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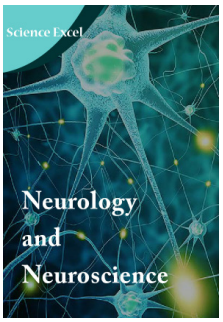
Review Article



Chronic Inflammatory Demyelinating Polyneuropathy (CIDP): Extension of Standard Therapy With Vitamin D Supplementation Based on Pathophysiology

Hans-Klaus Goischke

Internal Medicine, Rehabilitation, Social Medicine, D-97769 Bad Brückenau, Hochwaldstrasse 2; Germany

*Correspondence

Dr. med. Dipl.-Med. Hans-Klaus Goischke

Internal medicine, Rehabilitation, Social Medicine, D-97769 Bad Brückenau, Hochwaldstrasse 2; Germany

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Abstract

Chronic immune-mediated diseases of the peripheral nervous system, such as chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), are primarily characterized by demyelination. To attenuate persistent inflammation, early, continuous, synergistic vitamin D supplementation, with reduced immune tolerance, is a standard treatment option for effective treatment. The misguided autoimmune mechanisms persist for a lifelong. Calcitriol influences the players involved in CIDP, such as CD4+ helper T cells, CD8+ T cells, B cells, macrophages, T regulatory cells, complement activation, NLRP3 inflammasomes, and a dysfunctional blood-nerve barrier. 1,25-dihydroxyvitamin D3 is also a target of the immune-activating, pro-inflammatory cytokines and chemokines involved, such as TNF-alpha, INF-gamma, IL-2, and IL-6. It promotes the formation of the anti-inflammatory cytokine IL-10.

Immunological mechanisms indicate the potentiation of IVIG and glucocorticoid therapy by calcitriol. The protective effect of vitamin D, added to standard therapy, may offer promise for a more effective treatment of chronic immune-mediated neuropathies. The use of serum neurofilament light chain (NfL) and serum glial fibrillary acidic protein (GFAP) determination will reflect the dynamics of the disease progression and determine the intensity of treatment. The effect of vitamin D supplementation depends on the individual vitamin D response and the achieved serum 25-hydroxyvitamin D level. All therapeutic options must be used to slow chronic inflammation, demyelination, and progressive neurological deterioration in immune-mediated neuropathies.

Introduction

Increasing scientific attention up to the year 2025 has accumulated knowledge about biologically plausible mechanisms by which vitamin D deficiency leads to adverse consequences on the central nervous system (CNS) [1,2]. Multiple sclerosis (MS) has been and remains the focus of research [3]. The effects of 1,25-dihydroxy-vitamin D 3 (1,25(OH)2D3/ calcitriol), a pleiotropic secosteroid hormone on the peripheral nervous system (PN) have not been the focus of attention to date. Particularly in treatment recommendations/guidelines for chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) and recommendations for local practice, attention to vitamin D (Vit D) as a tolerogenic adjuvant is limited [4,5].

CIDP is the most common peripheral neuropathy (PNP), with a prevalence of approximately 3 per 100,000 (1.0–8.9) and an incidence of less than 1–1.6 per 100,000 per year [6,7,8]. The pooled prevalence rate is 2.81/100,000 [9].

CIDP is an immune-mediated peripheral nerve (PN) syndrome characterized by a progressive or relapsing-remitting course lasting more than eight weeks and typically resulting in proximal and distal weakness and sensory loss in the extremities [10-13].

CIDP is a heterogeneous, clinically well-described disease and is immunologically mediated by numerous, still poorly understood mechanisms and causes significant disability, particularly in treatment-refractory individuals with CIDP (PwCIDP) [14-16].

However, there is no single pathognomonic marker yet. Cell-mediated, humoral, and complement pathways, inflammasomes, and cytokine-driven immune responses synergistically target the myelin of the peripheral nervous system (PNS) [13, 14]. Nerve root and peripheral nerve inflammation leads to segmental demyelination and is also characterized by remyelination [17].

Vitamin D deficiency was already verified in 2014 in patients with primary immune-mediated peripheral neuropathies, particularly in Guillain-Barré syndrome (GBS) and CIDP, and monitoring of serum 25(OH)D [calcifediol] levels (s25(OH)D) with the consequence of achieving an optimal s25(OH)D value to alleviate symptoms was recommended [18],

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the transformation of vitamin D supplementation (vit D suppl) into practice is a gradual process.

Rapid diagnosis and treatment are essential to prevent mortality and ongoing morbidity [17]. Hypovitaminosis D is a relevant risk factor for acute acquired immune-mediated inflammatory demyelinating diseases, even in childhood [19]. The potential for improving the outcome of CIDP through supportive vit D suppl based on pathophysiological findings should be highlighted. Although the beneficial synergism of vitamin D is not yet incorporated into a therapeutic concept, it does offer a side-effect-free add-on therapy compared to standard therapy and newer therapies (B-cell inhibition, proteasome inhibitors, Fc receptor modulation, CAR-T cell therapy, etc.) with appropriate laboratory monitoring. This practice- and patient-oriented, non-systematic review is intended to promote the accelerated transfer of scientific findings (up to 2025) to PwCIDP. The currently known complex pathophysiological mechanisms of vitamin D supplementation are promising and should encourage therapists from various disciplines to improve the course of the disease, especially in cases of therapy resistance.

Etiology and pathophysiology of CIDP

Although the most common cases of CIDP are idiopathic (familial/genetic), there is evidence of relationships between previous diseases (including respiratory and intestinal infections, HIV, hepatitis B, C, E, EBV, CMV, HTLV-1, Zika virus, Bartonella henselae, Mycoplasma pneumonia, systemic lupus erythematosus) [20-23]. Three players are in the focus of pathoimmunology:

T cell , B cell and complement [24].

By 2025, a chorus of diverse immune components, such as macrophages, T cells, B cells, activated antigen-presenting cells, cytokines, and the complement system, have been verified to be involved in CIDP pathogenesis [15,25-28]. Elevated TNF-alpha levels in PwCIDP during the active phase of the disease were already verified 25 years ago [29].

Further details in Caballero-Àvila et al. [13].

Cellular immune response

Immune homeostasis is disturbed in autoimmune diseases by dysregulation of pathogenic effector cells (Th17) and Treg cells [30].

The activity of proinflammatory CD4+ T cells, IFN -gamma-producing Th1 and IL-17-producing Th17 cells, and polyfunctional CD8+ T cells is increased, and the anti-inflammatory regulatory function of CD4+CD25(high)FoxP3+ regulatory T cells (Treg) is reduced [31,32]. Treg dysfunction (defect in suppressive function) is a key factor in the underlying immunological dysfunction [32,33]. CD4+, CD8+, and macrophage infiltrates have been verified histopathological in the endoneurium at an early stage [34].

1,25(OH)2D3 inhibits the differentiation of Th17 cells by regulating NF-kB activity and IL-17 expression [35]. Calcitriol decreases IFN-gamma secretion, increases IL-10 production, and generates both conventional CD25+Foxp3+ regulatory T cells (Tregs) and IL-10-secreting regulatory cells type I (Tr1), which are essential for immune homeostasis [36].

Both resident and infiltrating macrophages are at the forefront of disrupting the integrity of the blood-nerve barrier (BNB). The inflammatory process is promoted by CD4+-activated cellular release of cytokines and chemokines, leading to further macrophage activation [14,37,38]. The inflammatory process is potentiated by high CD8+ cytotoxic T cell activity [37] (Figure 1).

Network of cytokines and chemokines in PwCIDP

Previous evidence has shown that interleukins (IL)-2, IL-6, IL-17, CXCL 10, CCL3, and tumor necrosis factor alpha (TNF-α) are elevated in PwCIDP and orchestrate inflammation [39,40]. This composition of cytokines and chemokines determines the continuous recruitment of immune cells and weakens the integrity of the BNB, allowing antibodies to gain access to the endoneurium [39,41,42,43].

Because IL-6 plays a crucial role in CIDP as an inflammatory cytokine and in the immune response through differentiation and activation of T cells, influencing this dysregulation is a therapeutic target [44-46]. Furthermore, IL-6 induces immunoglobulin production [47].

Calcitriol has been shown to inhibit TNF-alpha levels and increase IL-6 serum levels in various contexts and thus slow down inflammation. Vit D supplementation could have a dampening effect on inflammation [48-56].

Disruption of the blood-nerve barrier (BNP)- 1,25OH)2D3 as a sealing tool

If the pathogenesis of CIDP is characterized by the early breakdown of BNP and the transfer of activated T cells, macrophages, antibodies and complement is thus only possible, all therapeutic attempts should be made to reduce the increased permeability in the long term and effectively.

While the blood-brain barrier (BBB) has been well characterized by research on multiple sclerosis (MS) in recent decades, the BNB of the peripheral nervous system is less well defined [57]. Molecular, structural, and functional similarities exist between the BBB and BNB [57]. For sealing the barriers, both BBB and BNB, Tight (TJ) is involved. Claudins have an essential barrier function and occludine ensures tightness [58].

In multiple sclerosis (MS), the protective effect of calcitriol on the fragile BBB has been explained by upregulation of TJ proteins and downregulation of adhesion molecules [59,60]. In experiments, 1,25(OH)2D3 could inhibit the downregulation of zonula occludens (ZO-1) [61]. Claudin-5, a member of the TJ, which is a paracellular permeability regulator, is present in both the BBB and BNB [15,62-64].

However, PwCIDP shows a significant reduction in serum levels of Clauding-5 and translocated ZO-1 [15,65,66]. 1,25(OH)2D3 was able to reverse the decrease in the expression of TJs, zonula occludens , claudin-5, and occludin [67]. A deficiency of VDR (vitamin D receptors) led to a reduction of claudin-5 [68]. Experimentally, it was shown that vitamin D deficiency reduced the expression of the tight junction proteins occludin and claudin-5 [69]. However, calcitriol could increase claudin-5 [70].

Vitamin D regulates neurotrophic factors. 1,25(OH)2D3) induces the expression of nerve factor (NGF) in neurons. Neural stem cells upregulate brain-derived growth factor (BDNF), glial cell lineage-derived nerve factor (GDNF), and ciliary neurotrophic factor (CNTF) in the presence of calcitriol [71]. These effects may have a positive impact on the immune homeostasis of PwCIDP, as they showed a reduction in BDNF, GDNF, and granulocyte-macrophage colony-stimulating factors (GM-CSF) [28].

Oxidative stress is also associated with demyelinating diseases [72,73]. However, oxidative stress is reduced at relevant serum 25(OH)D levels >30 ng/mL. Optimal 25(OH)D levels are a prerequisite, as suboptimal levels lead to the opposite [71].

Macrophages – an active element in the autoimmune process in CIDP

Because macrophages (MK) are involved in autoimmune neuropathies, they may also be a therapeutic target of 1,25(OH)2D3. Polarization of classically activated MK (M1) to alternatively activated MK (M2) by calcitriol produces an immunosuppressive effect [74-76]. The balance between these two subsets is restored [77].

B cell homeostasis is disturbed in CIDP

B cell homeostasis is significantly altered in CIDP [27]. In PwCIDP , a reduction in naive B cells, plasma cells, and regulatory B cells (Breg cells) as well as an increase in the proportion of switched memory B cells has been observed. The ratio of memory B cells in the peripheral blood and IL-6 expression levels are associated with the severity of peripheral nerve (PN) injury [27].

Treg cells in PwCIDP

PwCIDP showed a significant reduction in the number and suppressive function of Tregs [28,78]. (Figure 2).

1,25(OH)2D3 could increase the number of tolerogenic Increase Treg cells and promote the necessary number even in old age, thus contributing to homeostasis [28, 79-82].

MicroRNAs as a feature of an effective and controlled immune response

The relevance of Treg cells is supported by the finding that they prevent aberrant immune responses and thus have a protective effect against autoimmunity. microRNA-142 has been identified as a central regulator of the development, homeostasis and function of Treg cells.. MicroRNA-142 attenuates IFN-gamma production and reactivity [83,84].

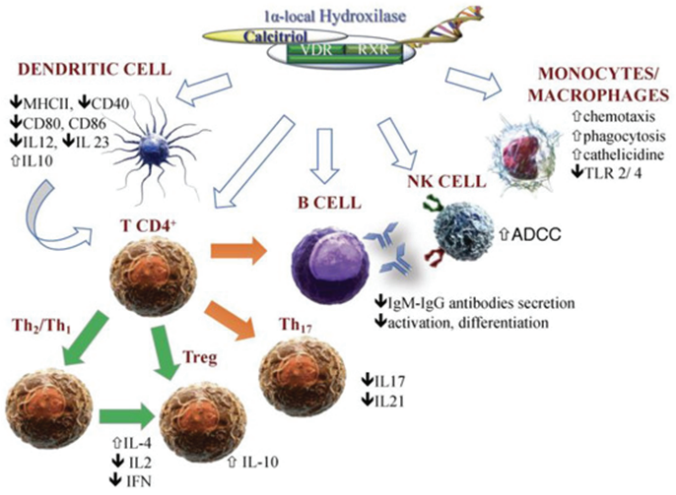


Figure 1. *Vitamin D and immune cells crosstalk. Vitamin D (calcitriol) directly and indirectly influences and regulates both innate and adaptive immune cells, which widely express the vitamin D receptor (VDR). RXR—retinoic acid receptor; NK—natural killer cells; ADCC—antibody-dependent cell-mediated cytotoxicity; IL—interleukin; MHCII—major histocompatibility complex class II; Th—T helper; TLR—toll-like receptor; green arrow—stimulation; orange arrow—inhibition. Original Figure from: Gallo D, Baci D, Kustrimovic N, Lanzo N, Patera B, Tanda ML, Piantanida E, Mortara L. How Does Vitamin D Affect Immune Cells Crosstalk in Autoimmune Diseases? International Journal of Molecular Sciences. 2023; 24(5):4689. https://doi.org/10.3390/ijms24054689 [80].*

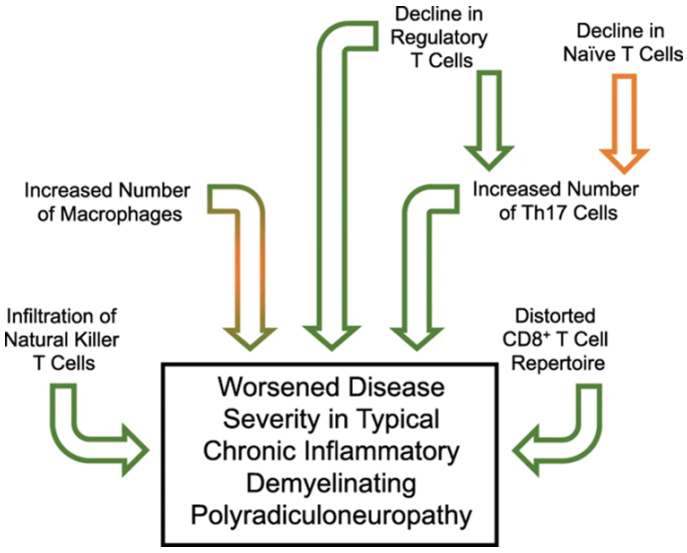


Figure 2. *Proposed mechanism of age and immunological contributions to typical CIDP pathology. In CIDP, there is a decline in regulatory T cells which are opposite to the age-related increase in these cells. In combination with a decline in naïve T cells with age, this May contribute to the CIDP- related increase in Th17 cells, thus creating an imbalance in Tregs and Th17 cells. due to dysregulation of the immune system, this May allow for further pathological contributions of the infiltrating natural killer T cells and distorted CD8+ T cells repertoire seen in CIDP. Also, with age, there is an increase in macrophages within the peripheral nerve and in combination with an increase in macrophages due to CIDP, and this could contribute to an age-related increase in disease severity. Orange arrows = age-related contribution ; green arrows = disease-related contribution; combination of green and orange arrows = cumulative contribution of age and disease. Original Figure from: Hagen, KM, Ousman, SS The immune response and aging in chronic inflammatory demyelinating polyradiculoneuropathy. J Neuroinflammation 2021;18, 78. https://doi.org/10.1186/s12974-021-02113-2 [28].*

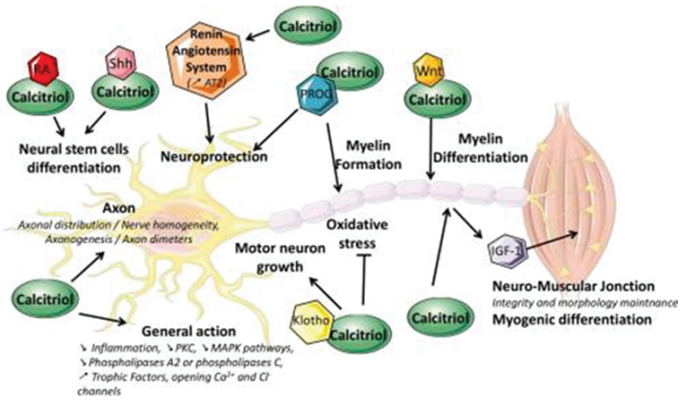


Figure 3. *Schematic representation of the putative roles of calcitriol in the peripheral nervous system. IGF-1, insulin-like growth factor-1; MAPK, mitogen activated protein kinase; PKC, protein kinase C; PROG, progesterone ; RA, retinoic acid ; Shh, Sonic hedgehog . Original illustration from: Faye PA, Poumeaud F, Miressi F, Lia AS, Demiot C, Magy L, Favreau F, Sturtz FG. Focus on 1,25-Dihydroxyvitamin D3 in the Peripheral Nervous system. Front Neurosci . 2019; 13:348. doi: 10.3389/fnins.2019.00348. [88].*

MicroRNA is modulated by vitamin D [85]. There is evidence that vitamin D alters the expression of enzymes involved in microRNA biogenesis as well as the direct and indirect induction of microRNA transcription [85]. The regulation of mRNA levels via microRNA signaling is recognized as a potential mechanism of action of calcitriol [86]. Increasing data show an influence of calcitriol on microRNA in various diseases [87]. The role of calcitriol on the peripheral nervous system is complex and multifaceted [88]. (Figure 3)

Role of the complement pathway in CIDP

There is extensive evidence for complement activation (CS) both systemically and in the PN in CIDP. It is suspected that persistent complement activity contributes to the chronicity of CIDP, and IVIG does not significantly reduce activation in the long term [38,89]. Elevated C5a levels have been observed in serum and CSF in PwCDIP [26]. On the other hand, reduced severity, demyelination, and inflammation have been verified in complement deficiency [15,90,91].

The CS is a complex system and an effector of innate and adaptive humoral immunity, and disturbances in its regulation trigger various neurological autoimmune diseases [92]. Autoantibodies can activate the CS and lead to tissue damage. Once activated, the complement cascade can trigger numerous local and systemic effects [93]. C5a subsequently leads to the proliferation and survival of effector T cells and simultaneously inhibits the induction and function of Treg cells; calcitriol counteracts this [79,82,94]. On the other hand, complement inhibitors may influence the adaptive immune response by reducing the stimulation of dendritic cells, T cells, and B cells via complement receptors [93,94].

Early intervention in inappropriate complement activation or control at the onset of CIDP should be a goal in PwCIDP . The theoretical basis for the influence of 1,25(OH)2D3 is provided by several observations. The vitamin DBP-[VitD binding protein]-VDR axis is crucial for maintaining immune homeostasis [95]. (Figure 4)

Vitamin D-binding protein (DBD) is a multifunctional plasma protein that can significantly enhance the chemotactic response to the complement fragment C5a. 1,25(OH)2D3 bound to DBP specifically inhibits the co-chemotactic activity of C5a [96].

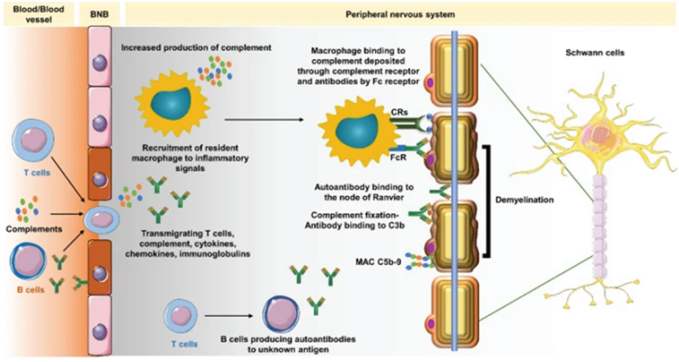


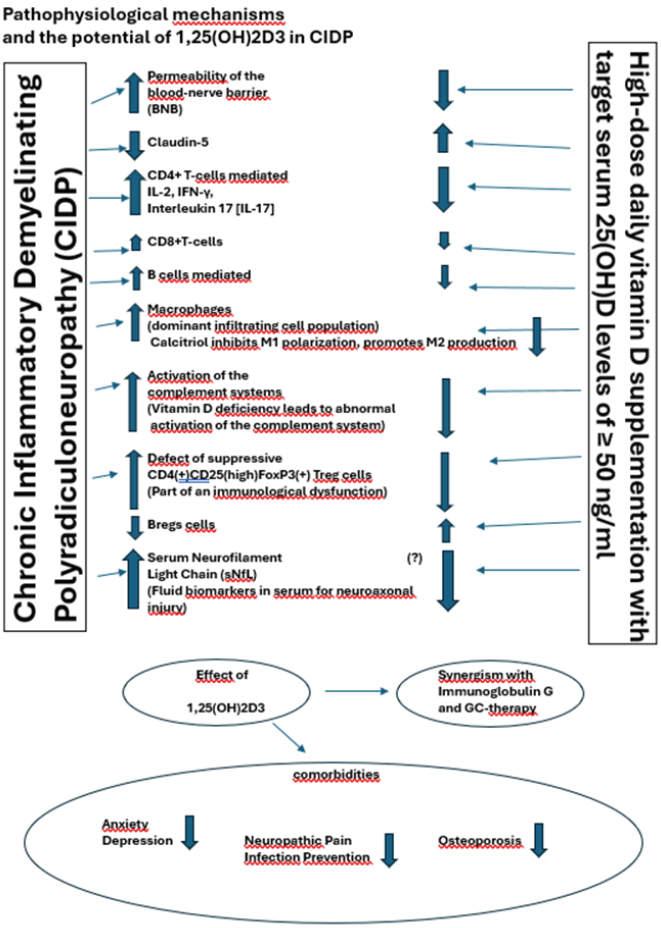
Figure 4. *Role of complement in CIDP pathogenesis. Original illustration from : Querol LA, Hartung HP, Lewis RA, van Doorn PA, Hammond TR, Atassi N, Alonso-Alonso M, Dalakas MC. The Role of the Complement System in Chronic Inflammatory Demyelinating Polyneuropathy: Implications for Complement-Targeted Therapies. Neurotherapeutics. 2022 ; 19(3):864-873. doi : 10.1007/s13311-022-01221-y. [15].*

Physical function was better when adequate s25(OH)D levels were associated with low complement levels. There was a negative association between complement C4 levels and physical activity in daily life [97].

Complement triggers CD4+ T helper cell (Th1) responses, and autocrine vitamin D signaling shuts down pro-inflammatory programs of Th1 cells. As part of a shutdown program, IFN-gamma is suppressed and the anti-inflammatory IL-10 is enhanced [98].

Hypovitaminosis D leads to abnormal expression of complement proteins, which in turn induces abnormal activation of the complement system [99].

It has also been shown that interactions exist between 1,25(OH)2D3, alpha-1-antitrypsin, and C3a. A deficiency of alpha-1-antitrypsin and vitamin D is associated with inflammation and autoimmunity [77, 100]. In addition, vitamin D positively modulates the immune and clinical response to glucocorticoids (GC). Thus, a GC-sparing effect could also result from vitamin D supplementation. In the autoimmune disease myasthenia gravis, complement inhibitory therapy could lead to a GC-sparing effect [101]. MAC (Membrane attack complex) destroys the structural integrity of the myelin sheath in PwCIDP and enhances demyelination induced by T cell and macrophage activity [38]. The effect of 1,25(OH)2D3 on MAC is indirect through its influence on cytokine production, thereby inhibiting MAC formation in autoimmune diseases and reducing cell damage [99, 102-104]. (Graphical Abstract)



Graphic abstract

If IVIG therapy enables complement fixation and inhibition and concomitant Vit D administration improves this effect, Vit D supplementation becomes plausible [77,105].

Too little is the earliest daily Vit D suppl Initiated due to years of controversial discussions about normal values of 25(OH)D and daily vitamin D dosage [106-109]. Doses recommended for the general population to improve health are largely used in practice out of unfounded caution against overdose. Intoxication can easily be ruled out by monitoring serum calcium levels and 25(OH)D levels. [110-114].

Intoxication is only to be expected at s25(OH)D levels > 150 ng/ml [115]. Without considering the therapeutic window, as is also the case in other autoimmune diseases such as MS [116-117], the potential of vitamin D as a tolerogenic adjuvant cannot be optimally utilized.

Interface between NLRP3 inflammasome and vitamin D

The role of vitamin D3 in modulating the interplay between NLRP3 (NLR Family Pyrin Domain Containing 3)- Inflammasomes are receiving increasing attention. 1,25(OH)2D3, the active form of vitamin D, and the NLRP3 inflammasome are associated with each other, particularly regarding the improvement of inflammatory processes in inflammasome -mediated autoimmune diseases [118]. The inflammasome plays an active role in the earliest stages of disease development in neurodegenerative diseases [119]. Calcitriol can influence the activation of the NLRP3 inflammasome by inhibiting the ROS-NLRP3-IL-1 beta signaling axis, leading to a reduction in inflammation [120].

The NLRP3 inflammasome is a protein complex that plays an important role in inflammatory signaling. In addition to nerve damage, excessive activation also leads to pain symptoms [121,122]. Activation of the NLRP3 inflammasome leads to the release of proinflammatory cytokines, such as IL-1 beta, IL-6, IL-17, and IL-18, in the serum of PwCIDP [123,124]. There is a positive correlation between NLRP3 inflammasome levels and the severity of CIDP disease [124].

Vit D receptor (VDR) signaling inhibits NLRP3 inflammasome activation and has the potential to be a treatment target for diseases involving inflammasome -associated mechanisms [125].

Synergism of 1,25(OH)2D3 and methylprednisolone through upregulation of the glucocorticoid receptor

Another argument for Vit D supplementation in PwCIDP is the increase in the efficacy of scheduled glucocorticoid therapy (GC) through mTORc1 (mechanistic target of rapamycin complex) inhibition. A reduced s25(OH)D level could lead to reduced expression of the GK (GC) receptor (GCR) in T cells, resulting in reduced induction of T cell apoptosis. However, the increase in GCR protein is dependent on the dose of vitamin D administration [126].

A similar potentiating mechanism has been described for the GC dexamethasone [127]. Administration of vitamin D and dexamethasone increased the anti-inflammatory IL-10 induction [128]. Vit D may enhance steroid responsiveness by upregulating the expression of steroid receptor GR-α. [129]. A glycoprotein-sparing effect of vitamin D is discussed [130]

Calcitriol to reduce adverse events in long-term GC therapy

Therapeutic doses of GC can reduce vitamin D receptors in various tissues and cells, leading to vitamin D resistance. Therefore, there is a consensus to use cholecalciferol to prevent GC-induced osteoporosis [107,131,132].

For long-term GC therapy, a minimum daily dose of vitamin D of 400–1000 IU/ day is required for bone health [133]. If the tolerable upper limit of 4000 IU/ day is not exceeded, elevated s25(OH)D levels are generally not to be expected [134].

The effect of a given daily dose on s25(OH) levels is individual and depends on numerous factors, such as body weight, degree of obesity, absorption, diet, CYP2R1 activity, single nucleotide polymorphisms [SNPs] (e.g. SNPs in the VDR gene) and vitamin D binding protein. Medications, such as PwCIDP and dexamethasone therapy, can increase VitD degradation [107,135].

1 ,25(OH)2D3 also increases GK-induced suppression of IFN-gamma and granzyme B.

T helper cells 17.1, which are characterized by the expression of high IFN-gamma, high IL-17 levels, GM-CSF, granzyme B, and CD 4+ levels exhibit the property of overexpression of multidrug resistance protein 1 (MDR1). This can render them refractory to GC. 1,25(OH)2D3 has been shown to improve GC sensitization [136].

1,25(OH)2D3 supports the immunomodulatory effects of IVIG

Calcitriol may synergistically accompany short-term and long-term IVIG therapy, both in monophasic and chronic relapsing or chronically progressive CIDP [137]. The immunomodulatory effect of immunoglobulins, which leads to a reduction in Th-17 cell proliferation and IL-17 secretion and the further downregulation of proinflammatory cytokines, is also enhanced by 1,25(OH)2D3. The increase in Treg cells is the target of both therapeutic agents [13,80,138-140].

Pain Relief and Association with Vitamin D

The prevalence of pain (of any type, but with no alternative cause other than CIDP) at any time during CIDP was estimated as 46% in a systematic review [141] and varied between 7% and 72% in different studies, reviewed by Thakur et al. [142,143,144].

Reduced s25-hydroxyvitamin D levels correlate well with the prevalence sensory neuropathy in diabetes mellitus and the severity of peripheral neuropathy [145].

In patients with rheumatoid arthritis, vitamin D deficiency could be a plausible cause of neuropathic pain. Pain perception in the peripheral nerves may be altered by hypersensitivity and hyperinnervation of the pain-transmitting nerve fibers [146, 147, 148]. Hypovitaminosis D enables increased inflammatory activity and leads to imbalances in interleukins (IL), TNF-alpha, and the regulation of macrophage activity [149]. Neuropathic pain is the result [146, 150]. Because hypovitaminosis D leads to pain exacerbation, and optimal vi t D suppl improves pain symptoms, and there are no contraindications, this therapeutic option should be a "conditio qua non."

Vit D suppl also increases the myelination of spinal ganglia neurons and regulates the expression of genes involved in axon growth. Therefore, calcitriol is a crucial neuroprotective factor for nerve cells [151,152].

Serum 25(OH)D levels showed an independent and inverse association with both the presence and severity of diabetic neuropathy. Each 1 ng/ml increase in s25(OH)D correlated with

a 2.2% and 3.4% decrease in the presence and severity of nerve conduction velocity (NCV) impairment, respectively [153].

Vit D is involved in the regulation of opioid signaling; low s25(OH)D levels are implicated in opioid side effects and dependence. Hypovitaminosis D increases sensitivity to morphine reward and exacerbates opioid dependence, leading to the conclusion that vit D regulates nociception and opioid analgesia [154,155].

In addition, it was shown that there is a significant correlation between low vit D levels and increased opioid consumption exists [152]. The urgent goal of reducing/terminating opioid use requires the therapist to use vitamin D as an alternative/ supplementary remedy for an effective and lasting pain management strategy [156].

When starting vitamin D supplementation for hypovitaminosis D, a single dose of up to 300,000 IU can be given initially, followed by approximately 2,000–5,000 IU/ day to achieve pain relief. The target is s25(OH)D levels of approximately 40–80 ng/ mL [156–159].

Therefore, a mere treatment of neuropathic pain without vitamin D supplementation cannot be justified based on the findings on pathophysiology [160].

Telomeres/ Inflammation and 1,25(OH)2D3

It has long been known that the telomere/telomerase system is involved in relevant physiological processes in autoimmune diseases and is associated with premature immune senescence [161-163]. Telomeres are repetitive nucleotide sequences that, together with the associated Shelterin complex, protect the ends of chromosomes and maintain genomic stability [164].

Accelerated shortening of telomere length (TL) may contribute to neurodegeneration and cellular senescence may contribute to disease progression in polyneuropathies [165] .

Vitamin D may reduce telomere shortening through anti-inflammatory and cell proliferation-inhibiting mechanisms [164]. Inflammation causes telomere shortening through chronic systemic inflammation, predominantly characterized by TNF-alpha and IL-6 [163,166].

It has been observed that shortened leukocyte telomeres are associated with clinical progression in MS [167,168].

Common pathogenic features exist in inflammatory diseases of the PNS and CNS [165], thus allowing the hypothesis that experiences from MS research can be applied early in the care of PwCIDP.

Telomere loss can contribute to the pathogenesis of various autoimmune diseases [169-172]. Telomere maintenance and telomerase regulation are also closely linked to the activation and differentiation of T and B cells [173].

Accelerated telomere loss is likely mediated by increased inflammation and oxidative stress. Oxidative stress (OS) is characterized by the imbalance between the production and degradation of reactive oxygen species (ROS) or reactive nitrogen species (RNA) [174]

Vit D has a positive effect on telomere dynamics, and this should have an impact on disease management [164,175,176].

Calcitriol, as an inhibitor of proinflammatory reactions, showed a positive association with TL [177,178] and may also have an influence on aging, although the results are not clear [179].

Vit D can attenuate oxidative stress and delay cell aging by improving mitochondrial homeostasis and inducing the expression of nuclear Factor Erythroid 2- related factor 2 (Nrf2) [180]. Furthermore, 1,25(OH)2D3 deficiency promotes skeletal muscle cell senescence through oxidative stress and impairs muscle regeneration [181,182].

For example, calcitriol may be indirectly beneficial through inhibition of pro-inflammatory TNF-alpha and IL-6, because telomere instability is associated with inflammatory processes [183]. Cellular senescence in neuroinflammation is enhanced by oxidative stress, and vitamin D may exert a protective function and be incorporated into the concept of early rehabilitation [184,185].

Higher plasma 25(OH)D levels were associated with longer leukocyte telomeres [186, 187,188].

A 4-year vitamin D supplement with 2000 IU/ day reduced telomere loss [189]. The difference in the effects of daily vit D suppl compared to bolus administration was demonstrated by a study that also followed up for at least 4 years, but in 1,519 elderly Australians (with 60,000 IU of vitamin D per month), which likely had no effect on telomere length. A predicted rather than measured baseline 25(OH)D serum level was used in the analysis. Telomere length was not measured at baseline [190].

Commonalities of CIDP/MS Pathophysiology in the Context of Calcitriol

In both MS and CIDP, a disruption of immune tolerance mechanisms leads to humoral and cellular autoimmunity of the myelin sheath-axon complex. Numerous case reports of patients with CIDP and MS confirm fundamental immunological similarities [191-198].

In cases of CNS-PNS involvement, immunological reactivity against antigens could occur in both peripheral and central myelin [199-201].

A repurposing /repositioning of MS immunotherapies [202] could also pave the way for early vit D administration. High-dose vitamin D supplementation in clinically isolated syndrome (early RRMS) with 100,000 IU of vitamin D every two weeks has shown a reduction in disease activity [60,117,203].

Neurofilaments : The “C- Reactive Protein” of Neurology

The neurofilament light chain in serum is essential for diagnostics, monitoring disease progression, and monitoring treatment outcomes in neurological diseases and is therefore also referred to as the "neurologist's CRP." In PwCIDP , a correlation between sNfL and the severity of the disease and response to therapy has been demonstrated [204-207]. For example, the efficacy of sustained inhibition of complement activity by riliprubart , a C1s complement inhibitor, in PwCIDP has been demonstrated by lowering NfL levels [208].

The observed adverse effects such as nasopharyngitis could be proactively counteracted by Vit D supplementation [209-212].

Almost 20 years ago, the importance of determining sNfL in Guillain-Barré syndrome (GBS) (with similar pathophysiological mechanisms as in CIDP) for disease severity as well as prognostic markers was verified and is currently being reinforced to detect possible long-term morbidity in a timely manner [214-216].

The glial fibrillary acidic protein (GFAP) in serum can reflect/ predict disease severity, and elevated levels are associated with poorer treatment outcome. GFAP is an intermediate filament

expressed by astrocytes in the CNS and by nonmyelinating Schwann cells in the PN [217-223].

By using the sNfL -Z-score (age, height, weight, BMI) [Body mass index]), precision is increased and advantageous over absolute values. Percentiles/Z-scores are interchangeable and reflect the deviation of a patient's sNfl from the meaning of healthy individuals with age and BMI match (50th percentile; Z-score = 0) [224].

In multiple sclerosis (MS) research, a "high " sNfL value was defined as >90th percentile. In individuals with MS and sNfL values above the 90th percentile (Z-score 1.28), an approximately twice as high risk of disease activity was verified [224,225].

Because sNfL parameters are dynamic in inflammatory neurological diseases, follow-up monitoring is indicated for interpretation [226]. There is increasing evidence of a close relationship between s25(OH)D levels and sNfl values [227]. Hypovitaminosis D has been correlated with elevated sNfL values [228].

The definition of sNfL values for PNP does not yet exist internationally. Repeated determination of sNfL also has the advantage of making the appropriate treatment intervals dependent on the course of sNfL values rather than on the deterioration of the clinical condition, as previously

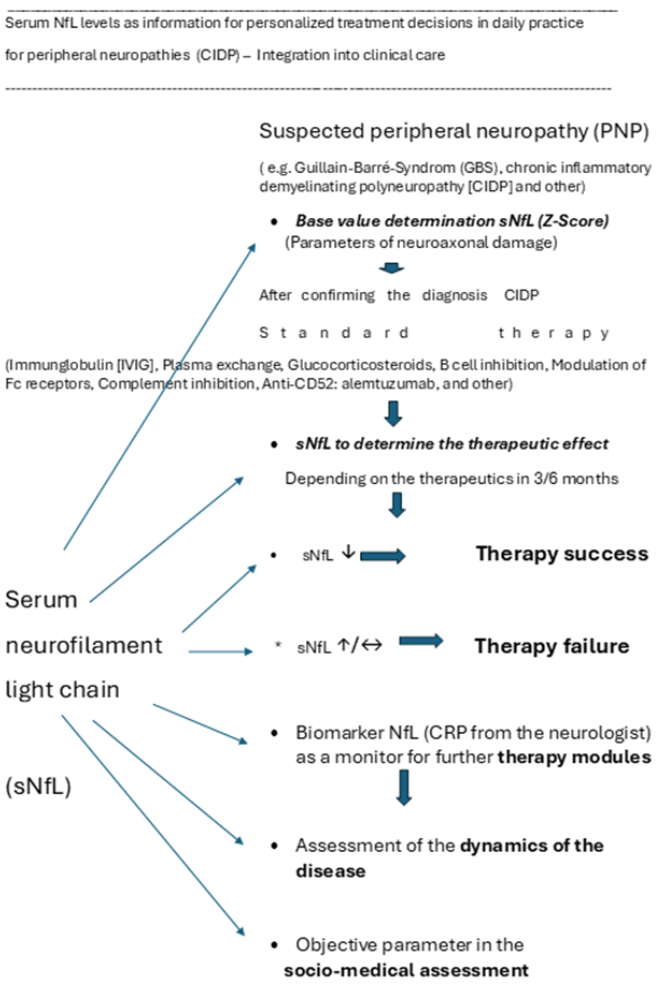


Figure 6.

recommended and practiced [17].

Furthermore, the response to GC therapy can take weeks to months [144]. Depending on the dosage regimen of the GC administered, the effect may occur in 8 weeks at the earliest, with maximum improvement after 6 months. Disability scores also improved as early as 2 weeks after initiating treatment with 60 mg prednisolone daily [229]. Thus, the sNfL biomarker is also an objective, easily measurable indicator of the efficacy of the chosen treatment approach. (Figure 6)

Discussion

Diagnostic accuracy in CIDP is currently a major challenge because approximately 50% of PwCIDP are misdiagnosed and, in some cases, extended observation periods of the disease in practice elapse or must be prolonged to make a definitive diagnosis [230]. 5% of individuals originally diagnosed with GBS are later reclassified as CIDP [23,143]. Patients with immune-mediated neuropathies may experience phases of overlapping acute and chronic courses [38].

We observed a young PwCIDP patient who was initially defined as having recurrent GBS for 2.5 years and who received a high-dose opioid for pain control for two years. Further diagnostic testing at a university center that was initially difficult to access necessitated reclassification .

Various long-term observational studies of CIDP treatment with GC, IVIG, and plasmapheresis showed a stable course for more than 5 years in only 11% to 26% of PwCIDP , 12% experienced a progressive course, and 39% to 51% required long-term treatment to prevent progression. 13% developed severe disability [231-233]. Overall, a clinically relevant response is observed in only 75% to 80% of PwCIDP [202].

There is a consensus that chronic immunogenic neuropathies require long-term immune tolerance-inducing treatment [38].

Calcitriol acts as a neurosteroid and plays an important role in peripheral neuropathies, and vit D suppl could positively influence homeostasis by regulating various processes, such as myelin genesis and axon maintenance [88].

Hypovitaminosis D is associated with various harmful conditions such as oxidative stress, inflammation, apoptosis, and reduced neurotrophin levels, and supplementation can therefore have significant effects on the prevention or treatment of neurological diseases and brain health in general [234]. The positive role of vitamin D in neuroprotection and myelin regeneration is no longer in doubt [235-236].

Vit D suppl may also reduce disease severity or enhance the therapeutic effect of standard medications. Vit D may also support muscle function and improve postural and dynamic balance [237]. The insights into the diverse molecular mechanisms of 1,25(OH)2D3 on immune modulation should be utilized in clinical practice [77,95,238-240].

Currently, no adjuvant therapy options, such as vit D suppl, are “officially” considered in management decisions regarding acute therapy and long-term care in chronic disease.

The diverse role of vit D in modulating immune responses and its potential influence on immune-mediated diseases is no longer in doubt [241].

Hypovitaminosis D is a key factor in the pathobiology of neurological diseases because it impairs gene expression, calcium homeostasis, oxidative stress, and immune functions [242].

Transferred from research results in MS with autoimmune

mechanisms, a proactive approach is the decisive momentum. Significant control of disease disability was observed when vit D was provided 1 or 7 days after illness induction, being the earlier even more efficient.

The sealing of the BBB is crucial in MS, and it is biologically plausible to transfer the pathophysiological mechanisms in PwCIDP to the sealing of the BNB [59,61,116,243].

However, there is an unmet need for alternative therapies when standard CIDP therapy does not lead to complete remission or cure and IVIG is not widely available [244].

Concurrent psychosocial stress in PwCIDP , especially in young people with occupational disadvantages because of the autoimmune disease, also necessitates therapy optimization [14].

Vit D Suppl in PwCIDP as a constant player in combination therapy

Calcitriol is involved in myelination, axonal homogeneity of the PN and neuronal cell differentiation [88].

Autoreactive inflammatory cells, including effector T cells (Th1, Th17, CD8+ cytotoxic T cells), activated B cells, and plasma cells producing autoantibodies (neurofascin-155 (NF-155), neurofascin-140 (NF-140), neurofascin-186 (NF-186), contactin-1 (CNTN-1), contactin -associated protein 1 (CASPR1, , Determination of myelin-associated glycoprotein [MAG] for differential diagnosis and therapy)) infiltrate the PNS [14, 38, 245]. Dysfunctional Treg cells (CD4 +CD25+Foxp3 regulatory T cells [Treg]) play a key role [32, 246, 247]. Tregs are significantly reduced in number. In addition, activated CD4+ T cells, B cells, macrophages, and dendritic cells are involved in the Treg-homeostasis [247].

Calcitriol promotes the development of regulatory T cells (Tregs), which help maintain immune homeostasis and prevent autoimmune responses [79,77,80,248].

Inflammatory mediators penetrate the leaky BNB and maintain the impaired barrier function. The TJs complex plays a central role in barrier leakage in a variety of diseases of the peripheral and central nervous system [58].

Despite differences in the pathophysiological mechanisms of CNS and PNS diseases, commonalities in the homeostatic influence of 1,25(OH)2D3 on the immune system in autoimmune diseases can be identified [60,77,80,88,95,250,251].

There is sufficient evidence that barrier leakage can be reduced by Vit D [67,252].

IL-6 is one of the stimulating factors in inflammatory processes and leads to the production of immunoglobulins. It functions as the most important cytokine in inflammatory diseases of the nervous system. S25(OH)D levels are inversely correlated with IL-6, and there is evidence of inhibition by calcitriol [2, 253-258].

1,25(OH)2D3 may also play a neuroprotective role by acting on pericytes through an anti-inflammatory response in neuroinflammation [259,260].

Given the homology in the pathogenesis of central and peripheral neurological autoimmune diseases and a high biological plausibility of the effect of vit D, it should be discussed as the first therapeutic option in comparison with DMTs with an increased side effect profile [236].

In the peripheral neuropathy Charcot-Marie-Tooth neuropathy (genetic cause), especially in CMT type 2 D, hypovitaminosis D showed pathological changes in the PN and neuromuscular junctions. The VitD / VitD receptor (VDR) and the VEGF (vascular endothelial growth factor) signaling pathway play a role [261].

The success of vit D suppl depends on whether one is convinced by the findings of the dose-response relationship and strives for s25(OH)D values above the otherwise recommended daily doses, which are largely given for phosphate-calcium homeostasis in the healthy population, and accepts that the latter are not relevant for autoimmune diseases [252,262,263].

Only in this way can cell- and tissue-specific changes be induced at the molecular level in TJs and in other mechanisms. An individual s25(OH)D value can be crucial, and vit D suppl must take into account age, gender, and body weight (obesity) [77, 249, 264]. Vit D has no direct influence on adipose tissue. However, it can bind vitamin D because it is a fat-soluble vitamin, which leads to lower bioavailability in the bloodstream [265]. For healthy individuals, “optimal” s25(OH) D levels of 40–90 ng/ml have been preferred [263, 266–271]. From a physiological point of view, serum vitamin D levels in autoimmune diseases should reach approximately 130 ng /ml to exert likely therapeutic effects [270].

A case report demonstrates which high doses of vitamin D are individually necessary to achieve an immunological effect [271].

Serum parathyroid hormone [PTH] levels can be used to determine precise supplementation in autoimmune diseases. A low PTH plateau should be in the lower third [249].

Calcitriol suppressed the disease in experimental autoimmune diseases [77].

Although most patients (approximately 80-90%) respond to first-line therapy, some PwCDIP show an incomplete or inadequate response to standard therapy [144]. In the future, vit D suppl could be used to complement IVIG and GI therapy, at least within the framework of a holistic treatment concept, resulting in a "dual drug therapy for relapses."

Complement , NLRP inflammasome

The role of the complement system is well documented in peripheral neuropathies, as well as in GBS, and there is sufficient evidence for complement activation in CIDP [15,105]. The complex influence of vitamin D on maintaining immune homeostasis also plays a key role [95].

Vit D is associated with the expression and function of CD59, a protein that inhibits the membrane attack complex of the complement system and may influence immune responses and inflammation, involving CD59. CD59 can inhibit complement-mediated lysis [272-277].

The physiologically activated version of vit D promotes a tolerogenic immunological state and modulates innate and adaptive immune cell responses that are impaired in PwCIDP [140].

Pain is a common and debilitating symptom commonly encountered in patients with peripheral neuropathy. Pain increases the burden of disease and significantly impacts patients' quality of life [141,278,279] .

Serum NfL levels can be a useful biomarker for other peripheral neuropathies, which is also consistent with autoimmune central CNS diseases such as MS [215]. Using this biomarker to objectify pain intensity would be of great benefit for the clinical and sociomedical assessment of PwCIDP. However, studies

have not shown a correlation in diabetic neuropathies [280]. Whether these results can be extrapolated to PwCIDP requires further studies. However, there was a correlation with the anti-inflammatory cytokine IL-10 in neuropathic pain [281], which could be increased by high-dose vit D suppl thus improving pain symptoms.

SNfL - Assessment of therapy effectiveness

There is a large body of evidence that sNfL (age-, weight-[BMI-, and sex-adjusted Z-scores) reflects neurodamage [282], sNfL levels reflect temporal dynamics, current or recent damage [283], and the anti-inflammatory neuroprotective role of 1,25(OH)2D3 defends axonal integrity [88, 60, 228, 284-288].

Although there are conflicting results of vit D suppl and the measurement of the success of 1,25(OH)2D3 by sNfL determination in MS, an additive therapeutic effect is to be expected due to its immunomodulatory effects on the peripheral and central nervous systems [228, 289, 290].

The initial and subsequent continuous determination of sNfL not only enables the diagnosis of inflammation and axonal damage in the PN, but is also an essential biomarker in the assessment of the effectiveness/dynamics of various therapeutics. It is important to monitor the therapy breaks with sNfL [291].

A possible excessive emphasis on subjective changes in diagnosis and misinterpretation as a "psychosomatic problem" as a misdiagnosis of an existing autoimmune disease can be avoided by this "neurologist's CRP." Early detection of CIDP or "axonal damage of unknown origin" is closely linked to the prognosis of the disease. Psychosomatic or psychiatric misdiagnoses in autoimmune diseases are associated with long-term disadvantages, such as anxiety, depression, suicidal thoughts and suicide attempts, self-doubt, and less frequent doctor visits [292].

A major problem with the strategy of IVIG treatment cycles is the assessment of effectiveness. It has been clearly shown that self-reported treatment-related symptom fluctuations may not necessarily be caused by neuroaxonal damage [204]. On the other hand, in cases of apparently more stable disease progression, the determination of sNfL levels could not be dispensed with, as in individual cases, elevated sNfL levels were found in patients without symptoms [204].

Multifactorial effect of calcitriol - justification for supplementation

If a daily vitamin D supplement from the onset of diagnosis of chronic inflammatory autoimmune demyelinating neuropathy were included in the long-term treatment strategy, the multifactorial immunological influence can be offered as a potential benefit to PwCIDP without disadvantages.

This cost-effective, widely available, and low-side-effect long-term therapy is also recommended because human immunoglobulin for intravenous or subcutaneous therapy is not available in all countries, and the economic problem is being discussed with international relevance [294].

The multifactorial effect of calcitriol could potentially prolong the time intervals in IVIG or glucocorticoid pulse therapy or allow dose escalation and/or dose reduction in GC therapy.

If a daily Vit D suppl of 4000 IU to 6000IU and reaching a s25(OH)D value D concentration of 40-70 ng/ mL is evidence-based and provides better protection against many negative health consequences in the general population [295], it is biologically plausible to target s25(OH)D levels in the range of 100 ng/mL in autoimmune diseases. The normal value for s25(OH)D should be defined in the clinical context and individually [268]. Low daily doses of 2000 IU demonstrate an insufficient s25(OH)D level and cannot achieve the expected modulations on the diseased immune system [296].

Knowing the vitamin D response index of a PwCIDP, whether high, medium or low response is present, allows for maximum benefit from vitamin D supplementation [297,298]. There is evidence that dysregulated TNF -alpha signaling is associated with either hypovitaminosis D or vitamin D hypo responsiveness , thus promoting autoimmunity, and that vitamin D promotes immune tolerance/immune homeostasis and may prevent autoimmunity [299].

The proven diverse immunological effects and the knowledge of the molecular mechanisms of calcitriol on the pathophysiological mechanisms of CIDP could convince hesitant/skeptics to accept vitamin D as an adjunctive proactive long-term basic therapy for the benefit of PwCIDP [242].

Vit D supplementation with maintenance of s25(OH)D levels of ≥ 40 ng/ml may reduce the risk of acute viral infections or reduce their severity. A particular benefit is expected in GC therapy [242,300].

This complementary therapy is motivated by patients' interest in comprehensive care [301-303]. Waiting for the reporting of randomized controlled trials (RCTs) of vit D suppl in PwCIDP should be reconsidered due to the years of time involved. Resistance to considering valid data not derived from RCTs should be abandoned in favor of personalized therapy [304]. The difficulties in designing RCTs on vit D suppl in general are manifold and, due to a lack of international consensus, currently represent an almost insoluble problem (insufficient sample sizes , duration, inappropriate dosage strategies, lack of consideration for individual vitamin D status) [251,305-313].

RCTs with designs developed for drug testing are not suitable for Vit D suppl [306].

Repurposing of MS immunotherapies for CIDP and other autoimmune neuropathies [202,314,315] could also be introduced into daily practice for vitamin D in a “fast-forward” manner.

“The practice of medicine remains more an art than a Science” [316]

Conclusion

Chronic immune-mediated peripheral neuropathies have the potential to severely reduce quality of life due to persistent or recurrent inflammation and demyelination and place a significant burden on professional development, especially in those affected at a young age in PwCIDP.

The immunopathogenic mechanisms in CIDP should promote the understanding of add-on therapy with vitamin D supplementation. The immunomodulatory effect of calcitriol on the relevant players, namely T cell-mediated and humoral immune responses, complement activation, the involved cytokines and inflammasomes, as well as on ongoing axonal damage, promises a benefit for PwCIDP. The impaired integrity of BNB is also a target of 1,25(OH)2D3.

The interindividual variations in the biological effect of vitamin D (low, medium, high) must be considered to achieve an optimal therapeutic effect.

Continuous determination of the biomarker NfL in serum to assess the severity of axonal damage, treatment success and

disease dynamics must become a reality, especially since sNfL can guide the intensity of therapy.

Conflict of Interest

The authors declare no conflict of interest.

Ethics Approval and Consent to Participate

Not applicable.

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