming and the subsequent modulation of autoimmune susceptibility later in life. Given the critical period of neurodevelopment during gestation, adequate maternal VitD levels may confer protection against MS and play a broader role in fostering optimal neuroimmune maturation. These findings suggest that maternal VitD status could represent a modifiable risk factor, offering a promising avenue for preventive interventions aimed at reducing the incidence of MS and other immune-mediated neurological disorders (Chang et al., 2025: 1, 9-10, Rodríguez et al., 2016: 954- 960). Although specific studies have suggested that UVB radiation may exert immunomodulatory effects through mechanisms independent of VitD synthesis, the prevailing

scientific consensus underscores VitD as a pivotal mediator linking sun exposure to the risk of MS, with profound implications for prevention strategies (Ljubic et al., 2021: 1, Breuer et al., 2014: 739-740, DeLuca & Plum, 2017: 411-415). A nuanced understanding of these mechanisms may inform more precise preventive interventions, including optimising VitD supplementation and public health recommendations concerning safe sun exposure.

The interplay between VitD and the susceptibility to MS is an intricate phenomenon shaped by a complex array of genetic, environmental, and immunological factors. Emerging research consistently highlights the substantial role of VitD in MS pathogenesis, with epidemiological data suggesting that early-life VitD supplementation, particularly during critical periods such as adolescence, coupled with dietary practices, including the consumption of fish liver oil and a diet rich in oily fish, may exert a protective effect, potentially reducing the long-term risk of MS development. (Fernandes de Abreu, Landel & Féron, 2011: 64, Pierrot-Deseilligny & Souberbielle, 35-45, Munger et al., 2004: 60-61, Cortese et al., 2015: 1856, 1858-1863, Bäärnhielm et al., 2012: 955). In a pivotal study, American soldiers exhibiting serum 25-OH-D levels greater than 40 ng/ml experienced a 62% reduction in the risk of developing MS when compared to individuals with serum levels below 25 ng/ml (Munger et al., 2006: 2832- 2838). Analogously, an analysis conducted on Swedish pregnant women revealed that those with 25-OH-D levels exceeding 30 ng/ml demonstrated a 61% reduced risk of developing MS compared to those with lower 25-OH-D levels. (Salzer et al., 2012: 2140-2145). Additionally, a longitudinal study conducted on neonates showed that for every 20 ng/ml increase in 25-OH-D levels, there was a notable 60% reduction in the risk of developing MS over a 10 to 15-year period (Nielsen et al., 2017: 44-51). These findings unequivocally establish that VitD deficiency, particularly during

early life or insufficient sun exposure, is a substantial and independent risk factor for the eventual development of MS. In parallel, there is an expanding body of evidence recognising VitD deficiency as a dual risk factor for MS, operating not only as an environmental determinant but also as a genetic susceptibility. Genetic variations in the enzyme 1-alpha-hydroxylase are of particular significance, as it plays a critical role in converting VitD into its active form, calcitriol. These genetic aberrations have been shown to significantly modulate the biosynthesis of calcitriol, thereby influencing the immune response and dramatically altering individual susceptibility to MS. (Voltan et al., 2023: 1-11, Simon et al., 2011: 1976-1977, Karaky et al., 2016: 999–1006). Moreover, mutations in the CYP24A1 gene, which encodes the enzyme responsible for the catabolism of calcitriol, have been implicated in an elevated risk of developing MS. These mutations disrupt the regulatory balance of VitD metabolism, potentially leading to altered immune function and an increased predisposition to MS (Voltan et al., 2023: 1-11, Ramasamy et al., 2014: 211-212).

The application of Mendelian randomisation studies has been instrumental in elucidating the role of VitD as both an environmental and genetic risk factor for MS. By examining large cohorts of MS patients and assessing various stages of VitD metabolism, these studies have leveraged genetic data from single-nucleotide polymorphisms (SNPs) and employed advanced Mendelian randomisation techniques. The findings robustly suggest that genetically predisposed VitD deficiency substantially increases the risk of developing MS, while the full genetic aetiology of MS remains incompletely defined. The genetic variations leading to VitD insufficiency are rarely encountered; these variations are nonetheless recognised as independent and significant risk factors for the onset of MS. A key insight emerging from these studies is the dominant influence of VitD metabolism, rather than UVB exposure

alone, on immune system modulation and its subsequent impact on MS susceptibility. (Yu et al., 2024: 1-15, Mokry et al., 2015: 15-20, Rhead et al., 2016: 2-5).

Oestrogen exerts a protective effect on MS. Oestrogen enhances VDR gene expression while suppressing CYP24A1, an enzyme responsible for VitD degradation. In turn, VitD stimulates the expression of the CYP19 gene, which encodes aromatase in glial cells, thereby enhancing oestrogen synthesis (Spanier et al., 2015: 48-58, Nashfold et al., 2009: 3672-3679).

The HLA-DRB1 locus, particularly the HLA-DRB1*1501 allele, represents the most significant genetic determinant of MS susceptibility and heritability. Of particular interest, the promoter region of the HLA-DRB1*1501 gene contains a VDRE, suggesting a plausible mechanistic interaction between genetic predisposition and environmental influences, notably serum VitD concentrations (Alcina et al., 2012: 2-7, Ramagopalan et al., 2009: 1- 5).

It has been well-established that calcitriol, VitD, and VDR engage in complex interactions with Epstein-Barr virus (EBV) nuclear antigens (EBNA), which are implicated as key factors in the pathogenesis of MS. In states of VitD deficiency, there is a marked increase in the reactivity of antibodies against EBNA-1, a critical component of EBV. This heightened immune response contributes to the autoimmune processes observed in MS. Conversely, the repletion of VitD reduces both the levels of EBNA-1 protein and the concentrations of antibodies against its fragments, thereby potentially mitigating the autoimmune response. In addition, it has been shown that EBNA-2 and VDR share common DNA binding sites, which have been associated with MS susceptibility. This finding suggests a direct molecular interaction between the viral antigens and the host's genetic machinery, which could influence the progression of MS. Notably, the activation of VDR target genes,

which are central to the regulation of immune function and inflammation, is inhibited when EBNA-3, another EBV protein, binds to the VDR. This interaction may disrupt the normal immune regulatory functions of VitD, thereby exacerbating the autoimmune response and contributing to the pathogenesis of MS. These findings underscore the intricate interplay between environmental (VitD), viral (EBV), and genetic (VDR) factors in the development of MS, providing insight into potential therapeutic strategies targeting these pathways (Røsjø et al., 2017: 395-402, Marcucci & Obeidat, 2020: 577116, Rolf et al., 2018: 1280–1285).

Among the myriad potential effects of VitD, remyelination is one of its more intriguing possibilities. VitD plays a pivotal role in promoting the microenvironment essential for the differentiation and proliferation of neuronal stem cells into oligodendrocyte progenitor cells, thereby fostering the remyelination process (Sangha et al., 2023: 3, Matias-Guiu et al., 2018: 181).

The growing corpus of evidence elegantly reveals the sophisticated interplay between environmental exposures, such as sunlight and dietary intake, and genetic predispositions that govern the regulation of VitD metabolism. Collectively, these findings imply that proactive measures to maintain optimal VitD levels, particularly in individuals genetically predisposed to MS, could offer a promising strategy to curb both the incidence and progression of the disease. As our understanding of the molecular underpinnings of MS deepens, it becomes increasingly evident that VitD occupies a central, multifaceted position within the intricate web of risk determinants, functioning as an environmental influence and a crucial modulator of immune function in MS pathogenesis.

Immunoregulation versus Neuroprotection: A Dual Narrative in Multiple Sclerosis

MS embodies a paradigmatic example of the convergence between immune dysregulation and neurodegeneration. It is increasingly understood not as a unidimensional autoimmune disease but as a dynamic interface where immunological and neurobiological processes collide. At the heart of MS pathology lies a complex bidirectional dialogue: immune cells infiltrate the CNS, instigating demyelination and axonal injury, while the CNS itself may shape the immune response through molecular vulnerability or resilience. This dual narrative—of immune provocation and neural susceptibility—offers a broader lens through which to re-examine disease onset and progression.

Genomic studies continue to implicate immune-related loci as the primary genetic architecture underpinning MS susceptibility, affirming its status as an immune-mediated condition. However, the CNS is not a passive bystander. Its singular role as the exclusive target of this aberrant immune activity raises critical questions: Why the CNS? Is there a unique neurobiological condition—developmental, metabolic, or structural—that predisposes it to such targeted immune aggression?

VitD may offer a conceptual bridge between these two domains. Extensively studied for its immunomodulatory properties, VitD influences the differentiation, activation, and function of innate and adaptive immune cells. Deficiency in VitD disrupts immune tolerance and is strongly associated with increased MS risk. Yet emerging evidence suggests that VitD is not merely an immunological actor but also a neuroactive molecule that shapes CNS development, supports neurogenesis, and modulates synaptic plasticity. In this regard, VitD may serve as a molecular fulcrum, and

its deficiency simultaneously compromises immune regulation and CNS integrity.

Epidemiological data highlight the temporal sensitivity of VitD's protective effects, particularly during gestation and early childhood—periods marked by rapid neurodevelopment and immune programming. During these early life stages, the immune system is subjected to frequent antigenic challenges, most of which are resolved without clinical consequence. Nonetheless, certain viruses with neurotropic potential—such as EBV, varicella-zoster virus, and selected influenza strains—can silently infect neural tissue. Although rarely symptomatic, these infections may act as environmental cofactors that shape neuroimmune imprinting and predispose to future autoimmunity.

Thus, MS may not arise solely from a misdirected immune system or intrinsic CNS fragility but rather from a subtle orchestration of both—a misalignment of immune surveillance and neurodevelopmental cues. VitD, at the intersection of these systems, may represent a modifiable determinant of this delicate balance (Gombash et al., 2022: 9).

It remains an open question whether certain viruses may exert differential effects on the CNS in children with suboptimal VitD levels, even in the absence of overt neurological manifestations. The partial deletion of the VDR, specifically in neurons during early development in mice, led to an increased susceptibility to EAE in adulthood, implying that diminished neuronal VitD signalling during critical developmental windows may heighten CNS vulnerability to inflammatory insults (Lee et al., 2020: 2-7). There is considerable evidence indicating that viral infections are modulated by VitD status. Of particular relevance in MS is the EBV, which has long been hypothesised to be a crucial environmental risk factor in disease pathogenesis. This relevance

has been substantiated by a recent large-scale cohort study involving over 10 million young adults (Bjornevik et al., 2022: 296-300). Although numerous mechanistic hypotheses have been proposed, emerging data suggest that EBV may act as a precipitating agent by initiating molecular mimicry phenomena (Lang et al., 2002: 940-943, Lindsey, 2017: 131-134, Tengvall et al., 2019: 16955, Lanz et al., 2022: 321-322). Notably, EBV-specific antibody titres in MS patients are inversely correlated with serum VitD levels (Pérez-Pérez et al., 2018: 1446-1447), suggesting potential synergism between these two environmental factors. Furthermore, EBV has been implicated in the activation of endogenous retroviruses (ERVs), the expression of which in MS lesions correlates with disease activity (Mameli et al., 2013: 2-7). These ERVs may serve as neoantigens that propagate neuroinflammatory processes. VitD supplementation has been observed to attenuate EBV reactivation (Zwart et al., 2011: 692-696), which may, in turn, limit downstream ERV expression and associated inflammatory cascades. In a humanised murine model, HLA-DR15-restricted T cells were found to control EBV infection inadequately, implying a mechanistic interplay between the principal genetic susceptibility locus for MS (HLA-DR15) and EBV in modulating disease risk (Zdimerova et al., 2021: 64-71). The intersection of ERVs, VitD, and MS is an area of increasing investigative focus, with some authors proposing that EBV may represent the mechanistic bridge linking VitD deficiency and ERV activation in the aetiology of MS (Brütting, Stangl & Staege, 2021: 233-235). Although numerous autoimmune disorders have been associated to varying degrees with insufficient VitD, the epidemiological data supporting its role in MS are particularly compelling, which suggests that inadequate VitD levels may contribute to increased MS risk through dysregulation of immune homeostasis and impairment of CNS immunological equilibrium.

A recent study demonstrated an inverse relationship between sun exposure and the incidence of MS. Moreover, elevated VitD concentrations in pwMS were associated with a reduced risk of relapses and a slower disability progression (Ostkamp et al., 2021: 1-8). While the evidence implicating VitD deficiency in both MS susceptibility and disease course is robust, uncertainties remain regarding the clinical efficacy of supplementation in pwMS. Since most MS patients exhibit low serum VitD, supplementation has become routine clinical practice. Despite the widespread fortification of food products with VitD in numerous countries, whether such measures are sufficient to support optimal neurological and immunological function remains unclear. The rarity of rickets in countries with fortified foods suggests adequacy for skeletal health; however, whether these levels suffice to confer neuroprotection remains ambiguous. The relatively high prevalence of MS in regions such as the United States raises the possibility that current supplementation strategies may be insufficient. Children residing at higher latitudes, where sunlight exposure is seasonally restricted, may particularly benefit from targeted VitD supplementation. Similarly, those with a familial predisposition to MS may warrant more vigilant nutritional oversight, given their elevated genetic risk. The widespread use of sunscreen, which inhibits UVB-induced cutaneous VitD synthesis by up to 95%, may inadvertently compromise immune and neurological integrity, necessitating a nuanced risk-benefit assessment. Sunlight remains the most efficacious and natural source of VitD. Accordingly, encouraging outdoor activity in children may represent a pragmatic and effective public health strategy to counter the growing prevalence of VitD deficiency (Gombash et al., 2022: 9-10).

Circadian Ecologies of MS: From Sunlight to Gut

Melatonin, often referred to as the chemical embodiment of darkness, is a chronobiotic neurohormone secreted primarily by the pineal gland in response to the absence of light stimuli (Reiter, 1991: 153-158). As a photoperiod-dependent molecule, its secretion exhibits a marked circadian rhythm, governed by the light–dark cycle. Notably, serum melatonin concentrations have been correlated with a range of neuroimmunological disorders, and several studies have demonstrated an inverse relationship between circulating melatonin levels and both the severity and relapse rate of MS (Akpinar et al., 2008: 253-257, Ghorbani et al., 2013: 180-184, Melamud et al., 2012: 37-40, Sandyk, 1993: 209-225, Lopez-Gonzalez et al., 2015: 173-177). These clinical associations have prompted preclinical investigations into melatonin's potential immunomodulatory role in MS, primarily through its effects in EAE models—an established animal paradigm for MS research. In these studies, administration of melatonin significantly attenuated disease severity, supporting its putative neuroprotective and anti-inflammatory properties (Kang et al., 2001: 85-89, Alvarez-Sanchez et al., 2015: 101-114, Chen et al., 2016: 169-177). However, previous findings suggest that the efficacy of melatonin in EAE may be modulated by age-related physiological variables, indicating a potentially age-dependent therapeutic window (Ghareghani et al., 2017: 52-60).

Clinically, the therapeutic potential of melatonin in MS has also been explored. In a longitudinal study, melatonin administered as a monotherapy over four years led to a functional improvement in MS patients, with Expanded Disability Status Scale (EDSS) scores improving from 8.0 to 6.0 (Lopez-Gonzalez et al., 2015: 173-177). While promising, these findings require further validation in large-scale, controlled trials.

Parallel to melatonin, the role of VitD in MS has been extensively scrutinised. Although several clinical studies have examined its immunological functions, the precise mechanisms by which VitD and melatonin influence MS pathophysiology remain incompletely elucidated. Numerous observational studies have documented significantly lower serum VitD levels in pwMS compared to healthy controls, suggesting that hypovitaminosis D may constitute a modifiable environmental risk factor for MS onset and progression (Dudani, Kalhan & Sharma, 2011: 71-72). Despite this, interventional trials have produced inconsistent outcomes regarding the efficacy of VitD supplementation. Specifically, low-dose VitD administration has not demonstrated statistically significant effects on EDSS scores or relapse frequency in MS cohorts (Shaygannejad et al., 2012: 1-6). In contrast, several studies have shown that elevated circulating levels of VitD are correlated with a reduced incidence of MS and a more favourable clinical trajectory. (Simpson et al., 2010: 193-202, Munger & Ascherio, 2011: 1406-1410, Holmøy et al., 2012: 63-68).

Intriguingly, recent evidence points towards a reciprocal regulatory relationship between VitD and melatonin. A study involving interferon beta (IFN-β)-treated MS patients revealed that high-dose VitD supplementation over three months resulted in a suppression of nocturnal melatonin secretion. Conversely, elevations in melatonin levels during the night were associated with reductions in serum VitD concentrations (Golan et al., 2013: 180-185). These findings underscore a complex, possibly antagonistic interplay between VitD and melatonin, with potential implications for circadian biology, endocrine-immune crosstalk, and therapeutic strategies in MS.

VitD and melatonin are each indispensable to cellular homeostasis, yet their physiological rhythms are characteristically antithetical. VitD is synthesised cutaneously via the photochemical

conversion of 7-dehydrocholesterol under UVB radiation, predominantly during daylight exposure. In contrast, melatonin, a chronobiotic hormone synthesised primarily by the pineal gland, is secreted nocturnally in response to darkness (Champney Thomas et al., 1984: 59-66, Brzezinski, 1997: 186-195). Although both compounds can be obtained through dietary sources (Reiter et al., 2001: 286-290), endogenous production remains the principal contributor to systemic levels.

Melatonin secretion exhibits a distinct circadian profile, reaching its zenith during the mid-dark phase and declining progressively thereafter (Reiter, 1993: 654-664, Malpaux et al., 2001: 336-345). Emerging evidence suggests that elevated daytime VitD concentrations may partially suppress nocturnal melatonin synthesis, reflecting a potential photoperiodic counter-regulation (Golan et al., 2013: 180-185).

Within the mammalian retina, classical photoreception is mediated by rod and cone photoreceptors, which utilise the visual pigments rhodopsin and photopsin to facilitate image-forming vision. However, the discovery of intrinsically photosensitive retinal ganglion cells (ipRGCs), localised in the inner retina, has elucidated a distinct non-image-forming visual pathway responsible for regulating circadian rhythms, and pupillary reflexes (Yamazaki, Goto & Menaker, 1999: 197-200, Ruby et al., 2002: 2211-2213, Gamlin et al., 2007: 946-953, Paul, Saafir & Tosini, 2009: 271-278). These ipRGCs express melanopsin, whose expression is confined to fewer than 2% of total retinal ganglion cells (Hattar et al., 2002: 1065-1070).

Unlike rhodopsin, melanopsin demonstrates bistability under broadband light conditions and exhibits maximal spectral sensitivity in the blue-light range (~482 nm) (Mure et al., 2007: 411-422, Melyan et al., 2005: 741-745). ipRGCs play a pivotal role in

circadian entrainment by transmitting photic signals via their axonal projections to the suprachiasmatic nucleus (SCN) of the hypothalamus, the central circadian pacemaker (Provencio, 2010: 290-295, Reppert et al., 1988: 78-81, Gooley et al., 2003: 7093-7104). This retinohypothalamic tract serves as the principal conduit for modulating pineal melatonin synthesis, thereby linking environmental light cues to endogenous hormonal rhythms.

Crucially, exposure to short-wavelength (blue) light activates melanopsin, resulting in SCN-mediated suppression of melatonin production (Brainard et al., 2001: 6405-6411, Mcdougal & Gamlin, 2010: 72-85, Maynard, Zele & Feigl, 2015:6906-6911). Recent data further suggest that retinal ganglion cell loss and axonal degeneration may be associated with VitD deficiency, potentially reflecting the neurosteroidal roles of VitD within the CNS (Annweiler et al., 2013: 1026-1028). Given the regulatory role of RGCs in melatonin release, such degeneration may indirectly affect melatonin synthesis, implicating VitD insufficiency as a contributory factor—a hypothesis warranting further investigation. From an immunological perspective, both VitD and melatonin exert significant influence on the integrity of the BBB, acting through distinct yet converging pathways that uphold neuroimmune homeostasis (Suzumura, 2017: 180, Alluri et al., 2016: 1-16).

Calcium, one of the most prevalent minerals within the human body, plays a key role in a multitude of physiological functions, including haemostasis, hormone secretion, bone mineralisation, neuromuscular transmission, and muscle contractility (Peacock, 2010: s23-s28). While melatonin has been shown to modulate calcium absorption to a limited extent (Sjoblom, Safsten & Flemstrom, 2003: G1034-G1043), it is calcitriol that serves as the principal regulator of intestinal calcium uptake (Christakos, 2017:73-76). The deleterious effects of VitD deficiency on intestinal calcium absorption have been well documented for

several decades (Devine et al., 2002: 283-286, Fraser, 1980: 551-613). Experimental models employing VDR knockout mice have demonstrated the indispensability of VitD signalling in facilitating transcellular calcium transport across the intestinal epithelium (Li et al., 1997: 9831-9835, Yoshizawa et al., 1997: 391-396). Consistent with these findings, both preclinical and clinical studies have affirmed that intestinal calcium absorption is markedly diminished in VitD-deficient animals and patients with suboptimal serum VitD concentrations (Pansu et al., 1983: G695-G700, Sheikh et al., 1988: 126-132). Gastrointestinal (GI) motility entails a highly orchestrated sequence of contractions and relaxations within smooth muscle layers, critical for maintaining effective propulsion and digestion. Although most contractile cells mobilise cytosolic calcium for this function, GI smooth muscle cells rely predominantly on calcium influx via extracellular channels (Karaki & Weiss, 1984: 960-970). The cyclical elevation and reduction of intracellular calcium concentrations are essential to coordinate contraction and subsequent relaxation of intestinal musculature (Somlyo & Somlyo, 1994: 231-236). These calcium dynamics are integral to intestinal motility, and accordingly, the concomitant administration of calcium and VitD has been proposed as a therapeutic strategy to restore normative GI function (Giraldi et al., 2015: 343-348).

Beyond its fundamental roles in calcium absorption and motility, VitD is increasingly recognised for its involvement in maintaining intestinal barrier integrity and protecting the gastrointestinal mucosa against inflammatory or mechanical injury (Kong et al., 2007: G208-215).

Impairment of intestinal calcium absorption is associated with disrupted GI motility, culminating in pathophysiological states such as aboral stasis and, in chronic cases, gastroparesis (Koenig & Cote, 2006: 351-361). Gut stasis refers to a potentially life-threatening condition wherein digestive transit is significantly

slowed or halted, while gastroparesis denotes delayed gastric emptying, characterised by prolonged gastric retention of ingested material (Parkman, Hasler & Fisher, 2004: 1592-1622).

A seminal work (Gill et al., 1994: 553-556) was the first to elucidate a potential link between impaired intestinal transit and refractory constipation in individuals with MS. Subsequent studies have underscored the efficacy of gut-targeted behavioural therapies, such as biofeedback, particularly in MS patients exhibiting non-progressive disease phenotypes and limited neurological disability (Wiesel et al., 2000: 240-243, Enck, Van Der Voort & Klosterhalfen, 2009: 1133-1141). Complementarily, abdominal massage has shown beneficial effects on constipation severity and overall symptom burden in MS patients (Mcclurg et al., 2010: 223-232).

Disorders of intestinal motility, including stasis and gastroparesis, are believed to facilitate increased absorption of luminal contents, including microbial toxins. This hypothesis is corroborated by robust evidence indicating that gut stasis leads to heightened intestinal permeability and systemic bacterial translocation (Somlyo & Somlyo, 1994: 231-236, Yacyshyn et al., 1996: 2493-2498, Nathens & Marshall, 1996: 386-391, Nieuwenhuijzen & Goris, 1999: 399-404, Hierholzer et al., 2001: 230-241). The resultant liberation of toxic microbial metabolites exacerbates mucosal disruption, thereby further compromising barrier function (Chieveley-Williams & Hamilton-Davies, 1998: 81-110, Overhaus et al., 2004: G685-G694, Swank & Deitch, 1996: 411-417, Zheyu, Qinghui & Lunan, 2007: 1389-1396).

Concurrently, alterations in the gut microbiome have been implicated in the pathogenesis of various neuroimmune and neurodegenerative disorders, notably MS (Wang & Kasper, 2014: 1-12, Wolfson & Talbot, 2002: 352-353). In RRMS, both active and remission phases have been associated with significant gut dysbiosis

(Chen et al., 2016: 1-8). Supporting this, paediatric cohorts diagnosed with MS within two years of onset exhibited elevated proportions of Gram-negative bacteria, potentially linked to neurodegenerative mechanisms (Tremlett et al., 2016: 1308-1321). Furthermore, emerging data suggest that gut microbial composition influences the permeability of the BBB, a central feature in MS pathophysiology (Braniste et al., 2014: 1-8).

The gastrointestinal tract of both humans and animals harbours a complex ecosystem of commensal microbiota, which includes numerous Gram-negative bacteria that produce endotoxic constituents such as lipopolysaccharides (LPS)—a principal component of the outer membrane of these microorganisms (Poltorak et al., 1998: 2085-2088, Harmsen & De Goffau, 2016: 95-108). Elevated levels of LPS within the gut microbiota have been implicated in enhanced systemic translocation of LPS, primarily through inflammation-induced disruption of intestinal barrier integrity (Jiang et al., 2016: 1-17).

Systemically, LPS is detected by LPS-binding protein (LBP), which facilitates its delivery to the surface of various immune and endothelial cells. Here, LPS forms a ternary complex with CD14, a pattern recognition receptor that disaggregates LPS micelles into monomeric units and promotes their transfer to the TLR4/ Myeloid differentiation factor (MD)2 complex. MD2, a secreted extracellular glycoprotein, functions as an essential adaptor in the TLR4-mediated recognition of LPS. Subsequent activation of the TLR4/MD2 complex leads to the stimulation of NF-κB signalling cascades, culminating in the transcriptional upregulation of pro-inflammatory cytokines, including TNF-α (Schumann et al., 1990: 1429- 1431, Dunzendorfer et al., 2004: 1166-1170, Da Silva et al., 2001: 21129-21134, Akira & Takeda, 2004: 499-511, Chow et al., 1999: 10689-10692, Buchholz & Bauer, 2010: 232-243, Zhang & Ghoah, 2000: 453-457, Kawai & Akira, 2010:373-384).

The role of the pineal gland and its neurohormonal output, melatonin, in modulating LPS-induced signalling remains contentious. Several studies have demonstrated that melatonin can attenuate the LPS–CD14–TLR4 pathway, notably in bovine mammary epithelial cells, where it downregulates LPS-stimulated production of TNF-α, IL-1β, and IL-6 (Yu et al., 2017: 1). Conversely, pinealocytes themselves express both CD14 and TLR4, rendering them responsive to circulating LPS, which activates NF-κB signalling and suppresses melatonin biosynthesis via TNF-α induction (Da Silverira et al., 2010: 183-192).

Given that CD14 serves as a principal surface receptor for LPS on monocytes/macrophages (Wright et al, 1990: 1431-1433), subsequent investigations have demonstrated that melatonin may, under certain conditions, enhance the secretion of IL-1 both in vitro and in vivo (Morrey et al., 1994: 1671-1680, Pioli et al., 1993: 463-467), and elevate TNF-α and IL-6 levels in vivo (Pioli et al., 1993: 463-467, Barjavel et al., 1998: 27-35). These findings collectively support the hypothesis that LPS derived from intestinal microbiota may trigger neuroinflammatory cascades via activation of pineal NF-κB signalling, resulting in elevated TNF-α production and inhibition of melatonin synthesis.

The global epidemiological distribution of MS reveals a pronounced latitudinal gradient, with higher incidence observed in regions of diminished UV exposure. This pattern has prompted substantial interest in the putative protective effects of solar radiation against MS pathogenesis. A recent investigation provided compelling evidence that regional UVB radiation levels inversely correlate with MS prevalence, implicating ultraviolet exposure as a modifiable environmental risk factor (Orton et al., 2011: 425-429). This observation is further substantiated by meta-regression analyses (Koch-Henriksen & Sørensen, 2010: 520-532) and incidence-based studies (Alonso & Hernán, 2008: 129-133), which

suggest a possible sex-specific influence of UVB exposure on MS risk.

Experimental data have shown that UVB irradiation ameliorates disease severity in EAE, a well-established animal model of MS, through mechanisms that appear to be independent of VitD synthesis (Wang et al., 2013: 81-85). While hypovitaminosis D is frequently documented in MS cohorts, definitive evidence supporting VitD supplementation as a prophylactic intervention remains inconclusive (Hart, Gorman & Finlay-Jones, 2011: 584-596, Kampman et al., 2012: 1144-1150, Rosjo et al., 2015: 2713-2721). Notably, therapeutic benefit appears contingent upon concurrent elevation of serum calcium levels (Cantorna, Humpal-Winter & Deluca, 1999: 1966-1971).

To further elucidate the role of UVB in MS modulation, Irving et al. reported a 74% reduction in EAE incidence following UVB exposure (Irving et al., 2017: 1-6). As UVB photons catalyse cutaneous production of cholecalciferol (Holick, 2008: 1-15), the same study identified a UVB-induced upregulation of skin cis-urocanic acid, a histidine metabolite. Interestingly, pharmacological elevation of cis-urocanic acid in the absence of UVB failed to alter disease trajectory, indicating UVB-specific effects (Irving et al., 2017: 1-6).

Moreover, cis-urocanic acid has been demonstrated to attenuate the severity of colitis, a chronic inflammatory disorder of the bowel (De Schepper et al., 2007: 195-201). It is noteworthy that experimental colitis has been associated with delayed gastric emptying and the onset of colitis-induced gastroparesis (De Schepper et al., 2007: 195-201). In this context, epidemiological data reveal a higher susceptibility to gastroparesis among females (Gangula, Sekhar &, Mukhopadhyay, 2011: 2520-2527), which parallels the threefold higher incidence of MS in women compared

to men. These observations collectively suggest that gastroparesis may serve as a potential contributory factor in MS pathogenesis.

References

Compston, A., & Coles, A. (2002). Multiple sclerosis. *Lancet*, *359* (9313), 1221–1231. Doi: 10.1016/S0140-6736(02)08220-X

Reich, D.S., Lucchinetti, C.F. & Calabresi, P.A. (2018). Multiple sclerosis, *N Engl J Med*., *378* (2), 169-180. Doi: 10.1056/NEJMra1401483.

Koch-Henriksen, N. & Sørensen, P. S. (2010). The changing demographic pattern of multiple sclerosis epidemiology. *The Lancet. Neurology, 9* (5), 520–532. Doi: 10.1016/S1474-4422(10)70064-8

GBD 2016 Multiple Sclerosis Collaborators. (2019). Global, regional, and national burden of multiple sclerosis 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *The Lancet. Neurology, 18* (3), 269–285. Doi: 10.1016/S1474-4422(18)30443-5

Milo, R. & Kahana, E. (2010). Multiple sclerosis: geoepidemiology, genetics and the environment. *Autoimmunity reviews, 9* (5), A387–A394. Doi: 10.1016/j.autrev.2009.11.010

Fox, R.J., Rae-Grant, A.D. & Béthoux, F. (2018). *Multiple sclerosis and related disorders: clinical guide to diagnosis, medical management, and rehabilitation*. (Second edit.). New York: Springer Publishing Company

Weerasinghe-Mudiyanselage, P. D. E., Kim, J. S., Shin, T. & Moon, C. (2024). Understanding the spectrum of non-motor symptoms in multiple sclerosis: insights from animal models. *Neural Regeneration Research, 19* (1), 84–91. Doi: 10.4103/1673-5374.375307

Dobson, R., & Giovannoni, G. (2019). Multiple sclerosis - a review. *European journal of neurology, 26* (1), 27–40. Doi: 10.1111/ene.13819

Bäärnhielm, M., Olsson, T., & Alfredsson, L. (2014). Fatty fish intake is associated with decreased occurrence of multiple sclerosis. *Multiple sclerosis, 20* (6), 726–732. Doi: 10.1177/1352458513509508

Kampman, M. T., & Brustad, M. (2008). Vitamin D: a candidate for the environmental effect in multiple sclerosis - observations from Norway. *Neuroepidemiology, 30* (3), 140–146. Doi: 10.1159/000122330

Jelinek, G. A., Hadgkiss, E. J., Weiland, T. J., Pereira, N. G., Marck, C. H., & van der Meer, D. M. (2013). Association of fish consumption and Ω 3 supplementation with quality of life, disability and disease activity in an international cohort of people with multiple sclerosis. *The International journal of neuroscience, 123* (11), 792–801. Doi: 10.3109/00207454.2013.803104

Ramagopalan, S. V., Maugeri, N. J., Handunnetthi, L., Lincoln, M. R., Orton, S. M., Dyment, D. A., Deluca, G. C., Herrera, B. M., Chao, M. J., Sadovnick, A. D., Ebers, G. C., & Knight, J. C. (2009). Expression of the multiple sclerosis-associated MHC class II Allele HLA-DRB1*1501 is regulated by vitamin D. *PLoS genetics, 5* (2), e1000369. Doi: 10.1371/journal.pgen.1000369

Cocco, E., Meloni, A., Murru, M. R., Corongiu, D., Tranquilli, S., Fadda, E., Murru, R., Schirru, L., Secci, M. A., Costa, G., Asunis, I., Cuccu, S., Fenu, G., Lorefice, L., Carboni, N., Mura, G., Rosatelli, M. C., Marrosu, M. G. (2012). Vitamin D responsive elements within the HLA-DRB1 promoter region in sardinian multiple sclerosis associated alleles. *PLoS ONE, 7*, e41678. Doi: 10.1371/journal.pone.0041678

Kular, L., Liu, Y., Ruhrmann, S., Zheleznyakova, G., Marabita, F., Gomez-Cabrero, D., James, T., Ewing, E., Lindén, M., Górnikiewicz, B., Aeinehband, S., Stridh, P., Link, J., Andlauer, T. F. M., Gasperi, C., Wiendl, H., Zipp, F., Gold, R., Tackenberg, B., Weber, F., … Jagodic, M. (2018). DNA methylation as a mediator of HLA-DRB1*15:01 and a protective variant in multiple sclerosis. *Nature communications, 9* (1), 2397. Doi:10.1038/s41467-018-04732-5

Munger, K. L., Zhang, S. M., O'Reilly, E., Hernán, M. A., Olek, M. J., Willett, W. C., & Ascherio, A. (2004). Vitamin D intake and incidence of multiple sclerosis. *Neurology, 62* (1), 60–65. Doi: 10.1212/01.wnl.0000101723.79681.38

Munger, K. L., Levin, L. I., Hollis, B. W., Howard, N. S., & Ascherio, A. (2006). Serum 25-hydroxyvitamin D levels and risk of multiple sclerosis. *JAMA, 296* (23), 2832–2838. Doi: 10.1001/jama.296.23.2832

Nielsen, N. M., Munger, K. L., Koch-Henriksen, N., Hougaard, D. M., Magyari, M., Jørgensen, K. T., Lundqvist, M., Simonsen, J., Jess, T., Cohen, A., Stenager, E., & Ascherio, A. (2017). Neonatal vitamin D status and risk of multiple sclerosis: A population-based case-control study. *Neurology, 88* (1), 44–51. Doi: 10.1212/WNL.0000000000003454

Munger, K. L., Hongell, K., Åivo, J., Soilu-Hänninen, M., Surcel, H. M., & Ascherio, A. (2017). 25-Hydroxyvitamin D deficiency and risk of MS among women in the Finnish Maternity Cohort. *Neurology, 89* (15), 1578–1583. Doi: 10.1212/WNL.0000000000004489

Burton, J. M., Kimball, S., Vieth, R., Bar-Or, A., Dosch, H. M., Cheung, R., Gagne, D., D'Souza, C., Ursell, M., & O'Connor, P. (2010). A phase I/II dose-escalation trial of vitamin D3 and calcium

in multiple sclerosis. *Neurology*, *74* (23), 1852–1859. Doi: 10.1212/WNL.0b013e3181e1cec2

Laursen, J. H., Søndergaard, H. B., Sørensen, P. S., Sellebjerg, F., & Oturai, A. B. (2016). Vitamin D supplementation reduces relapse rate in relapsing-remitting multiple sclerosis patients treated with natalizumab. *Multiple sclerosis and related disorders, 10,* 169–173. Doi: 10.1016/j.msard.2016.10.005

Goldberg, P., Fleming, M. C., & Picard, E. H. (1986). Multiple sclerosis: decreased relapse rate through dietary supplementation with calcium, magnesium and vitamin D. *Medical hypotheses, 21* (2), 193–200. Doi: 10.1016/0306-9877(86)90010-1

Achiron, A., Givon, U., Magalashvili, D., Dolev, M., Liraz Zaltzman, S., Kalron, A., Stern, Y., Mazor, Z., Ladkani, D., & Barak, Y. (2015). Effect of Alfacalcidol on multiple sclerosis-related fatigue: A randomized, double-blind placebo-controlled study. *Multiple sclerosis, 21* (6), 767–775. Doi: 10.1177/1352458514554053

Ascherio, A., Munger, K. L., White, R., Köchert, K., Simon, K. C., Polman, C. H., Freedman, M. S., Hartung, H. P., Miller, D. H., Montalbán, X., Edan, G., Barkhof, F., Pleimes, D., Radü, E. W., Sandbrink, R., Kappos, L., & Pohl, C. (2014). Vitamin D as an early predictor of multiple sclerosis activity and progression. *JAMA neurology, 71* (3), 306–314. Doi: 10.1001/jamaneurol.2013.5993

Mowry, E. M., Waubant, E., McCulloch, C. E., Okuda, D. T., Evangelista, A. A., Lincoln, R. R., Gourraud, P. -A., Brenneman, D., Owen, M. C., Qualley, P., Bucci, M., Hauser, S. L. and Pelletier, D. (2012), Vitamin D status predicts new brain magnetic resonance imaging activity in multiple sclerosis. *Ann Neurol., 72*: 234-240. Doi: 10.1002/ana.23591

Soilu-Hänninen, M., Aivo, J., Lindström, B. M., Elovaara, I., Sumelahti, M. L., Färkkilä, M., Tienari, P., Atula, S., Sarasoja, T., Herrala, L., Keskinarkaus, I., Kruger, J., Kallio, T., Rocca, M. A., & Filippi, M. (2012). A randomised, double blind, placebo controlled trial with vitamin D3 as an add on treatment to interferon β-1b in patients with multiple sclerosis. *Journal of neurology, neurosurgery, and psychiatry, 83* (5), 565–571. Doi: 10.1136/jnnp-2011-301876

Hupperts, R., Smolders, J., Vieth, R., Holmøy, T., Marhardt, K., Schluep, M., Killestein, J., Barkhof, F., Beelke, M., Grimaldi, L. M. E., & SOLAR Study Group (2019). Randomized trial of daily high-dose vitamin D3 in patients with RRMS receiving subcutaneous interferon β-1a. *Neurology, 93* (20), e1906–e1916. Doi: 10.1212/WNL.0000000000008445

Camu, W., Lehert, P., Pierrot-Deseilligny, C., Hautecoeur, P., Besserve, A., Jean Deleglise, A. S., Payet, M., Thouvenot, E., & Souberbielle, J. C. (2019). Cholecalciferol in relapsing-remitting MS: A randomized clinical trial (CHOLINE). *Neurology(R) neuroimmunology & neuroinflammation, 6 (*5), e597. Doi: 10.1212/NXI.0000000000000597

Kampman, M. T., Steffensen, L. H., Mellgren, S. I., & Jørgensen, L. (2012). Effect of vitamin D3 supplementation on relapses, disease progression, and measures of function in persons with multiple sclerosis: exploratory outcomes from a double-blind randomised controlled trial. *Multiple sclerosis, 18* (8), 1144–1151. Doi: 10.1177/1352458511434607

Golan, D., Halhal, B., Glass-Marmor, L., Staun-Ram, E., Rozenberg, O., Lavi, I., Dishon, S., Barak, M., Ish-Shalom, S., & Miller, A. (2013). Vitamin D supplementation for patients with multiple sclerosis treated with interferon-beta: a randomized controlled trial assessing the effect on flu-like symptoms and

immunomodulatory properties. *BMC neurology, 13*, 60. Doi: 10.1186/1471-2377-13-60

Scragg R. (2018). Limitations of vitamin D supplementation trials: Why observational studies will continue to help determine the role of vitamin D in health. The Journal of steroid biochemistry and molecular biology, *177,* 6–9. Doi: 10.1016/j.jsbmb.2017.06.006

Pardridge, W. M., Sakiyama, R., & Coty, W. A. (1985). Restricted transport of vitamin D and A derivatives through the rat blood-brain barrier. *Journal of neurochemistry, 44* (4), 1138–1141. Doi: 10.1111/j.1471-4159.1985.tb08735.x

Yu, J., Gattoni-Celli, M., Zhu, H., Bhat, N. R., Sambamurti, K., Gattoni-Celli, S., & Kindy, M. S. (2011). Vitamin D3-enriched diet correlates with a decrease of amyloid plaques in the brain of AβPP transgenic mice. *Journal of Alzheimer's disease, 25* (2), 295–307. Doi: 10.3233/JAD-2011-101986

Smolders, J., Schuurman, K. G., van Strien, M. E., Melief, J., Hendrickx, D., Hol, E. M., van Eden, C., Luchetti, S., & Huitinga, I. (2013). Expression of vitamin D receptor and metabolizing enzymes in multiple sclerosis-affected brain tissue. *Journal of neuropathology and experimental neurology, 72* (2), 91–105. Doi: 10.1097/NEN.0b013e31827f4fcc

Eyles, D. W., Smith, S., Kinobe, R., Hewison, M., & McGrath, J. J. (2005). Distribution of the vitamin D receptor and 1 alpha-hydroxylase in human brain. *Journal of chemical neuroanatomy, 29* (1), 21–30. Doi: 10.1016/j.jchemneu.2004.08.006

Boontanrart, M., Hall, S. D., Spanier, J. A., Hayes, C. E., & Olson, J. K. (2016). Vitamin D3 alters microglia immune activation by an IL-10 dependent SOCS3 mechanism. *Journal of neuroimmunology, 292*, 126–136. Doi: 10.1016/j.jneuroim.2016.01.015

Jiao, K. P., Li, S. M., Lv, W. Y., Jv, M. L., & He, H. Y. (2017). Vitamin D3 repressed astrocyte activation following lipopolysaccharide stimulation in vitro and in neonatal rats. *Neuroreport, 28* (9), 492–497. Doi: 10.1097/WNR.0000000000000782

de la Fuente, A. G., Errea, O., van Wijngaarden, P., Gonzalez, G. A., Kerninon, C., Jarjour, A. A., Lewis, H. J., Jones, C. A., Nait-Oumesmar, B., Zhao, C., Huang, J. K., ffrench-Constant, C., & Franklin, R. J. (2015). Vitamin D receptor-retinoid X receptor heterodimer signaling regulates oligodendrocyte progenitor cell differentiation. *The Journal of cell biology, 211* (5), 975–985. Doi: 10.1083/jcb.201505119

Sloka, S., Zhornitsky, S., Silva, C., Metz, L. M., & Yong, V. W. (2015). 1,25-Dihydroxyvitamin D3 Protects against Immune-Mediated Killing of Neurons in Culture and in Experimental Autoimmune Encephalomyelitis. *PloS one, 10* (12), e0144084. Doi: 10.1371/journal.pone.0144084

Lee, P. W., Selhorst, A., Lampe, S. G., Liu, Y., Yang, Y., & Lovett-Racke, A. E. (2020). Neuron-Specific Vitamin D Signaling Attenuates Microglia Activation and CNS Autoimmunity. *Frontiers in neurology, 11*, 19. Doi: 10.3389/fneur.2020.00019

Nurminen, V., Seuter, S., & Carlberg, C. (2019). Primary Vitamin D Target Genes of Human Monocytes. *Frontiers in physiology, 10*, 194. Doi: 10.3389/fphys.2019.00194

Sangha, A., Quon, M., Pfeffer, G., & Orton, S. M. (2023). The Role of Vitamin D in Neuroprotection in Multiple Sclerosis: An Update. *Nutrients, 15* (13), 2978. Doi: 10.3390/nu15132978

Van Schependom, J., Guldolf, K., D'hooghe, M. B., Nagels, G., & D'haeseleer, M. (2019). Detecting neurodegenerative pathology in multiple sclerosis before irreversible brain tissue loss

sets in. Translational neurodegeneration, 8, 37. Doi: 10.1186/s40035-019-0178-4

Goverman J. (2009). Autoimmune T cell responses in the central nervous system. *Nature reviews. Immunology, 9* (6), 393–407. Doi: 10.1038/nri2550

Høglund, R. A., & Maghazachi, A. A. (2014). Multiple sclerosis and the role of immune cells. *World journal of experimental medicine, 4* (3), 27–37. Doi: 10.5493/wjem.v4.i3.27

Coggan, J. S., Bittner, S., Stiefel, K. M., Meuth, S. G., & Prescott, S. A. (2015). Physiological Dynamics in Demyelinating Diseases: Unraveling Complex Relationships through Computer Modeling. *International journal of molecular sciences, 16* (9), 21215–21236. Doi: 10.3390/ijms160921215

Allanach, J. R., Farrell, J. W., 3rd, Mésidor, M., & Karimi-Abdolrezaee, S. (2022). Current status of neuroprotective and neuroregenerative strategies in multiple sclerosis: A systematic review. *Multiple sclerosis, 28* (1), 29–48. Doi: 10.1177/13524585211008760

Klotz, L., Antel, J., & Kuhlmann, T. (2023). Inflammation in multiple sclerosis: consequences for remyelination and disease progression. *Nature reviews. Neurology, 19* (5), 305–320. Doi:.1038/s41582-023-00801-6

Stangel, M., Kuhlmann, T., Matthews, P. M., & Kilpatrick, T. J. (2017). Achievements and obstacles of remyelinating therapies in multiple sclerosis. *Nature reviews. Neurology, 13* (12), 742–754. Doi: 10.1038/nrneurol.2017.139

Cadden, M. H., Koven, N. S., & Ross, M. K. Neuroprotective effects of vitamin d in multiple sclerosis. 2011. *Neurosci. Med., 2*, 198–207. Doi: 10.4236/nm.2011.23027

Gandhi, F., Jhaveri, S., Avanthika, C., Singh, A., Jain, N., Gulraiz, A., Shah, P., & Nasir, F. (2021). Impact of vitamin d supplementation on multiple sclerosis. *Cureus, 13* (10), e18487. Doi: 10.7759/cureus.18487

Gombash, S. E., Lee, P. W., Sawdai, E., & Lovett-Racke, A. E. (2022). Vitamin d as a risk factor for multiple sclerosis: immunoregulatory or neuroprotective?. *Frontiers in neurology, 13,* 796933. Doi: 10.3389/fneur.2022.796933

Wolf G. (2004). The discovery of vitamin d: the contribution of adolf windaus. *The Journal of nutrition, 134* (6), 1299–1302. Doi: 10.1093/jn/134.6.1299

Blunt, J. W., Tanaka, Y., & DeLuca, H. F. (1968). Biological activity of 25-hydroxycholecalciferol, a metabolite of vitamin D3. *Proceedings of the National Academy of Sciences of the United States of America, 61* (4), 1503–1506. Doi: 10.1073/pnas.61.4.1503

Ponchon, G., Kennan, A. L., & DeLuca, H. F. (1969). Activation of vitamin D by the liver. *The Journal of clinical investigation, 48* (11), 2032–2037. Doi: 10.1172/JCI106168

Norman, A. W., Myrtle, J. F., Midgett, R. J., Nowicki, H. G., Williams, V., Popják, G., Miogett, R. J., & Popjaak, G. (1971). 1,25-Dihydroxycholecalciferol: identification of the proposed active form of vitamin d3 in the intestine. *Science, 173* (3992), 51–54.

Holick, M. F., Schnoes, H. K., & DeLuca, H. F. (1971). Identification of 1,25-dihydroxycholecalciferol, a form of vitamin D3 metabolically active in the intestine. *Proceedings of the National Academy of Sciences of the United States of America, 68* (4), 803–804. Doi:10.1073/pnas.68.4.803

DeLuca H. F. (2004). Overview of general physiologic features and functions of vitamin D. *The American journal of*

clinical nutrition, 80 (6 Suppl), 1689S–96S. Doi:10.1093/ajcn/80.6.1689S

Dattola, A., Silvestri, M., Bennardo, L., Passante, M., Scali, E., Patruno, C., & Nisticò, S. P. (2020). Role of vitamins in skin health: a systematic review. *Current nutrition reports, 9* (3), 226–235. Doi: 10.1007/s13668-020-00322-4

Dominguez, L. J., Farruggia, M., Veronese, N., & Barbagallo, M. (2021). Vitamin d sources, metabolism, and deficiency: available compounds and guidelines for its treatment. *Metabolites, 11* (4), 255. Doi:10.3390/metabo11040255

Webb, A. R., & Engelsen, O. (2006). Calculated ultraviolet exposure levels for a healthy vitamin D status. *Photochemistry and photobiology, 82* (6), 1697–1703. Doi: 10.1562/2005-09-01-RA-670

Holick M. F. (2004). Vitamin D: importance in the prevention of cancers, type 1 diabetes, heart disease, and osteoporosis. *The American journal of clinical nutrition, 79* (3), 362–371. Doi: 10.1093/ajcn/79.3.362

Vieth R. (1999). Vitamin D supplementation, 25-hydroxyvitamin d concentrations, and safety. *The American journal of clinical nutrition, 69* (5), 842–856. Doi: 10.1093/ajcn/69.5.842

Haddad J. G. (1992). Vitamin D--solar rays, the Milky Way, or both?. *The New England journal of medicine, 326* (18), 1213–1215. Doi: 10.1056/NEJM199204303261808

Binkley, N., Novotny, R., Krueger, D., Kawahara, T., Daida, Y. G., Lensmeyer, G., Hollis, B. W., & Drezner, M. K. (2007). Low vitamin D status despite abundant sun exposure. *The Journal of clinical endocrinology and metabolism*, *92* (6), 2130–2135. Doi: 10.1210/jc.2006-2250

Neville, J. J., Palmieri, T., & Young, A. R. (2021). Physical determinants of vitamin d photosynthesis: a review. *JBMR plus, 5* (1), e10460. Doi: 10.1002/jbm4.10460

Christakos, S., Dhawan, P., Verstuyf, A., Verlinden, L., & Carmeliet, G. (2016). Vitamin d: metabolism, molecular mechanism of action, and pleiotropic effects. *Physiological reviews, 96* (1), 365–408. Doi: 10.1152/physrev.00014.2015

Bikle D. D. (2011). Vitamin D: an ancient hormone. *Experimental dermatology, 20* (1), 7–13. Doi: 10.1111/j.1600-0625.2010.01202.x

Haussler, M. R., & Norman, A. W. (1969). Chromosomal receptor for a vitamin D metabolite. *Proceedings of the National Academy of Sciences of the United States of America, 62* (1), 155–162. Doi: 10.1073/pnas.62.1.155

McDonnell, D. P., Mangelsdorf, D. J., Pike, J. W., Haussler, M. R., & O'Malley, B. W. (1987). Molecular cloning of complementary DNA encoding the avian receptor for vitamin D. *Science, 235* (4793), 1214–1217. Doi: 10.1126/science.3029866

Yoshizawa, T., Handa, Y., Uematsu, Y., Takeda, S., Sekine, K., Yoshihara, Y., Kawakami, T., Arioka, K., Sato, H., Uchiyama, Y., Masushige, S., Fukamizu, A., Matsumoto, T., & Kato, S. (1997). Mice lacking the vitamin D receptor exhibit impaired bone formation, uterine hypoplasia and growth retardation after weaning. *Nature genetics, 16* (4), 391–396. Doi: 10.1038/ng0897-391

Walters M. R. (1992). Newly identified actions of the vitamin D endocrine system. Endocrine reviews, 13(4), 719–764. Doi: 10.1210/edrv-13-4-719

Smith, J. E., & Goodman, D. S. (1971). The turnover and transport of vitamin D and of a polar metabolite with the properties

of 25-hydroxycholecalciferol in human plasma. *The Journal of clinical investigation, 50* (10), 2159–2167. Doi: 10.1172/JCI106710

Brown A. J. (1999). Regulation of vitamin D action. Nephrology, dialysis, transplantation : *official publication of the European Dialysis and Transplant Association - European Renal Association, 14* (1), 11–16. Doi: 10.1093/ndt/14.1.11

van Driel, M., Koedam, M., Buurman, C. J., Roelse, M., Weyts, F., Chiba, H., Uitterlinden, A. G., Pols, H. A. P., & van Leeuwen, J. P. T. M. (2006). Evidence that both 1alpha,25-dihydroxyvitamin D3 and 24-hydroxylated D3 enhance human osteoblast differentiation and mineralization. *Journal of Cellular Biochemistry, 99* (4), 922–935. Doi: 10.1002/jcb.20875

Takeyama, K., Kitanaka, S., Sato, T., Kobori, M., Yanagisawa, J., & Kato, S. (1997). 25-Hydroxyvitamin D3 1alpha-hydroxylase and vitamin D synthesis. *Science, 277* (5333), 1827–1830. Doi: 10.1126/science.277.5333.1827

Dominguez, L. J., Veronese, N., Guerrero-Romero, F., & Barbagallo, M. (2021). Magnesium in infectious diseases in older people. *Nutrients, 13* (1), 180. Doi: 10.3390/nu13010180

Anast, C. S., Mohs, J. M., Kaplan, S. L., & Burns, T. W. (1972). Evidence for parathyroid failure in magnesium deficiency. *Science, 177* (4049), 606–608. Doi: 10.1126/science.177.4049.606

Medalle, R., Waterhouse, C., & Hahn, T. J. (1976). Vitamin D resistance in magnesium deficiency. *The American journal of clinical nutrition, 29* (8), 854–858. Doi: 10.1093/ajcn/29.8.854

Rude, R. K., Oldham, S. B., Sharp, C. F., Jr, & Singer, F. R. (1978). Parathyroid hormone secretion in magnesium deficiency. *The Journal of clinical endocrinology and metabolism, 47* (4), 800–806. Doi: 10.1210/jcem-47-4-800

Mutnuri, S., Fernandez, I., & Kochar, T. (2016). Suppression of parathyroid hormone in a patient with severe magnesium depletion. *Case reports in nephrology*, 2016, 2608538. Doi: 10.1155/2016/2608538

Cheung, M. M., DeLuccia, R., Ramadoss, R. K., Aljahdali, A., Volpe, S. L., Shewokis, P. A., & Sukumar, D. (2019). Low dietary magnesium intake alters vitamin D-parathyroid hormone relationship in adults who are overweight or obese. *Nutrition research, 69,* 82–93. Doi: 10.1016/j.nutres.2019.08.003

Veronese, N., Stubbs, B., Solmi, M., Noale, M., Vaona, A., Demurtas, J., & Maggi, S. (2017). Dietary magnesium intake and fracture risk: data from a large prospective study. *The British journal of nutrition, 117* (11), 1570–1576. Doi: 10.1017/s0007114517001350

Deng, X., Song, Y., Manson, J. E., Signorello, L. B., Zhang, S. M., Shrubsole, M. J., Ness, R. M., Seidner, D. L., & Dai, Q. (2013). Magnesium, vitamin D status and mortality: results from US national health and nutrition examination survey (NHANES) 2001 to 2006 and NHANES III. *BMC medicine, 11*, 187. Doi: 10.1186/1741-7015-11-187

Dai, Q., Zhu, X., Manson, J. E., Song, Y., Li, X., Franke, A. A., Costello, R. B., Rosanoff, A., Nian, H., Fan, L., Murff, H., Ness, R. M., Seidner, D. L., Yu, C., & Shrubsole, M. J. (2018). Magnesium status and supplementation influence vitamin D status and metabolism: results from a randomized trial. *The American journal of clinical nutrition, 108* (6), 1249–1258. Doi: 10.1093/ajcn/nqy274

Zehnder, D., Bland, R., Walker, E. A., Bradwell, A. R., Howie, A. J., Hewison, M., & Stewart, P. M. (1999). Expression of 25-hydroxyvitamin D3-1alpha-hydroxylase in the human kidney.

Journal of the American Society of Nephrology, 10 (12), 2465–2473. Doi: 10.1681/ASN.V10122465

Prié, D., & Friedlander, G. (2010). Reciprocal control of 1,25-dihydroxyvitamin D and FGF23 formation involving the FGF23/Klotho system. *Clinical journal of the American Society of Nephrology, 5* (9), 1717–1722. Doi: 10.2215/CJN.02680310

Liu, S., Tang, W., Zhou, J., Stubbs, J. R., Luo, Q., Pi, M., & Quarles, L. D. (2006). Fibroblast growth factor 23 is a counter-regulatory phosphaturic hormone for vitamin D. *Journal of the American Society of Nephrology, 17* (5), 1305–1315. Doi:10.1681/ASN.2005111185

Negri A. L. (2006). Proximal tubule endocytic apparatus as the specific renal uptake mechanism for vitamin D-binding protein/25-(OH)D3 complex. *Nephrology (Carlton, Vic.), 11 (6)*, 510–515. Doi:10.1111/j.1440-1797.2006.00704.x

Hewison, M., Burke, F., Evans, K. N., Lammas, D. A., Sansom, D. M., Liu, P., Modlin, R. L., & Adams, J. S. (2007). Extra-renal 25-hydroxyvitamin D3-1alpha-hydroxylase in human health and disease. *The Journal of steroid biochemistry and molecular biology, 103* (3-5), 316–321. Doi: 10.1016/j.jsbmb.2006.12.078.

Zhou, Y., & Lower, E. E. (2020). Balancing altered calcium metabolism with bone health in sarcoidosis. *Seminars in respiratory and critical care medicine, 41* (5), 618–625. Doi: 10.1055/s-0040-1713009.

Miclea, A., Bagnoud, M., Chan, A., & Hoepner, R. (2020). A brief review of the effects of vitamin d on multiple sclerosis. *Frontiers in immunology, 11*, 781. Doi: 10.3389/fimmu.2020.00781.

Colotta, F., Jansson, B., & Bonelli, F. (2017). Modulation of inflammatory and immune responses by vitamin D. *Journal of autoimmunity, 85*, 78–97. Doi: 10.1016/j.jaut.2017.07.007

Liu, P. T., Stenger, S., Li, H., Wenzel, L., Tan, B. H., Krutzik, S. R., Ochoa, M. T., Schauber, J., Wu, K., Meinken, C., Kamen, D. L., Wagner, M., Bals, R., Steinmeyer, A., Zügel, U., Gallo, R. L., Eisenberg, D., Hewison, M., Hollis, B. W., Adams, J. S., … Modlin, R. L. (2006). Toll-like receptor triggering of a vitamin D-mediated human antimicrobial response. *Science*, *311* (5768), 1770–1773. Doi: 10.1126/science.1123933

Martínez-Moreno, J., Hernandez, J. C., & Urcuqui-Inchima, S. (2020). Effect of high doses of vitamin D supplementation on dengue virus replication, Toll-like receptor expression, and cytokine profiles on dendritic cells. *Molecular and cellular biochemistry, 464* (1-2), 169–180. Doi: 10.1007/s11010-019-03658-w

Li, P., Xu, X., Cao, E., Yu, B., Li, W., Fan, M., Huang, M., Shi, L., Zeng, R., Su, X., & Shi, Y. (2014). Vitamin D deficiency causes defective resistance to Aspergillus fumigatus in mice via aggravated and sustained inflammation. *PloS one, 9* (6), e99805. Doi: 10.1371/journal.pone.0099805

D'Ambrosio, D., Cippitelli, M., Cocciolo, M. G., Mazzeo, D., Di Lucia, P., Lang, R., … Panina-Bordignon, P. (1998). Inhibition of IL-12 production by 1,25-dihydroxyvitamin D3. Involvement of NF-κB downregulation in transcriptional repression of the p40 gene. *Journal of Clinical Investigation, 101* (1), 252–262. Doi: 10.1172/JCI1050

de Oliveira, L. R. C., Mimura, L. A. N., Fraga-Silva, T. F. C., Ishikawa, L. L. W., Fernandes, A. A. H., Zorzella-Pezavento, S. F. G., & Sartori, A. (2020). Calcitriol prevents neuroinflammation and reduces blood-brain barrier disruption and local

macrophage/microglia activation. *Frontiers in pharmacology, 11*, 161. Doi: 10.3389/fphar.2020.00161

Lee, P. W., Selhorst, A., Lampe, S. G., Liu, Y., Yang, Y., & Lovett-Racke, A. E. (2020). Neuron-Specific vitamin d signaling attenuates microglia activation and cns autoimmunity. *Frontiers in neurology, 11*, 19. Doi: 10.3389/fneur.2020.00019

Evans, M. A., Kim, H. A., Ling, Y. H., Uong, S., Vinh, A., De Silva, T. M., Arumugam, T. V., Clarkson, A. N., Zosky, G. R., Drummond, G. R., Broughton, B. R. S., & Sobey, C. G. (2018). Vitamin D3 supplementation reduces subsequent brain injury and inflammation associated with ischemic stroke. *Neuromolecular medicine, 20* (1), 147–159. Doi: 10.1007/s11481-016-9720-7

Calvello, R., Cianciulli, A., Nicolardi, G., De Nuccio, F., Giannotti, L., Salvatore, R., Porro, C., Trotta, T., Panaro, M. A., & Lofrumento, D. D. (2017). Vitamin D Treatment Attenuates Neuroinflammation and Dopaminergic Neurodegeneration in an animal model of parkinson's disease, shifting m1 to m2 microglia responses. *Journal of neuroimmune pharmacology, 12* (2), 327–339. Doi: 10.1007/s11481-016-9720-7

Cui, C., Xu, P., Li, G., Qiao, Y., Han, W., Geng, C., Liao, D., Yang, M., Chen, D., & Jiang, P. (2019). Vitamin D receptor activation regulates microglia polarization and oxidative stress in spontaneously hypertensive rats and angiotensin II-exposed microglial cells: Role of renin-angiotensin system. *Redox biology, 26,* 101295. Doi: 10.1016/j.redox.2019.101295

He, M. C., Shi, Z., Sha, N. N., Chen, N., Peng, S. Y., Liao, D. F., Wong, M. S., Dong, X. L., Wang, Y. J., Yuan, T. F., & Zhang, Y. (2019). Paricalcitol alleviates lipopolysaccharide-induced depressive-like behavior by suppressing hypothalamic microglia

activation and neuroinflammation. *Biochemical pharmacology, 163*, 1–8. Doi: 10.1016/j.bcp.2019.01.021

Cross, A. H., Stark, J. L., Lauber, J., Ramsbottom, M. J., & Lyons, J. A. (2006). Rituximab reduces B cells and T cells in cerebrospinal fluid of multiple sclerosis patients. *Journal of neuroimmunology, 180* (1-2), 63–70. Doi: 10.1016/j.jneuroim.2006.06.029

Lovett-Racke, A. E., Gormley, M., Liu, Y., Yang, Y., Graham, C., Wray, S., Racke, M. K., Shubin, R., Twyman, C., Alvarez, E., Bass, A., Eubanks, J. L., & Fox, E. (2019). B cell depletion with ublituximab reshapes the T cell profile in multiple sclerosis patients. *Journal of neuroimmunology, 332*, 187–197. Doi: 10.1016/j.jneuroim.2019.04.017

Lovett-Racke, A. E., Yang, Y., Liu, Y., Gormley, M., Kraus, E., Graham, C., Wray, S., Racke, M. K., Alvarez, E., Bass, A., & Fox, E. (2021). B cell depletion changes the immune cell profile in multiple sclerosis patients: one-year report. *Journal of neuroimmunology, 359*, 577676. Doi: 10.1016/j.jneuroim.2021.577676

Stumpf, W. E., Sar, M., Clark, S. A., & DeLuca, H. F. (1982). Brain target sites for 1,25-dihydroxyvitamin D3. *Science, 215* (4538), 1403–1405. Doi: 10.1126/science.6977846

McGrath, J. J., Féron, F. P., Burne, T. H., Mackay-Sim, A., & Eyles, D. W. (2004). Vitamin D3-implications for brain development. *The Journal of steroid biochemistry and molecular biology, 89-90* (1-5), 557–560. Doi: 10.1016/j.jsbmb.2004.03.070

Zehnder, D., Bland, R., Williams, M. C., McNinch, R. W., Howie, A. J., Stewart, P. M., & Hewison, M. (2001). Extrarenal expression of 25-hydroxyvitamin d(3)-1 alpha-hydroxylase. *The*

Journal of clinical endocrinology and metabolism, 86 (2), 888–894. Doi: 10.1210/jc.86.2.888

Eyles, D., Brown, J., Mackay-Sim, A., McGrath, J., & Feron, F. (2003). Vitamin D3 and brain development. *Neuroscience, 118* (3), 641–653. Doi: 10.1016/S0306-4522(03)00040-X

Brown, J., Bianco, J. I., McGrath, J. J., & Eyles, D. W. (2003). 1,25-dihydroxyvitamin D3 induces nerve growth factor, promotes neurite outgrowth and inhibits mitosis in embryonic rat hippocampal neurons. *Neuroscience letters, 343* (2), 139–143. Doi: 10.1016/S0304-3940(03)00303-3

Ko, P., Burkert, R., McGrath, J., & Eyles, D. (2004). Maternal vitamin D3 deprivation and the regulation of apoptosis and cell cycle during rat brain development. Brain research. *Developmental brain research, 153* (1), 61–68. Doi: 10.1016/j.devbrainres.2004.07.013

Sinkkonen, L., Malinen, M., Saavalainen, K., Väisänen, S., & Carlberg, C. (2005). Regulation of the human cyclin C gene via multiple vitamin D3-responsive regions in its promoter. *Nucleic acids research, 33* (8), 2440–2451. Doi: 10.1093/nar/gki502

Cui, X., McGrath, J. J., Burne, T. H., Mackay-Sim, A., & Eyles, D. W. (2007). Maternal vitamin D depletion alters neurogenesis in the developing rat brain. *International journal of developmental neuroscience, 25* (4), 227–232. Doi: 10.1016/j.ijdevneu.2007.03.006

Al-Amin, M. M., Sullivan, R. K. P., Kurniawan, N. D., & Burne, T. H. J. (2019). Adult vitamin D deficiency disrupts hippocampal-dependent learning and structural brain connectivity in BALB/c mice. *Brain structure & function, 224* (3), 1315–1329. Doi: 10.1007/s00429-019-01840-w

Annweiler, C., Bartha, R., Karras, S. N., Gautier, J., Roche, F., & Beauchet, O. (2015). Vitamin D and white matter abnormalities in older adults: a quantitative volumetric analysis of brain MRI. *Experimental gerontology, 63*, 41–47. Doi: 10.1016/j.exger.2015.01.049

Cui, X., Pelekanos, M., Burne, T. H., McGrath, J. J., & Eyles, D. W. (2010). Maternal vitamin D deficiency alters the expression of genes involved in dopamine specification in the developing rat mesencephalon. *Neuroscience letters, 486* (3), 220–223. Doi: 10.1016/j.neulet.2010.09.057

Orme, R. P., Bhangal, M. S., & Fricker, R. A. (2013). Calcitriol imparts neuroprotection in vitro to midbrain dopaminergic neurons by upregulating GDNF expression. *PloS one, 8* (4), e62040. Doi: 10.1371/journal.pone.0062040

Pertile, R. A., Cui, X., & Eyles, D. W. (2016). Vitamin D signaling and the differentiation of developing dopamine systems. *Neuroscience, 333*, 193–203. Doi: 10.1016/j.neuroscience.2016.07.020

Shirazi, H. A., Rasouli, J., Ciric, B., Rostami, A., & Zhang, G. X. (2015). 1,25-Dihydroxyvitamin D3 enhances neural stem cell proliferation and oligodendrocyte differentiation. *Experimental and molecular pathology, 98* (2), 240–245. Doi: 10.1016/j.yexmp.2015.02.004

de la Fuente, A. G., Errea, O., van Wijngaarden, P., Gonzalez, G. A., Kerninon, C., Jarjour, A. A., Lewis, H. J., Jones, C. A., Nait-Oumesmar, B., Zhao, C., Huang, J. K., ffrench-Constant, C., & Franklin, R. J. (2015). Vitamin D receptor-retinoid X receptor heterodimer signaling regulates oligodendrocyte progenitor cell differentiation. *The Journal of cell biology, 211* (5), 975–985. Doi: 10.1083/jcb.201505119

Di Somma, C., Scarano, E., Barrea, L., Zhukouskaya, V. V., Savastano, S., Mele, C., Scacchi, M., Aimaretti, G., Colao, A., & Marzullo, P. (2017). Vitamin D and Neurological Diseases: An Endocrine View. *International journal of molecular sciences, 18* (11), 2482. Doi: 10.3390/ijms18112482

Sivandzade, F., Prasad, S., Bhalerao, A., & Cucullo, L. (2019). NRF2 and NF-κB interplay in cerebrovascular and neurodegenerative disorders: Molecular mechanisms and possible therapeutic approaches. *Redox Biology, 21*, 101059. Doi: 10.1016/j.redox.2018.11.017

Wimalawansa S. J. (2019). Vitamin D deficiency: effects on oxidative stress, epigenetics, gene regulation, and aging. *Biology, 8* (2), 30. Doi: 10.3390/biology8020030

Trist, B. G., Hare, D. J., & Double, K. L. (2019). Oxidative stress in the aging substantia nigra and the etiology of Parkinson's disease. *Aging cell, 18* (6), e13031. Doi: 10.1111/acel.13031

Niedzielska, E., Smaga, I., Gawlik, M., et al. (2016). Oxidative stress in neurodegenerative diseases. *Molecular Neurobiology, 53* (6), 4094–4125. Doi: 10.1007/s12035-015-9337-5

Browne, S. E., & Beal, M. F. (2006). Oxidative damage in Huntington's disease pathogenesis. *Antioxidants & redox signaling, 8* (11-12), 2061–2073. Doi: 10.1089/ars.2006.8.2061

Rodrigo, R., Fernández-Gajardo, R., Gutiérrez, R., Matamala, J. M., Carrasco, R., Miranda-Merchak, A., & Feuerhake, W. (2013). Oxidative stress and pathophysiology of ischemic stroke: novel therapeutic opportunities. *CNS & neurological disorders drug targets, 12* (5), 698–714. Doi: 10.2174/18715273113120500015

Di Filippo, M., Chiasserini, D., Tozzi, A., Picconi, B., & Calabresi, P. (2010). Mitochondria and the link between

neuroinflammation and neurodegeneration. *Journal of Alzheimer's disease, 20 Suppl 2*, S369–S379. Doi: 10.3233/JAD-2010-100543

Khairy, E. Y., & Attia, M. M. (2021). Protective effects of vitamin D on neurophysiologic alterations in brain aging: role of brain-derived neurotrophic factor (BDNF). *Nutritional neuroscience, 24* (8), 650–659. Doi: 10.1080/1028415X.2019.1665854

Barlow, P. G., Svoboda, P., Mackellar, A., Nash, A. A., York, I. A., Pohl, J., Davidson, D. J., & Donis, R. O. (2011). Antiviral activity and increased host defense against influenza infection elicited by the human cathelicidin LL-37. *PloS one, 6* (10), e25333. Doi: 10.1371/journal.pone.0025333

Shahmiri, M., Enciso, M., Adda, C. G., Smith, B. J., Perugini, M. A., & Mechler, A. (2016). Membrane core-specific antimicrobial action of cathelicidin ll-37 peptide switches between pore and nanofibre formation. *Scientific reports, 6*, 38184. Doi: 10.1038/srep38184

Sousa, F. H., Casanova, V., Findlay, F., Stevens, C., Svoboda, P., Pohl, J., Proudfoot, L., & Barlow, P. G. (2017). Cathelicidins display conserved direct antiviral activity towards rhinovirus. *Peptides, 95*, 76–83. Doi: 10.1016/j.peptides.2017.07.013

Széles, L., Keresztes, G., Töröcsik, D., Balajthy, Z., Krenács, L., Póliska, S., Steinmeyer, A., Zuegel, U., Pruenster, M., Rot, A., & Nagy, L. (2009). 1,25-dihydroxyvitamin D3 is an autonomous regulator of the transcriptional changes leading to a tolerogenic dendritic cell phenotype. *Journal of immunology, 182* (4), 2074–2083. Doi: 10.4049/jimmunol.0803345

White J. H. (2012). Vitamin D metabolism and signaling in the immune system. *Reviews in endocrine & metabolic disorders, 13* (1), 21–29. Doi: 10.1007/s11154-011-9195-z

Zhang, Y., Leung, D. Y. M., & Goleva, E. (2013). Vitamin D enhances glucocorticoid action in human monocytes: Involvement of granulocyte-macrophage colony-stimulating factor and mediator complex subunit 14. *The Journal of Biological Chemistry, 288* (20), 14544–14553. Doi: 10.1074/jbc.m112.427054

Barragan, M., Good, M., & Kolls, J. K. (2015). Regulation of dendritic cell function by vitamin D. *Nutrients, 7* (9), 8127–8151. Doi: 10.3390/nu7095383

Piemonti, L., Monti, P., Sironi, M., Fraticelli, P., Leone, B. E., Dal Cin, E., Allavena, P., & Di Carlo, V. (2000). Vitamin D3 affects differentiation, maturation, and function of human monocyte-derived dendritic cells. *Journal of immunology, 164* (9), 4443–4451. Doi: 10.4049/jimmunol.164.9.4443.

Provvedini, D. M., Tsoukas, C. D., Deftos, L. J., & Manolagas, S. C. (1983). 1,25-dihydroxyvitamin D3 receptors in human leukocytes. *Science, 221* (4616), 1181–1183. Doi: 10.1126/science.6310748

Chen, S., Sims, G. P., Chen, X. X., Gu, Y. Y., Chen, S., & Lipsky, P. E. (2007). Modulatory effects of 1,25-dihydroxyvitamin D3 on human B cell differentiation. *Journal of immunology, 179* (3), 1634–1647. Doi: jimmunol.179.3.1634

Cantorna M. T. (2010). Mechanisms underlying the effect of vitamin D on the immune system. *The Proceedings of the Nutrition Society, 69* (3), 286–289. Doi: 10.1017/S0029665110001722

Fletcher, J., Bishop, E. L., Harrison, S. R., Swift, A., Cooper, S. C., Dimeloe, S. K., Raza, K., & Hewison, M. (2022).

Autoimmune disease and interconnections with vitamin D. *Endocrine connections, 11* (3), e210554. Doi: 10.1530/EC-21-0554

Arnson, Y., Amital, H., & Shoenfeld, Y. (2007). Vitamin D and autoimmunity: new aetiological and therapeutic considerations. *Annals of the rheumatic diseases, 66* (9), 1137–1142. Doi: 10.1136/ard.2007.069831

Baeke, F., Korf, H., Overbergh, L., Verstuyf, A., Thorrez, L., Van Lommel, L., Waer, M., Schuit, F., Gysemans, C., & Mathieu, C. (2011). The vitamin D analog, TX527, promotes a human CD4+CD25highCD127low regulatory T cell profile and induces a migratory signature specific for homing to sites of inflammation. *Journal of immunology, 186* (1), 132–142. Doi: 10.4049/jimmunol.1000695

Lemire, J. M., Archer, D. C., Beck, L., & Spiegelberg, H. L. (1995). Immunosuppressive actions of 1,25-dihydroxyvitamin D3: preferential inhibition of Th1 functions. *The Journal of nutrition, 125* (6), 1704S–1708S. Doi: 10.1093/jn/125.suppl_6.1704S

Ohl, K., Tenbrock, K., & Kipp, M. (2016). Oxidative stress in multiple sclerosis: Central and peripheral mode of action. *Experimental neurology, 277*, 58–67. Doi: 10.1016/j.expneurol.2015.11.010

Genestra M. (2007). Oxyl radicals, redox-sensitive signalling cascades and antioxidants. *Cellular signalling, 19* (9), 1807–1819. Doi: 10.1016/j.cellsig.2007.04.009

Gray, E., Thomas, T. L., Betmouni, S., Scolding, N., & Love, S. (2008). Elevated activity and microglial expression of myeloperoxidase in demyelinated cerebral cortex in multiple sclerosis. *Brain pathology, 18* (1), 86–95. Doi: 10.1111/j.1750-3639.2007.00110.x

Gray, E., Thomas, T. L., Betmouni, S., Scolding, N., & Love, S. (2008). Elevated myeloperoxidase activity in white matter in multiple sclerosis. *Neuroscience letters, 444* (2), 195–198. Doi: 10.1016/j.neulet.2008.08.035

Cross, A. H., Manning, P. T., Keeling, R. M., Schmidt, R. E., & Misko, T. P. (1998). Peroxynitrite formation within the central nervous system in active multiple sclerosis. *Journal of neuroimmunology, 88* (1-2), 45–56. Doi: 10.1016/s0165-5728(98)00078-2

Liu, J. S., Zhao, M. L., Brosnan, C. F., & Lee, S. C. (2001). Expression of inducible nitric oxide synthase and nitrotyrosine in multiple sclerosis lesions. *The American journal of pathology, 158* (6), 2057–2066. Doi: 10.1016/S0002-9440(10)64677-9

van Horssen, J., Schreibelt, G., Drexhage, J., Hazes, T., Dijkstra, C. D., van der Valk, P., & de Vries, H. E. (2008). Severe oxidative damage in multiple sclerosis lesions coincides with enhanced antioxidant enzyme expression. *Free radical biology & medicine, 45* (12), 1729–1737. Doi: 10.1016/j.freeradbiomed.2008.09.023

van Horssen, J., Witte, M. E., Schreibelt, G., & de Vries, H. E. (2011). Radical changes in multiple sclerosis pathogenesis. *Biochimica et biophysica acta, 1812* (2), 141–150. Doi: 10.1016/j.bbadis.2010.06.011

Craner, M. J., Newcombe, J., Black, J. A., Hartle, C., Cuzner, M. L., & Waxman, S. G. (2004). Molecular changes in neurons in multiple sclerosis: altered axonal expression of Nav1.2 and Nav1.6 sodium channels and Na+/Ca2+ exchanger. *Proceedings of the National Academy of Sciences of the United States of America, 101* (21), 8168–8173. Doi: 10.1073/pnas.0402765101

Witte, M. E., Bø, L., Rodenburg, R. J., Belien, J. A., Musters, R., Hazes, T., Wintjes, L. T., Smeitink, J. A., Geurts, J. J., De Vries, H. E., van der Valk, P., & van Horssen, J. (2009). Enhanced number and activity of mitochondria in multiple sclerosis lesions. *The Journal of pathology, 219* (2), 193–204. Doi: 10.1002/path.2582

Campbell, G., & Mahad, D. J. (2018). Mitochondrial dysfunction and axon degeneration in progressive multiple sclerosis. *FEBS letters, 592* (7), 1113–1121. Doi: 10.1002/1873-3468.13013

Waxman S. G. (2006). Ions, energy and axonal injury: towards a molecular neurology of multiple sclerosis. *Trends in molecular medicine, 12* (5), 192–195. Doi: 10.1016/j.molmed.2006.03.001

Hybertson, B. M., Gao, B., Bose, S. K., & McCord, J. M. (2011). Oxidative stress in health and disease: The therapeutic potential of Nrf2 activation. *Molecular Aspects of Medicine, 32* (4–6), 234–246. Doi: 10.1016/j.mam.2011.10.006

Johnson, D. A., Amirahmadi, S., Ward, C., Fabry, Z., & Johnson, J. A. (2010). The absence of the pro-antioxidant transcription factor Nrf2 exacerbates experimental autoimmune encephalomyelitis. *Toxicological sciences, 114* (2), 237–246. Doi: 10.1093/toxsci/kfp274

Larabee, C. M., Desai, S., Agasing, A., Georgescu, C., Wren, J. D., Axtell, R. C., & Plafker, S. M. (2016). Loss of Nrf2 exacerbates the visual deficits and optic neuritis elicited by experimental autoimmune encephalomyelitis. *Molecular vision, 22*, 1503–1513. Doi:

Morales Pantoja, I. E., Hu, C. L., Perrone-Bizzozero, N. I., Zheng, J., & Bizzozero, O. A. (2016). Nrf2-dysregulation correlates with reduced synthesis and low glutathione levels in experimental

autoimmune encephalomyelitis. *Journal of neurochemistry, 139* (4), 640–650. Doi: 10.1111/jnc.13837

Linker, R. A., Lee, D. H., Ryan, S., van Dam, A. M., Conrad, R., Bista, P., Zeng, W., Hronowsky, X., Buko, A., Chollate, S., Ellrichmann, G., Brück, W., Dawson, K., Goelz, S., Wiese, S., Scannevin, R. H., Lukashev, M., & Gold, R. (2011). Fumaric acid esters exert neuroprotective effects in neuroinflammation via activation of the Nrf2 antioxidant pathway. *Brain: a journal of neurology, 134* (3), 678–692. Doi: 10.1093/brain/awq386

van Horssen, J., Drexhage, J. A., Flor, T., Gerritsen, W., van der Valk, P., & de Vries, H. E. (2010). Nrf2 and DJ1 are consistently upregulated in inflammatory multiple sclerosis lesions. *Free radical biology & medicine, 49* (8), 1283–1289. Doi: 1016/j.freeradbiomed.2010.07.013

Licht-Mayer, S., Wimmer, I., Traffehn, S., Metz, I., Brück, W., Bauer, J., Bradl, M., & Lassmann, H. (2015). Cell type-specific Nrf2 expression in multiple sclerosis lesions. *Acta neuropathologica, 130* (2), 263–277. Doi: 10.1007/s00401-015-1452-x

Bresciani, G., Manai, F., Davinelli, S., Tucci, P., Saso, L., & Amadio, M. (2023). Novel potential pharmacological applications of dimethyl fumarate-an overview and update. *Frontiers in pharmacology, 14*, 1264842. Doi: 10.3389/fphar.2023.1264842

aha, S., Buttari, B., Panieri, E., Profumo, E., & Saso, L. (2020). An overview of nrf2 signaling pathway and its role in inflammation. *Molecules, 25* (22), 5474. Doi: 10.3390/molecules25225474

Salehi, M. S., Borhani-Haghighi, A., Pandamooz, S., Safari, A., Dargahi, L., Dianatpour, M., & Tanideh, N. (2019). Dimethyl fumarate up-regulates expression of major neurotrophic factors in

the epidermal neural crest stem cells. *Tissue and Cell, 56,* 114–120. Doi: 10.1016/j.tice.2018.12.004

Nachliely, M., Trachtenberg, A., Khalfin, B., Nalbandyan, K., Cohen-Lahav, M., Yasuda, K., Sakaki, T., Kutner, A., & Danilenko, M. (2019). Dimethyl fumarate and vitamin D derivatives cooperatively enhance VDR and Nrf2 signaling in differentiating AML cells in vitro and inhibit leukemia progression in a xenograft mouse model. *The Journal of steroid biochemistry and molecular biology, 188*, 8–16. Doi: 10.1016/j.jsbmb.2018.11.017

Häusler, D., Torke, S., Peelen, E., Bertsch, T., Djukic, M., Nau, R., Larochelle, C., Zamvil, S. S., Brück, W., & Weber, M. S. (2019). High dose vitamin D exacerbates central nervous system autoimmunity by raising T-cell excitatory calcium. *Brain: a journal of neurology, 142* (9), 2737–2755. Doi: 10.1093/brain/awz190

Long, T., Yang, Y., Peng, L., & Li, Z. (2018). Neuroprotective Effects of Melatonin on Experimental Allergic Encephalomyelitis Mice Via Anti-Oxidative Stress Activity. *Journal of molecular neuroscience: MN, 64* (2), 233–241. Doi: 10.1007/s12031-017-1022-x

Ghareghani, M., Reiter, R. J., Zibara, K., & Farhadi, N. (2018). Latitude, vitamin d, melatonin, and gut microbiota act in concert to initiate multiple sclerosis: a new mechanistic pathway. *Frontiers in immunology, 9*, 2484. Doi: 10.3389/fimmu.2018.02484

Gooch, H., Cui, X., Anggono, V., Trzaskowski, M., Tan, M. C., Eyles, D. W., Burne, T. H. J., Jang, S. E., Mattheisen, M., Hougaard, D. M., Pedersen, B. N., Cohen, A., Mortensen, P. B., Sah, P., & McGrath, J. J. (2019). 1,25-Dihydroxyvitamin D modulates L-type voltage-gated calcium channels in a subset of neurons in the developing mouse prefrontal cortex. *Translational psychiatry, 9* (1), 281. Doi: 10.1038/s41398-019-0626-z

Fernandes de Abreu, D. A., Eyles, D., & Féron, F. (2009). Vitamin D, a neuro-immunomodulator: implications for neurodegenerative and autoimmune diseases. *Psychoneuroendocrinology, 34* (1), 265–277. Doi: 10.1016/j.psyneuen.2009.05.023

Chauss, D., Freiwald, T., McGregor, R., et al. (2022). Autocrine vitamin D signaling switches off pro-inflammatory programs of TH1 cells. *Nature Immunology, 23* (1), 62–74. Doi: 10.1038/s41590-021-01080-3

Waddell, A., Zhao, J., & Cantorna, M. T. (2015). NKT cells can help mediate the protective effects of 1,25-dihydroxyvitamin D3 in experimental autoimmune encephalomyelitis in mice. *International immunology, 27* (5), 237–244. Doi:10.1093/intimm/dxu147

Nystad, A. E., Wergeland, S., Aksnes, L., Myhr, K. M., Bø, L., & Torkildsen, O. (2014). Effect of high-dose 1.25 dihydroxyvitamin D3 on remyelination in the cuprizone model. *APMIS, 122* (12), 1178–1186. Doi: 10.1111/apm.12281

Mirarchi, A., Albi, E., Beccari, T., & Arcuri, C. (2023). Microglia and brain disorders: the role of vitamin d and its receptor. *International journal of molecular sciences, 24* (15), 11892. Doi: 10.3390/ijms241511892

Bock, G., Pieber, T. R., & Prietl, B. (2012). Vitamin D: Role in autoimmunity. *CABI Reviews*, 1–7. Doi: 10.1079/PAVSNNR20127041

Sabel, C. E., Pearson, J. F., Mason, D. F., Willoughby, E., Abernethy, D. A., & Taylor, B. V. (2021). The latitude gradient for multiple sclerosis prevalence is established in the early life course. *Brain, 144* (7), 2038–2046. Doi: 10.1093/brain/awab104

Shi, M., Liu, Y., Gong, Q., & Xu, X. (2024). Multiple sclerosis: An overview of epidemiology, risk factors, and serological biomarkers. *Acta Neurologica Scandinavica, 2024*, 7372789. Doi: 10.1155/2024/7372789

Simpson, S., Jr, Blizzard, L., Otahal, P., Van der Mei, I., & Taylor, B. (2011). Latitude is significantly associated with the prevalence of multiple sclerosis: a meta-analysis. *Journal of neurology, neurosurgery, and psychiatry, 82* (10), 1132–1141. Doi: 10.1136/jnnp.2011.240432

Sintzel, M. B., Rametta, M., & Reder, A. T. (2018). Vitamin d and multiple sclerosis: a comprehensive review. *Neurology and therapy, 7* (1), 59–85. Doi: 10.1007/s40120-017-0086-4

Sloka, S., Silva, C., Pryse-Phillips, W., Patten, S., Metz, L., & Yong, V. W. (2011). A quantitative analysis of suspected environmental causes of MS. *The Canadian journal of neurological sciences. 38* (1), 98–105. Doi:10.1017/s0317167100011124

Orton, S. M., Wald, L., Confavreux, C., Vukusic, S., Krohn, J. P., Ramagopalan, S. V., Herrera, B. M., Sadovnick, A. D., & Ebers, G. C. (2011). Association of UV radiation with multiple sclerosis prevalence and sex ratio in France. *Neurology, 76* (5), 425–431. Doi: 10.1212/WNL.0b013e31820a0a9f

Kampman, M. T., Wilsgaard, T., & Mellgren, S. I. (2007). Outdoor activities and diet in childhood and adolescence relate to MS risk above the Arctic Circle. *Journal of neurology, 254* (4), 471–477. Doi: 10.1007/s00415-006-0395-5

Chang, G., Sebastian, P., Virupakshaiah, A., Schoeps, V. A., Cherbuin, N., Casper, T. C., Gorman, M. P., Benson, L. A., Chitnis, T., Rensel, M., Abrams, A. W., Lotze, T., Mar, S. S., Schreiner, T. L., Wheeler, Y. S., Rose, J. W., Graves, J., Krupp, L. B., Waldman, A. T., Lucas, R., & Waubant, E. (2025). Association between sun

exposure and risk of relapse in pediatric-onset multiple sclerosis. *Neurology Neuroimmunology Neuroinflammation, 12* (e200375). Doi:10.1212/NXI.0000000000200375

Rodríguez Cruz, P. M., Matthews, L., Boggild, M., et al. (2016). Time- and region-specific season of birth effects in multiple sclerosis in the United Kingdom. *JAMA Neurology, 73* (8), 954–960. Doi: 10.1001/jamaneurol.2016.1463

Ljubic, N., Thulesen, E. T., Jacobsen, C., & Jakobsen, J. (2021). UVB exposure stimulates production of vitamin D_3 in selected microalgae. *Algal Research, 59*, 102472. Doi: 10.1016/j.algal.2021.102472

Breuer, J., Schwab, N., Schneider-Hohendorf, T., Marziniak, M., Mohan, H., Bhatia, U., Gross, C. C., Clausen, B. E., Weishaupt, C., Luger, T. A., Meuth, S. G., Loser, K., & Wiendl, H. (2014). Ultraviolet B light attenuates the systemic immune response in central nervous system autoimmunity. *Annals of neurology, 75* (5), 739–758. Doi: 10.1002/ana.24165

DeLuca, H. F., & Plum, L. (2017). UVB radiation, vitamin D and multiple sclerosis. *Photochemical & photobiological sciences, 16* (3), 411–415. Doi: 10.1039/c6pp00308g

Fernandes de Abreu, D. A., Landel, V., & Féron, F. (2011). Seasonal, gestational and postnatal influences on multiple sclerosis: the beneficial role of a vitamin D supplementation during early life. *Journal of the neurological sciences, 311* (1-2), 64–68. Doi: 10.1016/j.jns.2011.08.044

Pierrot-Deseilligny, C., & Souberbielle, J.-C. (2017). Vitamin D and multiple sclerosis: an update. *Multiple Sclerosis and Related Disorders, 14*, 35–45. Doi: 10.1016/j.msard.2017.03.014

Munger, K. L., Zhang, S. M., O'Reilly, E., Hernán, M. A., Olek, M. J., Willett, W. C., & Ascherio, A. (2004). Vitamin D intake

and incidence of multiple sclerosis. *Neurology, 62* (1), 60–65. Doi: 10.1212/01.wnl.0000101723.79681.38

Cortese, M., Riise, T., Bjørnevik, K., Holmøy, T., Kampman, M. T., Magalhaes, S., Pugliatti, M., Wolfson, C., & Myhr, K. M. (2015). Timing of use of cod liver oil, a vitamin D source, and multiple sclerosis risk: The EnvIMS study. *Multiple sclerosis, 21* (14), 1856–1864. Doi: 10.1177/1352458515578770

Bäärnhielm, M., Hedström, A. K., Kockum, I., Sundqvist, E., Gustafsson, S. A., Hillert, J., Olsson, T., & Alfredsson, L. (2012). Sunlight is associated with decreased multiple sclerosis risk: No interaction with human leukocyte antigen-DRB1*15. *European Journal of Neurology, 19* (7), 955–962. Doi: 10.1111/j.1468-1331.2011.03650.x

Salzer, J., Hallmans, G., Nyström, M., Stenlund, H., Wadell, G., & Sundström, P. (2012). Vitamin D as a protective factor in multiple sclerosis. *Neurology, 79* (21), 2140–2145. Doi: 10.1212/WNL.0b013e3182752ea8

Voltan, G., Cannito, M., Ferrarese, M., Ceccato, F., & Camozzi, V. (2023). Vitamin D: an overview of gene regulation, ranging from metabolism to genomic effects. *Genes, 14* (9), 1691. Doi: 10.3390/genes14091691

Simon, K. C., Munger, K. L., Kraft, P., Hunter, D. J., De Jager, P. L., & Ascherio, A. (2011). Genetic predictors of 25-hydroxyvitamin D levels and risk of multiple sclerosis. *Journal of neurology, 258* (9), 1676–1682. Doi: 10.1007/s00415-011-6001-5

Yu, X. H., Lu, H. M., Li, J., Su, M. Z., Li, X. M., & Jin, Y. (2024). Association between 25(oh) vitamin d and multiple sclerosis: cohort, shared genetics, and causality. *Nutrition journal, 23* (1), 151. Doi: 10 .1186/s12937-024-01059-4

Karaky, M., Alcina, A., Fedetz, M., Barrionuevo, C., Potenciano, V., Delgado, C., Izquierdo, G., & Matesanz, F. (2016). The multiple sclerosis-associated regulatory variant rs10877013 affects expression of CYP27B1 and VDR under inflammatory or vitamin D stimuli. *Multiple sclerosis, 22* (8), 999–1006. Doi: 10.1177/1352458515610208

Mokry, L. E., Ross, S., Ahmad, O. S., Forgetta, V., Smith, G. D., Goltzman, D., Leong, A., Greenwood, C. M., Thanassoulis, G., & Richards, J. B. (2015). Vitamin D and risk of multiple sclerosis: a mendelian randomization study. *PLoS medicine, 12* (8), e1001866. Doi: 10.1371/journal.pmed.1001866

Rhead, B., Bäärnhielm, M., Gianfrancesco, M., Mok, A., Shao, X., Quach, H., Shen, L., Schaefer, C., Link, J., Gyllenberg, A., Hedström, A. K., Olsson, T., Hillert, J., Kockum, I., Glymour, M. M., Alfredsson, L., & Barcellos, L. F. (2016). Mendelian randomization shows a causal effect of low vitamin D on multiple sclerosis risk. *Neurology. Genetics, 2* (5), e97. Doi: 10.1212/NXG.0000000000000097

Alcina, A., Abad-Grau, M. d. M., Fedetz, M., Izquierdo, G., Lucas, M., et al. (2012). Multiple sclerosis risk variant HLA-DRB11501 associates with high expression of DRB1 gene in different human populations. *PLOS ONE, 7* (1), e29819. Doi: 10.1371/journal.pone.0029819

Spanier, J. A., Nashold, F. E., Mayne, C. G., Nelson, C. D., & Hayes, C. E. (2015). Vitamin D and estrogen synergy in Vdr-expressing CD4(+) T cells is essential to induce Helios(+)FoxP3(+) T cells and prevent autoimmune demyelinating disease. *Journal of neuroimmunology, 286*, 48–58. Doi: 10.1016/j.jneuroim.2015.06.015

Nashold, F. E., Spach, K. M., Spanier, J. A., & Hayes, C. E. (2009). Estrogen controls vitamin D3-mediated resistance to experimental autoimmune encephalomyelitis by controlling vitamin D3 metabolism and receptor expression. *Journal of immunology, 183* (6), 3672–3681. Doi: 10.4049/jimmunol.0901351

Røsjø, E., Lossius, A., Abdelmagid, N., Lindstrøm, J. C., Kampman, M. T., Jørgensen, L., Sundström, P., Olsson, T., Steffensen, L. H., Torkildsen, Ø., & Holmøy, T. (2017). Effect of high-dose vitamin D3 supplementation on antibody responses against Epstein-Barr virus in relapsing-remitting multiple sclerosis. *Multiple sclerosis, 23* (3), 395–402. Doi: 10.1177/1352458516654310

Marcucci, S. B., & Obeidat, A. Z. (2020). EBNA1, EBNA2, and EBNA3 link Epstein-Barr virus and hypovitaminosis D in multiple sclerosis pathogenesis. *Journal of neuroimmunology, 339,* 577116. Doi: 10.1016/j.jneuroim.2019.577116

Rolf, L., Muris, A. H., Mathias, A., Du Pasquier, R., Koneczny, I., Disanto, G., Kuhle, J., Ramagopalan, S., Damoiseaux, J., Smolders, J., & Hupperts, R. (2018). Exploring the effect of vitamin D3 supplementation on the anti-EBV antibody response in relapsing-remitting multiple sclerosis. *Multiple sclerosis, 24* (10), 1280–1287. Doi: 10.1177/1352458517722646

Matías-Guíu, J., Oreja-Guevara, C., Matias-Guiu, J. A., & Gomez-Pinedo, U. (2018). Vitamin D and remyelination in multiple sclerosis. Vitamina D y remielinización en la esclerosis múltiple. *Neurologia, 33* (3), 177–186. Doi: 10.1016/j.nrl.2016.05.00

Bjornevik, K., Cortese, M., Healy, B. C., Kuhle, J., Mina, M. J., Leng, Y., Elledge, S. J., Niebuhr, D. W., Scher, A. I., Munger, K. L., & Ascherio, A. (2022). Longitudinal analysis reveals high

prevalence of Epstein-Barr virus associated with multiple sclerosis. *Science, 375* (6578), 296–301. Doi: 10.1126/science.abj8222

Lang, H. L., Jacobsen, H., Ikemizu, S., Andersson, C., Harlos, K., Madsen, L., Hjorth, P., Sondergaard, L., Svejgaard, A., Wucherpfennig, K., Stuart, D. I., Bell, J. I., Jones, E. Y., & Fugger, L. (2002). A functional and structural basis for TCR cross-reactivity in multiple sclerosis. *Nature immunology, 3* (10), 940–943. Doi: 10.1038/ni835

Lindsey J. W. (2017). Antibodies to the Epstein-Barr virus proteins BFRF3 and BRRF2 cross-react with human proteins. *Journal of neuroimmunology, 310*, 131–134. Doi: 10.1016/j.jneuroim.2017.07.013

Tengvall, K., Huang, J., Hellström, C., Kammer, P., Biström, M., Ayoglu, B., Lima Bomfim, I., Stridh, P., Butt, J., Brenner, N., Michel, A., Lundberg, K., Padyukov, L., Lundberg, I. E., Svenungsson, E., Ernberg, I., Olafsson, S., Dilthey, A. T., Hillert, J., Alfredsson, L., … Kockum, I. (2019). Molecular mimicry between Anoctamin 2 and Epstein-Barr virus nuclear antigen 1 associates with multiple sclerosis risk. *Proceedings of the National Academy of Sciences of the United States of America, 116* (34), 16955–16960. Doi: 10.1073/pnas.1902623116

Lanz, T. V., Brewer, R. C., Ho, P. P., Moon, J. S., Jude, K. M., Fernandez, D., Fernandes, R. A., Gomez, A. M., Nadj, G. S., Bartley, C. M., Schubert, R. D., Hawes, I. A., Vazquez, S. E., Iyer, M., Zuchero, J. B., Teegen, B., Dunn, J. E., Lock, C. B., Kipp, L. B., Cotham, V. C., … Robinson, W. H. (2022). Clonally expanded B cells in multiple sclerosis bind EBV EBNA1 and GlialCAM. *Nature, 603* (7900), 321–327. Doi: 10.1038/s41586-022-04432-7

Pérez-Pérez, S., Domínguez-Mozo, M. I., García-Martínez, M. Á., Aladro, Y., Martínez-Ginés, M., García-Domínguez, J. M.,

López de Silanes, C., Casanova, I., Ortega-Madueño, I., López-Lozano, L., Torrejón, M. J., Arroyo, R., & Álvarez-Lafuente, R. (2018). Study of the possible link of 25-hydroxyvitamin D with Epstein-Barr virus and human herpesvirus 6 in patients with multiple sclerosis. *European journal of neurology, 25* (12), 1446–1453. Doi: 10.1111/ene.13749

Mameli, G., Madeddu, G., Mei, A., Uleri, E., Poddighe, L., Delogu, L. G., Maida, I., Babudieri, S., Serra, C., Manetti, R., Mura, M. S., & Dolei, A. (2013). Activation of MSRV-type endogenous retroviruses during infectious mononucleosis and Epstein-Barr virus latency: the missing link with multiple sclerosis?. *PloS one, 8* (11), e78474. Doi: journal.pone.0078474

Zwart, S. R., Mehta, S. K., Ploutz-Snyder, R., Bourbeau, Y., Locke, J. P., Pierson, D. L., & Smith, S. M. (2011). Response to vitamin d supplementation during antarctic winter is related to bmi, and supplementation can mitigate epstein-barr virus reactivation. *The Journal of nutrition, 141* (4), 692–697. Doi: 10.3945/jn.110.134742

Zdimerova, H., Murer, A., Engelmann, C., Raykova, A., Deng, Y., Gujer, C., Rühl, J., McHugh, D., Caduff, N., Naghavian, R., Pezzino, G., Capaul, R., Zbinden, A., Ferlazzo, G., Lünemann, J. D., Martin, R., Chatterjee, B., & Münz, C. (2021). Attenuated immune control of Epstein-Barr virus in humanized mice is associated with the multiple sclerosis risk factor HLA-DR15. *European journal of immunology, 51* (1), 64–75. Doi: 10.1002/eji.202048655

Brütting, C., Stangl, G. I., & Staege, M. S. (2021). Vitamin D, Epstein-Barr virus, and endogenous retroviruses in multiple sclerosis - facts and hypotheses. *Journal of integrative neuroscience, 20* (1), 233–238. Doi: 10.31083/j.jin.2021.01.392

Ostkamp, P., Salmen, A., Pignolet, B., Görlich, D., Andlauer, T. F. M., Schulte-Mecklenbeck, A., Gonzalez-Escamilla, G., Bucciarelli, F., Gennero, I., Breuer, J., Antony, G., Schneider-Hohendorf, T., Mykicki, N., Bayas, A., Then Bergh, F., Bittner, S., Hartung, H. P., Friese, M. A., Linker, R. A., Luessi, F., … German Competence Network Multiple Sclerosis (KKNMS) and the BIONAT Network. (2021). Sunlight exposure exerts immunomodulatory effects to reduce multiple sclerosis severity. *Proceedings of the National Academy of Sciences of the United States of America, 118* (1), e2018457118. Doi: 10.1073/pnas.2018457118

Reiter, R. J. (1991). Melatonin: the chemical expression of darkness. *Molecular and cellular endocrinology, 79* (1-3), C153–C158. Doi: 10.1016/0303-7207(91)90087-9

Akpinar, Z., Tokgöz, S., Gökbel, H., Okudan, N., Uğuz, F., & Yilmaz, G. (2008). The association of nocturnal serum melatonin levels with major depression in patients with acute multiple sclerosis. *Psychiatry research, 161* (2), 253–257. Doi: 10.1016/j.psychres.2007.11.022

Ghorbani, A., Salari, M., Shaygannejad, V., & Norouzi, R. (2013). The role of melatonin in the pathogenesis of multiple sclerosis: A case-control study. *International Journal of Preventive Medicine, 4* (Suppl 2), S180–S184.

Melamud, L., Golan, D., Luboshitzky, R., Lavi, I., & Miller, A. (2012). Melatonin dysregulation, sleep disturbances and fatigue in multiple sclerosis. *Journal of the neurological sciences, 314* (1-2), 37–40. Doi: 10.1016/j.jns.2011.11.003

Sandyk R. (1993). Multiple sclerosis: the role of puberty and the pineal gland in its pathogenesis. *The International journal of*

neuroscience, 68 (3-4), 209–225. Doi: 10.3109/00207459308994277

López-González, A., Álvarez-Sánchez, N., Lardone, P. J., Cruz-Chamorro, I., Martínez-López, A., Guerrero, J. M., Reiter, R. J., & Carrillo-Vico, A. (2015). Melatonin treatment improves primary progressive multiple sclerosis: a case report. *Journal of pineal research, 58* (2), 173–177. Doi: 10.1111/jpi.12203

Kang, J. C., Ahn, M., Kim, Y. S., Moon, C., Lee, Y., Wie, M. B., Lee, Y. J., & Shin, T. (2001). Melatonin ameliorates autoimmune encephalomyelitis through suppression of intercellular adhesion molecule-1. *Journal of veterinary science, 2* (2), 85–89.

Álvarez-Sánchez, N., Cruz-Chamorro, I., López-González, A., Utrilla, J. C., Fernández-Santos, J. M., Martínez-López, A., Lardone, P. J., Guerrero, J. M., & Carrillo-Vico, A. (2015). Melatonin controls experimental autoimmune encephalomyelitis by altering the T effector/regulatory balance. *Brain, behavior, and immunity, 50*, 101–114. Doi: 10.1016/j.bbi.2015.06.021

Chen, S. J., Huang, S. H., Chen, J. W., Wang, K. C., Yang, Y. R., Liu, P. F., Lin, G. J., & Sytwu, H. K. (2016). Melatonin enhances interleukin-10 expression and suppresses chemotaxis to inhibit inflammation in situ and reduce the severity of experimental autoimmune encephalomyelitis. *International immunopharmacology, 31*, 169–177. Doi: 10.1016/j.intimp.2015.12.020

Ghareghani, M., Dokoohaki, S., Ghanbari, A., Farhadi, N., Zibara, K., Khodadoust, S., Parishani, M., Ghavamizadeh, M., & Sadeghi, H. (2017). Melatonin exacerbates acute experimental autoimmune encephalomyelitis by enhancing the serum levels of lactate: A potential biomarker of multiple sclerosis progression.

Clinical and experimental pharmacology & physiology, 44 (1), 52–61. Doi: 10.1111/1440-1681.12678

Dudani, S. J., Kalhan, S., & Sharma, S. P. (2011). Vitamin D and multiple sclerosis: Potential pathophysiological role and clinical implications. *International journal of applied & basic medical research, 1* (2), 71–74. Doi: 10.4103/2229-516X.91146

Shaygannejad, V., Janghorbani, M., Ashtari, F., & Dehghan, H. (2012). Effects of adjunct low-dose vitamin d on relapsing-remitting multiple sclerosis progression: preliminary findings of a randomized placebo-controlled trial. *Multiple sclerosis international, 2012* (452541), 1-7. Doi: 10.1155/2012/452541

Simpson, S., Jr, Taylor, B., Blizzard, L., Ponsonby, A. L., Pittas, F., Tremlett, H., Dwyer, T., Gies, P., & van der Mei, I. (2010). Higher 25-hydroxyvitamin D is associated with lower relapse risk in multiple sclerosis. *Annals of neurology, 68* (2), 193–203. Doi: 10.1002/ana.22043

Munger, K. L., & Ascherio, A. (2011). Prevention and treatment of MS: studying the effects of vitamin D. *Multiple sclerosis, 17* (12), 1405–1411. Doi: 10.1177/1352458511425366

Holmøy, T., Torkildsen, Ø., Myhr, K. M., & Løken-Amsrud, K. I. (2012). Vitamin D supplementation and monitoring in multiple sclerosis: who, when and wherefore. *Acta neurologica Scandinavica. Supplementum,* (195), 63–69. Doi: 10.1111/ane.12028

Golan, D., Staun-Ram, E., Glass-Marmor, L., Lavi, I., Rozenberg, O., Dishon, S., Barak, M., Ish-Shalom, S., & Miller, A. (2013). The influence of vitamin D supplementation on melatonin status in patients with multiple sclerosis. *Brain, behavior, and immunity, 32*, 180–185. Doi: 10.1016/j.bbi.2013.04.010

Champney, T. H., Holtorf, A. P., Steger, R. W., & Reiter, R. J. (1984). Concurrent determination of enzymatic activities and substrate concentrations in the melatonin synthetic pathway within the same rat pineal gland. *Journal of neuroscience research, 11* (1), 59–66. Doi: 10.1002/jnr.490110107

Brzezinski A. (1997). Melatonin in humans. *The New England journal of medicine, 336* (3), 186–195. Doi: 10.1056/NEJM199701163360306

Reiter, R. J., Tan, D. X., Burkhardt, S., & Manchester, L. C. (2001). Melatonin in plants. *Nutrition reviews, 59* (9), 286–290. Doi: 10.1111/j.1753-4887.2001.tb07018.x

Reiter R. J. (1993). The melatonin rhythm: both a clock and a calendar. *Experientia, 49* (8), 654–664. Doi: 10.1007/BF01923947

Malpaux, B., Migaud, M., Tricoire, H., & Chemineau, P. (2001). Biology of mammalian photoperiodism and the critical role of the pineal gland and melatonin. *Journal of biological rhythms, 16* (4), 336–347. Doi: 10.1177/074873001129002051

Yamazaki, S., Goto, M., & Menaker, M. (1999). No evidence for extraocular photoreceptors in the circadian system of the Syrian hamster. *Journal of biological rhythms, 14* (3), 197–201. Doi: 10.1177/074873099129000605

Ruby, N. F., Brennan, T. J., Xie, X., Cao, V., Franken, P., Heller, H. C., & O'Hara, B. F. (2002). Role of melanopsin in circadian responses to light. *Science, 298* (5601), 2211–2213. Doi: 10.1126/science.1076701

Gamlin, P. D., McDougal, D. H., Pokorny, J., Smith, V. C., Yau, K. W., & Dacey, D. M. (2007). Human and macaque pupil responses driven by melanopsin-containing retinal ganglion cells. *Vision research, 47* (7), 946–954. Doi: 10.1016/j.visres.2006.12.015

Paul, K. N., Saafir, T. B., & Tosini, G. (2009). The role of retinal photoreceptors in the regulation of circadian rhythms. *Reviews in endocrine & metabolic disorders, 10* (4), 271–278. Doi: 10.1007/s11154-009-9120-x

Hattar, S., Liao, H. W., Takao, M., Berson, D. M., & Yau, K. W. (2002). Melanopsin-containing retinal ganglion cells: architecture, projections, and intrinsic photosensitivity. *Science, 295* (5557), 1065–1070. Doi: 10.1126/science.1069609

Mure, L. S., Rieux, C., Hattar, S., & Cooper, H. M. (2007). Melanopsin-dependent nonvisual responses: evidence for photopigment bistability in vivo. *Journal of biological rhythms, 22* (5), 411–424. Doi: 10.1177/0748730407306043

Melyan, Z., Tarttelin, E. E., Bellingham, J., Lucas, R. J., & Hankins, M. W. (2005). Addition of human melanopsin renders mammalian cells photoresponsive. *Nature, 433* (7027), 741–745. Doi: 10.1038/nature03344

Provencio, I. (2010). Circadian Photoreception. Darlene A. Dartt, Joseph C. Besharse, Reza Dana (Ed.), *Encyclopedia of the Eye* (p. 290-295). Boston: Elsevier/Academic Press.

Reppert, S. M., Weaver, D. R., Rivkees, S. A., & Stopa, E. G. (1988). Putative melatonin receptors in a human biological clock. *Science, 242* (4875), 78–81. Doi: 10.1126/science.2845576

Gooley, J. J., Lu, J., Fischer, D., & Saper, C. B. (2003). A broad role for melanopsin in nonvisual photoreception. *The Journal of neuroscience : the official journal of the Society for Neuroscience, 23* (18), 7093–7106. Doi: 10.1523/JNEUROSCI.23-18-07093.2003

Brainard, G. C., Hanifin, J. P., Greeson, J. M., Byrne, B., Glickman, G., Gerner, E., & Rollag, M. D. (2001). Action spectrum for melatonin regulation in humans: evidence for a novel circadian photoreceptor. *The Journal of neuroscience : the official journal of*

the Society for Neuroscience, 21 (16), 6405–6412. Doi: 10.1523/JNEUROSCI.21-16-06405.2001

McDougal, D. H., & Gamlin, P. D. (2010). The influence of intrinsically-photosensitive retinal ganglion cells on the spectral sensitivity and response dynamics of the human pupillary light reflex. *Vision research, 50* (1), 72–87. Doi: 10.1016/j.visres.2009.10.012

Maynard, M. L., Zele, A. J., & Feigl, B. (2015). Melanopsin-mediated post-illumination pupil response in early age-related macular degeneration. *Investigative ophthalmology & visual science, 56* (11), 6906–6913. Doi: 10.1167/iovs.15-17357

Annweiler, C., Beauchet, O., Bartha, R., Graffe, A., Milea, D., & Montero-Odasso, M. (2013). Association between serum 25-hydroxyvitamin D concentration and optic chiasm volume. *Journal of the American Geriatrics Society, 61* (6), 1026–1028. Doi: 10.1111/jgs.12249

Suzumura, A. (2017). Effect of vitamin D on blood–brain barrier function in multiple sclerosis. *Clinical and Experimental Neuroimmunology, 8* (3), 180. Doi: 10.1111/cen3.12410

Alluri, H., Wilson, R. L., Shaji, C. A., Wiggins-Dohlvik, K., Patel, S., Liu, Y., Peng, X., Beeram, M. R., Davis, M. L., Huang, J. H., & Tharakan, B. (2016). Melatonin Preserves Blood-Brain Barrier Integrity and Permeability via Matrix Metalloproteinase-9 Inhibition. *PLoS ONE, 11* (5), e0154427. Doi: 10.1371/journal.pone.0154427

Peacock M. (2010). Calcium metabolism in health and disease. *Clinical journal of the American Society of Nephrology : CJASN, 5* Suppl 1, S23–S30. Doi: 10.2215/CJN.05910809

Sjöblom, M., Säfsten, B., & Flemström, G. (2003). Melatonin-induced calcium signaling in clusters of human and rat

duodenal enterocytes. *American journal of physiology. Gastrointestinal and liver physiology*, *284* (6), G1034–G1044. Doi: 10.1152/ajpgi.00500.2002

Christakos S. (2012). Recent advances in our understanding of 1,25-dihydroxyvitamin D(3) regulation of intestinal calcium absorption. *Archives of biochemistry and biophysics, 523* (1), 73–76. Doi: 10.1016/j.abb.2011.12.020

Devine, A., Wilson, S. G., Dick, I. M., & Prince, R. L. (2002). Effects of vitamin D metabolites on intestinal calcium absorption and bone turnover in elderly women. *The American journal of clinical nutrition, 75* (2), 283–288. Doi: 10.1093/ajcn/75.2.283

Fraser D. R. (1980). Regulation of the metabolism of vitamin D. *Physiological reviews, 60* (2), 551–613. Doi: 10.1152/physrev.1980.60.2.551

Li, Y. C., Pirro, A. E., Amling, M., Delling, G., Baron, R., Bronson, R., & Demay, M. B. (1997). Targeted ablation of the vitamin D receptor: An animal model of vitamin D-dependent rickets type II with alopecia. *Proceedings of the National Academy of Sciences, 94* (18), 9831-9835. Doi: 10.1073/pnas.94.18.9831

Pansu, D., Bellaton, C., Roche, C., & Bronner, F. (1983). Duodenal and ileal calcium absorption in the rat and effects of vitamin D. *The American journal of physiology, 244* (6), G695–G700. Doi: 10.1152/ajpgi.1983.244.6.G695

Sheikh, M. S., Ramirez, A., Emmett, M., Santa Ana, C., Schiller, L. R., & Fordtran, J. S. (1988). Role of vitamin D-dependent and vitamin D-independent mechanisms in absorption of food calcium. *The Journal of clinical investigation, 81* (1), 126–132. Doi: 10.1172/JCI113283

Karaki, H., & Weiss, G. B. (1984). Calcium channels in smooth muscle. *Gastroenterology, 87* (4), 960–970.

Somlyo, A. P., & Somlyo, A. V. (1994). Signal transduction and regulation in smooth muscle. *Nature, 372* (6503), 231–236. Doi: 10.1038/372231a0

Giraldi, G., Fioravanti, A., De Luca d'Alessandro, E., Palmery, M., & Martinoli, L. (2015). Investigation of the effects of vitamin D and calcium on intestinal motility: In vitro tests and implications for clinical treatment. *Acta pharmaceutica (Zagreb, Croatia), 65* (3), 343–349. Doi: 10.1515/acph-2015-0023

Kong, J., Zhang, Z., Musch, M. W., Ning, G., Sun, J., Hart, J., Bissonnette, M., & Li, Y. C. (2008). Novel role of the vitamin D receptor in maintaining the integrity of the intestinal mucosal barrier. *American journal of physiology. Gastrointestinal and liver physiology, 294* (1), G208–G216. Doi: 10.1152/ajpgi.00398.2007

Koenig, J., & Cote, N. (2006). Equine gastrointestinal motility--ileus and pharmacological modification. *The Canadian veterinary journal = La revue veterinaire canadienne, 47* (6), 551–559.

Parkman, H. P., Hasler, W. L., Fisher, R. S., & American Gastroenterological Association (2004). American Gastroenterological Association technical review on the diagnosis and treatment of gastroparesis. *Gastroenterology, 127* (5), 1592–1622. Doi: 10.1053/j.gastro.2004.09.055

Gill, K. P., Chia, Y. W., Henry, M. M., & Shorvon, P. J. (1994). Defecography in multiple sclerosis patients with severe constipation. *Radiology, 191* (2), 553–556. Doi: 10.1148/radiology.191.2.8153339

Wiesel, P. H., Norton, C., Roy, A. J., Storrie, J. B., Bowers, J., & Kamm, M. A. (2000). Gut focused behavioural treatment

(biofeedback) for constipation and faecal incontinence in multiple sclerosis. *Journal of neurology, neurosurgery, and psychiatry, 69* (2), 240–243. Doi: 10.1136/jnnp.69.2.240

Enck, P., Van der Voort, I. R., & Klosterhalfen, S. (2009). Biofeedback therapy in fecal incontinence and constipation. *Neurogastroenterology and motility, 21* (11), 1133–1141. Doi: 10.1111/j.1365-2982.2009.01345.x

McClurg, D., Hagen, S., Hawkins, S., & Lowe-Strong, A. (2011). Abdominal massage for the alleviation of constipation symptoms in people with multiple sclerosis: a randomized controlled feasibility study. *Multiple sclerosis, 17* (2), 223–233. Doi: 10.1177/1352458510384899

Yacyshyn, B., Meddings, J., Sadowski, D., & Bowen-Yacyshyn, M. B. (1996). Multiple sclerosis patients have peripheral blood CD45RO+ B cells and increased intestinal permeability. *Digestive diseases and sciences, 41* (12), 2493–2498. Doi: 10.1007/BF02100148

Nathens, A. B., & Marshall, J. C. (1996). Sepsis, SIRS, and MODS: what's in a name?. *World journal of surgery, 20* (4), 386–391. Doi: 10.1007/s002689900061

Nieuwenhuijzen, G. A., & Goris, R. J. (1999). The gut: the 'motor' of multiple organ dysfunction syndrome?. *Current opinion in clinical nutrition and metabolic care, 2* (5), 399–404. Doi: 10.1097/00075197-199909000-00008

Hierholzer, C., Kalff, J. C., Chakraborty, A., Watkins, S. C., Billiar, T. R., Bauer, A. J., & Tweardy, D. J. (2001). Impaired gut contractility following hemorrhagic shock is accompaied by IL-6 and G-CSF production and neutrophil infiltration. *Digestive diseases and sciences, 46* (2), 230–241. Doi: 10.1023/a:1005524021552

Chieveley-Williams, S., & Hamilton-Davies, C. (1999). The role of the gut in major surgical postoperative morbidity. International anesthesiology clinics, 37 (2), 81–110. Doi: 10.1097/00004311-199903720-00006

Overhaus, M., Tögel, S., Pezzone, M. A., & Bauer, A. J. (2004). Mechanisms of polymicrobial sepsis-induced ileus. American journal of physiology. *Gastrointestinal and liver physiology, 287* (3), G685–G694. Doi: 10.1152/ajpgi.00359.2003

Swank, G. M., & Deitch, E. A. (1996). Role of the gut in multiple organ failure: bacterial translocation and permeability changes. *World journal of surgery, 20* (4), 411–417. Doi: 10.1007/s002689900065

Zheyu, C., Qinghui, Q., & Lunan, Y. (2007). Roles of calcium and IP3 in impaired colon contractility of rats following multiple organ dysfunction syndrome. *Brazilian journal of medical and biological research = Revista brasileira de pesquisas medicas e biologica, 40* (10), 1389–1397. Doi: 10.1590/s0100-879x2006005000147

Wang, Y., & Kasper, L. H. (2014). The role of microbiome in central nervous system disorders. *Brain, behavior, and immunity, 38*, 1–12. Doi: 10.1016/j.bbi.2013.12.015

Wolfson, C., & Talbot, P. (2002). Bacterial infection as a cause of multiple sclerosis. *Lancet, 360* (9330), 352–353. Doi: 10.1016/S0140-6736(02)09603-4

Chen, J., Chia, N., Kalari, K. R., Yao, J. Z., Novotna, M., Paz Soldan, M. M., Luckey, D. H., Marietta, E. V., Jeraldo, P. R., Chen, X., Weinshenker, B. G., Rodriguez, M., Kantarci, O. H., Nelson, H., Murray, J. A., & Mangalam, A. K. (2016). Multiple sclerosis patients have a distinct gut microbiota compared to healthy controls. *Scientific reports, 6,* 28484. Doi: 10.1038/srep28484

Tremlett, H., Fadrosh, D. W., Faruqi, A. A., Zhu, F., Hart, J., Roalstad, S., Graves, J., Lynch, S., & Waubant, E. (2016). Gut microbiota in early pediatric multiple sclerosis: A case−control study. *European Journal of Neurology, 23* (8), 1308-1321. Doi: 10.1111/ene.13026

Braniste, V., Al-Asmakh, M., Kowal, C., Anuar, F., Abbaspour, A., Tóth, M., Korecka, A., Bakocevic, N., Ng, L. G., Kundu, P., Gulyás, B., Halldin, C., Hultenby, K., Nilsson, H., Hebert, H., Volpe, B. T., Diamond, B., & Pettersson, S. (2014). The gut microbiota influences blood-brain barrier permeability in mice. *Science translational medicine, 6* (263), 263ra158. Doi: 10.1126/scitranslmed.3009759

Poltorak, A., He, X., Smirnova, I., Liu, Y., Huffel, C. V., Du, X., Birdwell, D., Alejos, E., Silva, M., Galanos, C., Freudenberg, M., Ricciardi-Castagnoli, P., Layton, B., & Beutler, B. (1998). Defective LPS signaling in c3h/hej and c57bl/10sccr mice: mutations in tlr4 gene. *Science, 282* (5396), 2085-2088. Doi: 10.1126/science.282.5396.2085

Harmsen, H. J. M. (2016). The human gut microbiota. Andreas Schwiertz (Ed.), *Microbiata of the Human Body* (95-108). Switzerland: Springer

Jiang, T., Gao, X., Wu, C., Tian, F., Lei, Q., Bi, J., Xie, B., Wang, H. Y., Chen, S., & Wang, X. (2016). Apple-derived pectin modulates gut microbiota, improves gut barrier function, and attenuates metabolic endotoxemia in rats with diet-induced obesity. *Nutrients, 8* (3), 126. Doi: 10.3390/nu8030126

Schumann, R. R., Leong, S. R., Flaggs, G. W., Gray, P. W., Wright, S. D., Mathison, J. C., Tobias, P. S., & Ulevitch, R. J. (1990). Structure and function of lipopolysaccharide binding

protein. *Science, 249* (4975), 1429–1431. Doi: 10.1126/science.2402637

Dunzendorfer, S., Lee, H. K., Soldau, K., & Tobias, P. S. (2004). TLR4 is the signaling but not the lipopolysaccharide uptake receptor. *Journal of immunology, 173* (2), 1166–1170. Doi: 10.4049/jimmunol.173.2.1166

da Silva Correia, J., Soldau, K., Christen, U., Tobias, P. S., & Ulevitch, R. J. (2001). Lipopolysaccharide is in close proximity to each of the proteins in its membrane receptor complex. transfer from CD14 to TLR4 and MD-2. The *Journal of biological chemistry, 276* (24), 21129–21135. Doi: 10.1074/jbc.M009164200

Akira, S., & Takeda, K. (2004). Toll-like receptor signalling. nature reviews. *Immunology, 4* (7), 499–511. Doi: 10.1038/nri1391

Chow, J. C., Young, D. W., Golenbock, D. T., Christ, W. J., & Gusovsky, F. (1999). Toll-like receptor-4 mediates lipopolysaccharide-induced signal transduction. *The Journal of biological chemistry, 274* (16), 10689–10692. Doi: 10.1074/jbc.274.16.10689

Buchholz, B. M., & Bauer, A. J. (2010). Membrane TLR signaling mechanisms in the gastrointestinal tract during sepsis. *Neurogastroenterology and motility, 22* (3), 232–245. Doi: 10.1111/j.1365-2982.2009.01464.x

Zhang, G., & Ghosh, S. (2000). Molecular mechanisms of NF-kappaB activation induced by bacterial lipopolysaccharide through Toll-like receptors. *Journal of endotoxin research, 6* (6), 453–457. Doi: 10.1179/096805100101532414

Kawai, T., & Akira, S. (2010). The role of pattern-recognition receptors in innate immunity: update on Toll-like receptors. *Nature immunology, 11* (5), 373–384. Doi: 10.1038/ni.1863

Wang, Y., Marling, S. J., McKnight, S. M., Danielson, A. L., Severson, K. S., & Deluca, H. F. (2013). Suppression of experimental autoimmune encephalomyelitis by 300-315nm ultraviolet light. *Archives of biochemistry and biophysics, 536* (1), 81–86. Doi: 10.1016/j.abb.2013.05.010

Hart, P. H., Gorman, S., & Finlay-Jones, J. J. (2011). Modulation of the immune system by UV radiation: more than just the effects of vitamin D?. *Nature reviews. Immunology, 11* (9), 584–596. Doi: 10.1038/nri3045

Røsjø, E., Steffensen, L. H., Jørgensen, L., Lindstrøm, J. C., Šaltytė Benth, J., Michelsen, A. E., Aukrust, P., Ueland, T., Kampman, M. T., Torkildsen, Ø., & Holmøy, T. (2015). Vitamin D supplementation and systemic inflammation in relapsing-remitting multiple sclerosis. *Journal of neurology, 262* (12), 2713–2721. Doi: 10.1007/s00415-015-7902-5

Cantorna, M. T., Humpal-Winter, J., & DeLuca, H. F. (1999). Dietary calcium is a major factor in 1,25-dihydroxycholecalciferol suppression of experimental autoimmune encephalomyelitis in mice. *The Journal of nutrition, 129* (11), 1966–1971. Doi: 10.1093/jn/129.11.1966

Irving, A. A., Marling, S. J., Plum, L. A., & DeLuca, H. F. (2017). Suppression of experimental autoimmune encephalomyelitis by ultraviolet light is not mediated by isomerization of urocanic acid. *BMC neuroscience, 18* (1), 8. Doi: 10.1186/s12868-016-0323-2

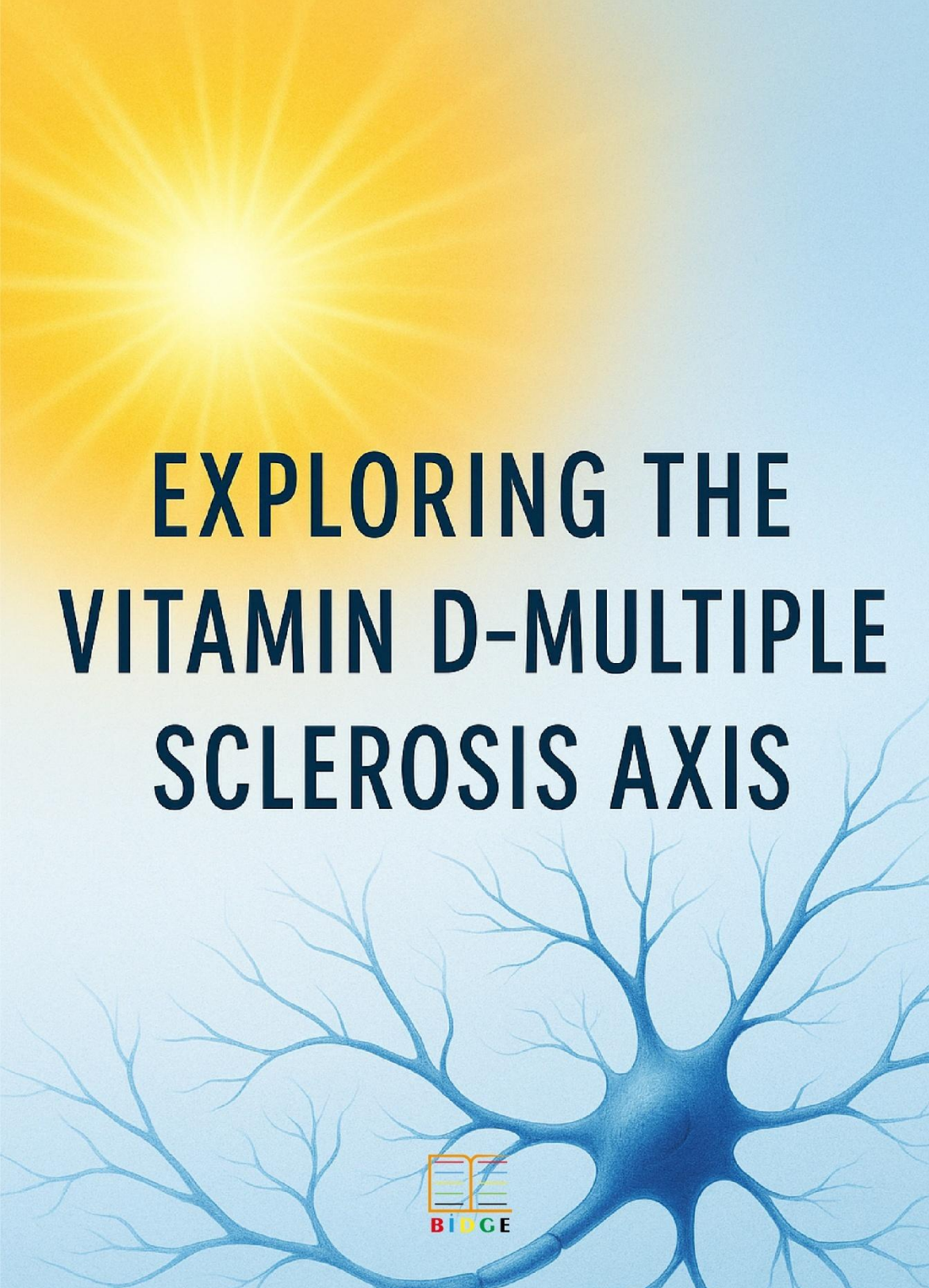
Holick M. F. (2008). Sunlight, UV-radiation, vitamin D and skin cancer: how much sunlight do we need?. *Advances in experimental medicine and biology, 624,* 1–15. Doi: 10.1007/978-0-387-77574-6_1

De Schepper, H. U., De Man, J. G., Van Nassauw, L., Timmermans, J. P., Herman, A. G., Pelckmans, P. A., & De Winter,

B. Y. (2007). Acute distal colitis impairs gastric emptying in rats via an extrinsic neuronal reflex pathway involving the pelvic nerve. *Gut, 56* (2), 195–202. Doi: gut.2006.104745

Gangula, P. R., Sekhar, K. R., & Mukhopadhyay, S. (2011). Gender bias in gastroparesis: is nitric oxide the answer?. *Digestive diseases and sciences, 56* (9), 2520–2527. Doi: 10.1007/s10620-011-1735-6

EXPLORING THE VITAMIN D–MULTIPLE SCLEROSIS AXIS



BIDGE