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Chapter

The Effects of Vitamin D Deficiency on Neurodegenerative Diseases

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Abstract

Approximately 90% of the elderly population in the western countries has at least a mild to moderate vitamin D hypovitaminosis. Besides the well-known function of vitamin D in calcium homeostasis, it has been recently found that several enzymes and receptors involved in its homeostasis are expressed in the nervous system and brain suggesting also an important role in the brain homeostasis. Interestingly, epidemiological and clinical studies found reduced vitamin D level associated with an increased risk of several neurodegenerative disorders. In this chapter, we focus on a potential link between vitamin D and Alzheimer's disease, Parkinson's disease, multiple sclerosis, prion disease, and motor neuron disease. Epidemiological studies were summarized, an overview of the known potential underlying pathomolecular mechanisms are given, and results from clinical studies dealing with vitamin D supplementation were presented. As an outlook, recent literature suggesting an impact of vitamin D on autism spectrum disease, depression, and schizophrenia are briefly discussed. In conclusion, the identification of an abundant vitamin D metabolism in the brain and the tight link between the increasing number of several neurological and mental disorders emphasize the need of further research making a clear recommendation of the intake and supplementation of vitamin D in a growing elderly population.

Keywords: vitamin D hypovitaminosis, Alzheimer's disease, Parkinson's disease, multiple sclerosis, prion disease, neuropsychiatric diseases

1. Introduction: relationship between vitamin D and neurodegenerative diseases

The secosteroid vitamin D_3 was identified in the year 1928 by Adolf Windaus and colleagues. Its synthesis starts in the skin based on 7-dehydrocholesterol through extraneous cause of ultraviolet B radiation in a spectrum of 290–315 nm wavelengths. Via the vitamin D-binding protein, it is transported in the blood to the liver where the 25-hydroxylase CYP2R1 hydroxylates vitamin D_3 to 25-hydroxyvitamin D_3 ($25(OH)D_3$). Because of its serum half-life of weeks, this 25-hydroxylated form of vitamin D_3 is clinically measured as an indicator for the patients' vitamin D_3 level [1, 2]. The active form of vitamin D_3, 1,25-dihydroxyvitamin D_3 ($1\alpha,25(OH)_2D_3$) or calcitriol, is synthesized in the kidney by the 1α-hydroxylase

CYP27B1. To a limited extent, vitamin D_3 can also be taken up with diet as well as vitamin D_2 (ergo-calciferol), which is largely found in food.

Calcitriol can perform its genomic actions via vitamin D receptor (VDR) binding. Hence this undergoes a conformational change and forms a complex with the retinoid X receptor (RXR) which interacts with the vitamin D response element (VDRE) to regulate the expression of numerous genes. Because of this ability of transcriptional modulation, vitamin D has influence on various cellular processes, for example, the mitochondrial function by maintaining the mitochondrial respiratory chain activity [3]. Dysfunctional mitochondria will normally be removed by autophagy, a process that is also promoted by vitamin D [4]. Damaged mitochondria could induce inflammation. Vitamin D is able to downregulate the expression of pro-inflammatory cytokines such as the tumor necrosis factor-α (TNF-α) or interleukin-6 (IL-6), thereby reducing inflammation [5]. Additionally to these cellular processes, vitamin D antagonizes oxidative stress by enhancing the expression of antioxidants and thereby reduces levels of reactive oxygen species (ROS) [6]. Furthermore the expression of the voltage sensitive L-type Ca^{2+} channels is suppressed by vitamin D to regulate intraneural calcium [7, 8]. Vitamin D also plays a role in DNA-related cellular processes, for example, epigenetic changes. These are influenced on the one hand by oxidative stress which is regulated by vitamin D, as described before, and on the other hand by histone methylation which is also modulated by vitamin D due to its influence on the transcription of key DNA demethylases [9, 10].

Based on the fact that up to 90% of the elderly population is suffering from a vitamin D hypovitaminosis because of a homebound lifestyle and the reduced ability of their skin to generate vitamin D_3, the idea arose to analyze the impact of a vitamin D deficit on the abovementioned cellular processes which are all involved in ageing [11]. Moreover, ageing is a risk factor for neurodegenerative disorders. Michael J. Berridge published a very detailed article 2 years ago reviewing the influence of vitamin D deficiency on ageing and age-related diseases. He figured out that hypovitaminosis D promotes those ageing-related processes, for example, due to a decline of mitochondrial respiration or the electron transport chain. This dysfunction leads to an increase in oxidative stress and inflammation, main drivers of ageing. Furthermore, he describes elevated Ca^{2+} levels in neurons during ageing which are accompanied by a decline in cognition. This observation can be restored by vitamin D due to its ability to reduce the levels of Ca^{2+}. Additionally, telomere shortening, a DNA-related process that is involved in ageing, is reported to be decreased by vitamin D [12]. Those upregulated ageing processes under vitamin D-deficient conditions in the elderly population could further lead to age-related disorders like dementia or declines in cognition.

A relationship between vitamin D and age-related cognitive disorders was further strengthened by the findings that vitamin D and its metabolites are able to cross the blood-brain barrier. Early research reported the presence of vitamin D metabolism intermediates and products in human cerebrospinal fluid [13]. Furthermore, due to the presence of the metabolizing hydroxylases in the brain, the active form of this hormone-like secosteroid can be synthesized in the human brain. The additive existence of the VDR in neuronal and glial cells suggests that vitamin D might influence functioning of the central nervous system (CNS) [14]. As mentioned earlier, the VDR-mediated nuclear functions of $1,25(OH)_2D_3$ influence cellular processes, for example, immune modulation and cell growth or differentiation. Those biological systems have also an impact on maintaining the function of the brain. Annweiler et al. reported increased risks of cognitive disorders for patients with $25(OH)D_3$ serum concentrations lower than 10 ng/ml [15]. Vitamin D influences the structure of the brain, like changes in volume and vasculature as

well as its metabolism [16]. Furthermore, in vivo studies using offspring of vitamin D-deficient rats could show that vitamin D plays an important role in the developing brain [17]. Eyles et al. give a detailed overview in their review over all the different animal studies that have been made in this context. One exemplary finding is that rats with a vitamin D deficiency during their development have impairments in their adult behavior [18].

In a retrospective study from 2007, Przybelski and colleagues reported that serum 25(OH)D_3 can be positively associated with increased cognitive function [19]. Consistent finding results from a prospective cohort study in older adults that showed a vitamin D hypovitaminosis (levels <30 ng/mL) in 68% of the participants and moreover that these ones have lower baseline cognitive function and increased decline over the 4 years of follow-up [20]. In the same year, another prospective study including 1185 women also pointed out an association of higher plasma 25(OH)D_3 levels and better cognitive performance [21]. A meta-analysis showed that participants with insufficient vitamin D levels have a 2.4-fold increased risk of cognitive impairments than those with sufficient levels [22]. In line with this, further systematic reviews and meta-analysis support an association between hypovitaminosis D and declined cognitive functions [23, 24]. Additionally, some longitudinal studies suggest a link between low serum 25(OH)D_3 levels and cognitive performance. Toffanello et al. reported decreasing scores at Mini-Mental State Examination (MMSE) in participants having serum 25(OH)D_3 levels below 75 nmol/L in their 4.4-year follow-up study including 1927 elderly subjects [25]. One year later, Miller et al. published a vitamin D-associated accelerated decline in cognitive performance in their study of a multiethnic cohort of older adults [26]. In line with these data, a more recent clinical study in the elderly US population (3325 participants) reported that low serum levels of vitamin D_3 are linked to an enhanced risk of cognitive impairment [27].

Due to the suggested role of vitamin D in brain function, several studies examining the effect of dietary supplemented vitamin D exist. Animal studies and epidemiological studies generate biological evidences for a relationship between vitamin D levels and brain health. Latimer et al. could show that a 6-month supplementation of vitamin D improves cognitive function in a rat model of aging [28]. One study from Annweiler and colleagues in the year 2010, including 5596 women with a mean age of 80.5 years, concluded that higher weekly dietary vitamin D intake is associated with better cognitive performance in older adults [29]. In line with this, a current cross-sectional and longitudinal study describes a significant association between serum vitamin D levels below 30 nmol/L and reduced general cognitive performance [30].

Unlike those animal and epidemiological findings, clinical studies using randomized controls examining the role of vitamin D in individuals without any form of dementia show heterogeneous data [31–34]. In general, it should not be disregarded that differences in clinical intervention studies might be because included participants who already had sufficient vitamin D levels at baseline could mask the benefit of supplementation on cognitive function. To prevent this, it would be beneficial including exclusively participants affected by a hypovitaminosis D at the baseline measurement. These inconclusive data also support the idea of individually adjusted supplementation protocols for each patient. Furthermore, methodological differences between the studies, for example, duration, form, and dose of vitamin D supplementation, have to be considered. A current study from Pettersen et al. [35] considered these abovementioned methodological pitfalls by administering 4000 IU/day of vitamin D_3 for 18 weeks to healthy adults and by baseline as well as endpoint measurements of serum 25(OH)D_3 levels. Furthermore, they were able to distinguish between the two cognitive domains, verbal and visual memory, with

several cognitive tests. High doses of vitamin D enhanced visual memory, while low doses (400 IU/day) improved verbal memory. As summarized by the authors, there seems to be a small positive effect of vitamin D_3 supplementation on executive functioning, despite the outlined limitations (modest sample size with wide range of ages, no true placebo group) [35]. Recently, Aspell et al. give a well elaborated overview over a possible supporting role of vitamin D in cognitive function in age [36]. In the following chapter, we will present the results of current available studies examining the impact of vitamin D supplementation on brain-related disorders for each neurodegenerative disease itself. Up to this date, also the nutrition research field examines the influence of dietary components on brain health. In a recent review from Moore et al., the authors describe a potential protective role for vitamin D among others [37].

2. Alzheimer's disease

Alzheimer's disease (AD) can be described as a multifactorial, metabolic disease as this disease is characterized by impairments in multiple cellular processes. For example, AD pathology includes alterations in the sequential proteolytic processing of the amyloid precursor protein (APP) which results in the formation of neurotoxic Aβ plaques, in the phosphorylation of the microtubule-associated protein Tau, in lipid and energy metabolism, and in inflammation. Among others, AD pathogenesis is influenced by lipophilic vitamins [38].

Epidemiological studies indicate a relationship between vitamin D deficiency and AD. A systematic review and meta-analysis concluded that patients affected by AD have lower levels of serum 25(OH)D_3 than healthy controls [39]. Furthermore the level of vitamin D is shown to be significantly reduced in the cerebrospinal fluid of AD patients [40]. Another meta-analysis from Shen and colleagues shows that vitamin D hypovitaminosis (25(OH)D_3 level < 50 nmol/L) is associated with a 21% increased risk of AD [41]. Different results were obtained by a study, measuring serum level of 25(OH)D_3 via radioimmunoassay in patients with MCI or diagnosed dementia compared to healthy controls. Analysis of the cognitive performance showed significant differences between these groups. Vitamin D levels of 65.2 ± 17.9 nmol/L for controls, 61.4 ± 18.8 nmol/L for MCI, and 65.0 ± 20.3 nmol/L for AD were reported in this study; however the differences in vitamin D concentrations between these groups were not statistically significant. Interestingly, the authors show that approximately 12% of the MCI and AD patients used some kind of vitamin D supplementation, whereas only 5% of healthy controls did so. Furthermore, 80% of the MCI patients, 50% of the AD patients, and 62% of the control individuals regularly used nutritional supplements, which could have influenced the results as discussed by the authors. In conclusion, the authors comment that their "findings cannot exclude the possibility that targeted vitamin supplementation can act as a modifying measure, although it is less likely that vitamin intake can prevent dementia onset" [42].

Several longitudinal studies provide homogeneous results indicating that a deficiency in serum 25(OH)D_3 is linked to a greater risk and incidence of dementia and AD [43–47]. A current prospective study analyzed 25(OH)D_3 level, cognitive decline, and incidence of dementia in 916 patients for 12 years and reported a more pronounced cognitive decline and a threefold increased risk of AD in individuals with hypovitaminosis D [48].

In line, a study from 2018 analyzing the serum vitamin D level in AD patients described decreased levels in various stages of AD. Additionally, the authors indicate 25(OH)D_3 as significant predictor for severe AD and argue for vitamin D

supplementation in AD patients [49]. Moreover, Wang et al. recently reported a delayed onset of psychotic symptoms when vitamin D was used in AD patients and suggest variations in vitamin D-influenced genes as biomarkers for those individuals who can have a benefit from supplementation [50].

These studies consistently indicate a link between insufficient dietary intake of vitamin D and cognitive diseases like AD. However, these studies did not address the question whether vitamin D deficiency is a cause and thus risk factor for AD or a consequence of this neurodegenerative disease mediated by accompanying dietary and behavioral changes. Some more evidence of a causal relationship between hypovitaminosis D and AD was achieved by Mendelian randomization (MR) studies that use genetic associations on inherited alleles unaffected by confounding factors or disease progression. It was reported that two polymorphisms in the *VDR* gene are associated with AD risk in patients younger than 76 years [51]. A subsequent meta-analysis including six AD studies also revealed this relationship [52], as well as an earlier study using genotyping of 213 participants [53]. Wang et al. also provide this genetic evidence and could further generate functional data indicating a link between the VDR and the genetic AD risk [54]. Furthermore, the study of Mokry and colleagues supports genetically decreased vitamin D levels as causal risk of AD, by analyzing the effect of single-nucleotide polymorphisms (SNPs) involved in vitamin D metabolism on $25(OH)D_3$ levels and the risk of AD in more than 56,000 participants [55]. A recently published MR study from Larsson and colleagues including 17,008 AD cases and 37,154 controls reported an inverse association between 7 SNPs related to elevated vitamin D_3 levels with AD, in which 2 of them were significant [56]. A study creating a vitamin D synthesis risk score analyzing more than 1000 Swedish men in a follow-up of 18 years is controversially discussed as this study revealed no link between baseline vitamin D status and the long-term risk of dementia [57].

Concerning clinical studies, randomized placebo-controlled trials analyzing the effect of vitamin D supplementation on AD risk and progression are still missing. However, recently nonrandomized studies showed positive findings about that relationship. A current study reported improvements in the cognitive status of MCI patients (n = 16) in an 18-month follow-up after 6 months of vitamin D supplementation. Additionally, vitamin D supplementation protected lymphocytes from oxidative stress [58].

In contrast to the missing clinical trials, several animal and cell culture studies underline a causal relationship between vitamin D and AD. One study described an increased neurogenesis and enhanced cognition after feeding a transgenic mouse model of AD (5xFAD mouse model) with a daily dose of 500 IU/kg vitamin D for 5 months [59]. Additionally, animal and cell culture studies allow analyzing combination therapies, for example, a supplementation of both vitamin D and resveratrol. This resulted in an improvement of cognitive function and reduced levels of $A\beta_{42}$ in the hippocampus along with decreased tau phosphorylation in the parietal cortex of a mouse model with AD-related memory impairment [60]. In line, a novel study from 2019 reported an improvement of the AD-related pathology in 5xFAD mice after intravenous injection of vitamin D-binding protein which was loaded on a biocompatible polymer (PLGA) [61]. Especially cell culture and animal-based studies are indispensable for clarifying the molecular mechanisms of vitamin D action in neurodegenerative diseases. They revealed that vitamin D exerts its protective effects via VDR-related, genomic, as well as non-genomic actions directed to processes like Aβ metabolism, neurogenesis, immune modulation, and neuronal calcium homeostasis. A study from Landel et al. examined the transcriptome of 5xFAD mice after 5 months of vitamin D_3 supplementation and reported a large number of differentially expressed genes. The authors suggest an

interaction of vitamin D with estrogen and insulin signaling to regulate the identified pathways [62]. Consistently, we could show that a deficit of vitamin D causes a dysregulation of numerous genes that are involved in multiple cellular processes like neurogenesis, inflammation, mitochondrial function, oxidative stress, signal transduction, and APP homeostasis in brains of hypovitaminosis D mice [63]. In respect to the impaired APP homeostasis, several studies using primary cortical neurons or human neuroblastoma cell lines were able to show beneficial effects of vitamin D and its analogues on anabolism and catabolism of the neurotoxic Aβ peptide [64, 65]. In line with these findings, a vitamin D_3-enriched diet leads to an increased Aβ clearance in mouse models of AD [66–68]. Consistent with the results of animal studies, Hooshmand et al. could demonstrate an association of increased plasma 25(OH)D_3 levels with higher concentrations of CSF $A\beta_{1\text{-}42}$ in 75 patients, reflecting a decreased $A\beta_{1\text{-}42}$ aggregation in human brain parenchyma [69]. In contrast, a recent cross-sectional study failed to find significant associations between plasma vitamin D levels at baseline and Aβ load in different brain regions. But the authors themselves argue that those findings could be explained by an improper timing of measurements or rather no analysis over time or by a hypovitaminosis D-related cognitive decline independent of APP homeostasis [70]. The potential neuroprotective role of vitamin D_3 is based on findings that it regulates the transcription of the neurotrophin nerve growth factor, glial-derived nerve factor, and neurotrophin 3 which are important for neuronal survival [71–73]. Furthermore, the expression of the neuroprotective cytokine IL-34 was shown to be increased in dose- and time-dependent manner by calcitriol in neuroblastoma cells [74]. In respect to a relationship between vitamin D and neuronal calcium levels, a review describes a reduced autophagy due to impairments in calcium signaling as a consequence of hypovitaminosis D [6].

3. Parkinson's disease

As one of the most common neurodegenerative diseases, Parkinson's disease (PD) is characterized by the loss of dopamine-producing neurons in the substantia nigra pars compacta and typical Lewy bodies, aggregates of α-synuclein, provoking oxidative stress and further cell death, leading to impairments in cognition and behavior and to dysautonomia [75].

A number of epidemiological studies were able to indicate an association of vitamin D and PD. Several evidences exist that hypovitaminosis D is more frequent in PD patients [76, 77], and a cohort study with a 29-year follow-up reported a decreased risk of PD in individuals with higher vitamin D serum levels [78]. These findings are supported by the outcomes of recent studies describing significantly reduced levels of serum 25(OH)D_3, daily vitamin D intake, and sunlight exposure in PD patients [79]. Besides significantly decreased serum 25(OH)D_3 levels, also an association of vitamin D at baseline and disease motor severity after 36 months was observed in a recently published prospective observational study [80]. A clinical study found an inverse relationship between serum vitamin D concentrations and disease severity as well as an influence on balance function in PD patients [81]. A current study reported that vitamin D status of PD patients has no influence on nocturnal changes in blood pressure, a marker of cardiac autonomic dysfunction as non-motor symptom in PD [82]. However, the tight link between serum vitamin D concentrations and risk as well as severity of PD is also underlined by a recent systematic review and meta-analysis of Luo et al. [83].

PD is not only caused by environmental factors, for example, the vitamin D status, but also by genetic components. The first monogenetic mutation, which was

found to be associated with early onset familial PD, is located in the *SNCA* gene that encodes the α-synuclein protein [84]. A recent study was able to show an altered expression of *Snca* in brains of vitamin D-deficient mice, underlining a causal relationship between hypovitaminosis and PD [63]. Consistent with several previous publications, this is also supported by two recent studies analyzing SNPs in *VDR* and the vitamin D-binding protein. Besides the functional VDR polymorphism, FokI was reported to be associated with cognitive decline in PD and ApaI with the risk of PD, while vitamin D-binding protein gene was suggested as a risk factor for PD [85, 86]. In line with this, a double-blind, placebo-controlled intervention study from Suzuki and colleagues, including 114 PD patients, was able to reveal that supplementation of 1200 IU vitamin D_3/day prevents disease progression in a VDR FokI genotype-dependent manner [87]. Moreover, high-dose supplementation of vitamin D (10,000 IU/day) resulted in significant improved balance measured via sensory organization test in PD patients with an age of 52–66 but not in older individuals [88].

To elucidate the underlying molecular mechanisms by which vitamin D exerts its potential beneficial role, animal and cell culture experiments were performed. Vitamin D_3 seems to have a positive influence on synthesis and storage of dopamine in CNS by protecting against dopaminergic toxins such as 6-hydroxydopamine or hydrogen peroxide in rats [89]. This neuroprotective effect could be due to its ability to elevate the expression of the glial cell line-derived neurotrophic factor (GDNF) that influences the dopaminergic nigrostriatal system [90] and due to its antioxidative properties described before. Furthermore vitamin D_3 administration was shown to prevent zinc-induced oxidative stress in substantia nigra of rat brain [91]. Oxidative stress and elevated intracellular-free calcium promote the aggregation of α-synuclein synergistically, and a recent study could show that the vitamin D_3 analogue calcipotriol is able to induce the expression of calbindin-D28k, thereby inhibiting the calcium-mediated aggregation of α-synuclein in human neuroblastoma cells [92].

4. Multiple sclerosis

Multiple sclerosis (MS) is a multifactorial, chronic disease of the CNS characterized by demyelination, inflammation, and neurodegeneration.

Epidemiological studies indicate that genetic and environmental factors interact and influence the risk of MS, for example, several SNPs or environmental exposures like an infection with Epstein-Barr virus (EBV), vitamin D status, sunlight exposure, or smoking. There is a high prevalence for MS in areas with low sun/ultraviolet sun exposure [93, 94], and this could be explained by vitamin D [95]. A study from Lucas and colleagues revealed that vitamin D and sun exposure are independent risk factors of CNS demyelination [96]. For an overview over environmental factors and MS, we suggest an article from Ebers GC [97]. Genetic predispositions which are associated with MS are found in genes of the immune system. The strongest correlation was found for genes of the major histocompatibility complex (MHC), especially the HLA genotype HLA-DRB1 [98]. Findings from Ramagopalan and colleagues suggest a direct functional link between known environmental risk factors, for example, vitamin D, and established genetic predispositions. The authors described the localization of a vitamin D response element on the promotor region of *HLA-DRB1* and underlined its functional role by the finding that treatment with calcitriol results in an increased expression [99]. Later on this research group could show that mutations in the *CYP27B1* gene, involved in vitamin D_3 metabolism, are causative associated with the risk of MS [100]. Moreover, genetic variations

in the *CYP24A1* gene, involved in catabolism of vitamin D, were found to play a pathogenic role in MS [101]. For detailed information about the results of several genome-wide association studies analyzing the genetic risk of developing MS, we recommend a recent publication from Baranzini and Oksenberg [102].

Clinical studies indicate that vitamin D influences MS development and disease activity including the risk of relapse, gray matter volume loss, and clinical course of MS. A prospective study from Munger et al. included participants from the US military personnel and reported a significantly decreased risk of MS with elevated levels of 25(OH)D_3 [103]. Furthermore, a cross-sectional study described a link of serum 25(OH)D_3 levels with both relapse rate and disability in MS patients [104]. In line with this, an association of reduced serum 25(OH)D_3 levels with a higher risk of relapse in MS was reported in a prospective longitudinal study including 73 individuals with relapsing-remitting MS [105]. Consistent findings are obtained from a retrospective study describing an association of a 10 ng/ml increase in 25(OH)D_3 level with a 34% reduced relapse rate in pediatric-onset MS [106] and from a prospective study reporting a 25(OH)D_3 elevation of 10 nmol/L to be associated with a 12% decreased risk of relapse in a cohort including 145 participants [107]. A 5-year longitudinal study from Mowry and colleagues using magnetic resonance imaging (MRI) as marker of disease activity provided evidences for a lower risk of developing new T2 lesions and gadolinium-enhancing lesions as well as reduced subsequent disability attended by an 10 ng/ml increase in 25(OH)D_3 level [108].

As mentioned before in the context of AD, these clinical studies are not able to rule out the possibility of reverse causality. In this context MR studies are of great interest analyzing this potential causal relationship of vitamin D and MS risk. Mokry et al. identified four 25(OH)D_3 level-associated SNPs in a large genome-wide association study for vitamin D, called SUNLIGHT, and performed an MR study to examine the influence of genetically reduced vitamin D_3 levels on the odds of MS in a large genetic association study for MS. This leads to the finding that genetically reduced vitamin D_3 levels are strongly linked to an elevated MS risk [109]. This thesis is furthermore supported by another novel MR study that described causal effects of decreased vitamin D_3 levels on pediatric-onset MS [110]. A very recent study from Graves et al. provides evidence for a causal link between 25(OH)D_3 and MS relapses in children. The authors indicate that a vitamin D genetic risk score (vitDGRS) can support the identification of patients at greater relapse risk [111].

The protective role of vitamin D could be exerted on the molecular level mainly due to its several potential immunomodulatory effects. These are summarized in a review from Smolders and colleagues. The authors pointed out that vitamin D causes a shift to an anti-inflammatory immune response and increased regulatory T cells as well as reduced pro-inflammatory helper cells like Th1 and Th17 selectively [112]. In line with this, a study from Munger et al. reported an overlap of genes associated with vitamin D_3 and those associated with processes of immune regulation. Furthermore they suggest the sphingosine-1-phosphate receptor-dependent migration of lymphocytes from secondary lymphoid tissue as potential vitamin D_3-mediated mechanism [113]. Additional evidences for the MS-underlying molecular mechanisms arise from a recent study using the L-type calcium channel antagonist nimodipine, showing decreased neurodegeneration in experimental autoimmune encephalomyelitis (EAE), a mouse model of MS. The authors reported calcium channel-independent, microglia-specific effects: induction of apoptosis, reduced levels of NO and ROS, as well as positive effects on remyelination [114].

Based on the results of all these studies demonstrating a causal link between vitamin D hypovitaminosis and the risk of MS, the role of vitamin D_3 supplementation in MS therapy was investigated. A study from Munger et al. reported an approximately 41% reduced relative risk of MS due to the supplementation of

400 IU vitamin D/day in two large cohorts of women [115]. Several following studies also describe beneficial effects of vitamin D_3 supplementation on gadolinium-enhancing lesions, relapses, and T-cell proliferation without unrequested calcemic side effects [116–118]. Inconsistent with these results, another study revealed no positive effect of high-dose vitamin D_3 supplementation (20,000 IU/week) on course and activity of the disease, for example, the relapse risk. A possible explanation for this finding could be individuals with high vitamin D_3 levels in the placebo group. Furthermore the authors could not preclude that the used vitamin D dose was too low or that the sample size was too small [119]. In this context it should be mentioned that the individual vitamin D metabolism, which could be influenced by genetically mutations in the enzymes required for the anabolism and catabolism of vitamin D_3 as discussed before, has to be analyzed since this would influence the response to identical supplemented doses of vitamin D in different individuals [120]. Subsequent studies were able to show a reduction in relapse rate after supplementation of vitamin D_3 [121] and an improved cognitive performance [122]. Oral supplementation of 20,000 IU vitamin D_3/week in a 96-week randomized double-blind placebo-controlled study in 68 MS patients results in reduced levels of anti-EBV nuclear antigen 1 (EBNA1) protein and fragment antibody [123]. A previous study could show a remarkable overlap of EBNA2 with VDR binding sites and thereby demonstrates a genetic argument for an interaction between genetic and environmental risk factors of MS [124]. A current study reports that long-term supplementation for several months with high doses of cholecalciferol results in a significantly promoted aggravation of clinical and histological EAE, but simultaneously they find a direct, anti-inflammatory, beneficial effect of vitamin D on lymphocytes of human and murine origin [125].

5. Prion diseases

Prion diseases are a group of neurodegenerative disorders whose pathology is caused by the conversion of the cellular prion protein (PrPC) into a misfolded form of the protein, called prion or "scrapie prion protein" (PrPSc), a proteinaceous, insoluble, infectious particle which is resistant to proteases and seems to act as template for exponential transformation and further accumulation of prion proteins. One characteristic of prion diseases is their appearance by sporadic (spontaneously conversion, Jakob-Creutzfeldt disease), genetic (familial mutations in the prion protein gene, PRNP), or acquired (accidentally transmission or infection) mechanisms [126].

A study on transgenic mice was able to identify a naturally occurring polymorphism in the human PRNP which is very rare but seems to completely prevent prion disease [127]. Up to this date, no clinical trial on human prion disease was successful, and most of the analyzed chemical compounds failed as potential therapeutics because of their toxicity. A study from Suenaga and colleagues intended to identify compounds that interfere with the direct PrPC-PrPSc interaction by screening hydrophobic vitamins. The authors reported for the first time that vitamin D_2 was able to interact with a truncated form of human recombinant PrPC leading to a reduced oligomerization in vitro. The absence of such an effect mediated by vitamin D_3 could be due to structural differences between these two vitamin D forms. This study suggests vitamin D_2 as suitable therapeutic candidate to target PrPC in the brain of patients with prion disease because of its direct inhibition of PrPC oligomerization, its blood–brain barrier permeability, and its safety compared to other synthetic compounds [128]. But apart from that, more studies, especially clinical trials, are essential to elucidate the relationship of vitamin D and prion diseases.

6. Amyotrophic lateral sclerosis

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease that affects upper and lower motor neurons in the brain and spinal cord resulting in paralysis [129]. It is characterized, similar to the abovementioned vitamin D_3-associated diseases, by oxidative stress, inflammation, mitochondrial dysfunction, and neurodegeneration [130].

Clinical studies result in inhomogeneous findings about a possible role of vitamin D on ALS. A retrospective study including 57 ALS patients reported neither significant differences in 25(OH)D_3/D_2 blood levels in comparison to 57 healthy individuals nor an improvement of the recorded clinical, ALS-related variables after oral supplementation of 100,000 IU of vitamin D_3/week for 4 weeks and thereafter 25,000 IU every 15 days compared to untreated participants. But as discussed by the authors, potential limitations of this study are its retrospective character and the sample size [131]. Two earlier studies also described an absent relationship between serum 25(OH)D_3 levels and prognosis in ALS [132, 133]. A very recent study examined the outcome of supplementation of 50,000, 75,000, and 100,000 IU vitamin D_3/month on motor dysfunction and clinical progression of ALS. After 6 months, they reported increased levels of serum 25(OH)D3 from approximately 14 ng/mL at starting point to approximately 40 ng/mL after supplementation of 75,000 and 100,000 IU vitamin D_3 monthly, but there were no statistically significant differences in the tested clinical ALS characteristics. As the authors mention, the sample size of 10–12 participants per group as well as the short duration of the follow-up study has to be taken into consideration [134].

In contrast to these findings, a study from Karam et al. reported vitamin D level less than 30 ng/mL for 81% of their patients with ALS and additionally improvements in the Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS-R) score after supplementation of 2000 IU vitamin D/day for 9 months in 20 participants [135]. In line, a subsequent study described a neuroprotective role for the biologically active form of vitamin D_3 as well as a four-time accelerated decline and reduced expectation of life due to hypovitaminosis D [136]. These variable outcomes strengthen the need of further clinical studies with an adequate sample size to reach statistical power and follow-up period analyzing the effect of vitamin D_3 on ALS. A first evidence of a genetic link between vitamin D_3 and ALS arises from a study from Török and colleagues describing that a SNP in the *VDR* gene is associated with ALS [137]. Further suggestions of a potential role of the VDR in ALS derived from the finding that VDR-knockout mice have muscular and motor disruptions but no reduced cognitive performance [138].

In contrast to the ambiguous clinical studies, animal trials provide evidences for a positive effect of supplemented vitamin D_3 on ALS. Studies from Gianforcaro and colleagues reported beneficial functions of high-dose dietary vitamin D_3 supplementation on the paw grip endurance and motor performance of transgenic G93A ALS mouse model while decreased performance of functional outcome in vitamin D_3 deficient mice [139, 140].

In reference to the above itemized similarities in ALS characteristics with other neurodegenerative diseases, it is not remarkable that the molecular mechanisms of which vitamin D_3 is suggested to have a beneficial influence on ALS are overlapping. Vitamin D_3 could decrease the elevated levels of TNF-α or IL-6 found in ALS patients [141] or influence calcium metabolism by regulating the expression of calcium-binding proteins, known to be impaired in ALS [142]. More detailed information can be found in the publications from Gianforcaro et al. and Long et al. [143, 144].

7. Huntington's disease

Up to this date, only a few studies are available examining a possible relationship between vitamin D_3 and Huntington's disease (HD), a neurodegenerative disorder characterized by impairments in cognition, motor behavior, and psychiatrics. HD is caused on molecular level by an expansion of an autosomal dominantly inherited CAG trinucleotide repeat in the huntingtin (*HTT*) gene which is located on chromosome four in humans. This leads to the expression of a mutant huntingtin protein containing an abnormal long polyglutamine repeat [145]. The number of repeats is associated with the risk of developing HD [146]. A recent clinical review describes the consequences of mutant huntingtin on cellular level, including interferences in transcription and protein homeostasis as well as mitochondrial dysfunction and direct toxicity of the altered protein itself. This leads to a disruption in neuronal function and further cell death and neurodegeneration [147]. To our knowledge, there are no current epidemiological or clinical studies suggesting a relationship between vitamin D status and HD, just an explorative study from Chel and colleagues. They reported a high prevalence of deficient or insufficient serum vitamin D level (<50 nmol/L) in 28 individuals with manifest HD [148]. In line with this, a recent study on HD transgenic mice showed no effect on motor performance but a significantly prolonged lifespan after subcutaneous supplementation of 12,000 IU vitamin D_3 per kilogram weight [149]. Further evidences for an influence of vitamin D_3 on HD arise from a recent publication of Seuter and colleagues analyzing the epigenome-wide effects of vitamin D in THP-1 human monocytes. They identified 165 physiologically important target genes after supplementation of 1,25-dihydroxyvitamin D_3 being one of them the *HTT* gene [150].

8. Neuropsychiatric diseases

Beside neurodegenerative disorders also neuropsychiatric diseases affect the nervous system, and therefore we would like to give a brief summary of recent studies analyzing a possible influence of vitamin D on autism spectrum disorders (ASD), depression, and schizophrenia. Epidemiological studies demonstrated an elevated prevalence for ASD in children born at higher latitudes [151] and in offspring of highly pigmented women [152] as well as lower vitamin D levels of children with autism [153]. Furthermore maternal, gestational hypovitaminosis D is associated with a higher ASD risk [154, 155]. Recent findings of strong associations of ASD with polymorphisms in the VDR or other genes involved in vitamin D_3 metabolism [156, 157] hypothesize vitamin D_3 as environmental and genetic factor influencing ASD [158]. On the molecular level, cellular processes like oxidative stress or neuroinflammation were shown to play a role in ASD [159], and they could present a potential contact point for vitamin D_3. In line with the abovementioned link between ASD and vitamin D, a vitamin D-deficient rat model revealed broad behavioral similarities between vitamin D-deficient models and ASD-associated behavior [160]. Treatment of an ASD rat model with high-dose vitamin D revealed significant protective effects [161]. In contrast to supplementation in animal trials, the first randomized controlled clinical study analyzing the daily supplementation of 300 IU vitamin D3/kg for 4 months on 109 children with ASD, resulting in significant improvement of autism symptoms, was retracted 1 month ago [162]. This lets us conclude that vitamin D_3 can be suggested as possible preventive treatment for the prevention of ASD, but more studies supplementing pregnant women and their children with adequate levels of vitamin D_3 have to be performed.

A potential link between vitamin D_3 and depression is subject of current research, and for more detailed information about the potential role of vitamin D on major depressive disorder, we recommend a review from Casseb et al. [163]. A meta-analysis from Parker and colleagues concluded that there are increasing evidences for an influence of vitamin D on depression [164], and in line with this, another review also postulated hypovitaminosis D as risk factor for late-life depression [165]. Consistently, a very recent meta-analysis reported a negative association of serum 25(OH)D_3 levels with the risk of depression [166].

A following cross-sectional study including 100 women in reproductive age also shows that the depression score inverse correlated with the vitamin D serum level [167]. Contradictorily, a supplementation with 1200 IU vitamin D for 12 months failed to have an influence on the prevention of depression in a very recent, randomized clinical trial including 155 participants having clinically relevant depressive symptoms [168]. Furthermore, a recent MR study from Libuda and colleagues indicates no causal relationship between both depressive symptoms and broad depression and vitamin D levels due to a missing association of six vitamin D-related SNPs with depression [169]. In summary, the current research investigating the role of vitamin D_3 in depression is much less clear than other neurological disorders.

In respect to the chronic mental illness schizophrenia, it could be shown that hypovitaminosis D is common in patients [170]. This fits to the environmental risk factors that have been described for schizophrenia, like season of birth [171] and latitude [172]. Also a link between neonatal vitamin D levels and the schizophrenia risk was reported [173]. A recent randomized, placebo-controlled study from Krivoy and colleagues examined psychosis severity, mood, cognition, and metabolic profile in 47 schizophrenia patients during an 8-week supplementation of 14,000 IU vitamin D/week. The authors described no significant effects on psychosis, mood, or metabolic status, but a trend to an improved cognitive function accompanied by significant elevated vitamin D levels in the supplemented group. A possible explanation for these findings, given by the authors, could be that a medical score that measures the symptom severity in schizophrenia patients decreased during the study in the placebo as well as in the treated group and could thereby veil the influence of supplemented vitamin D [174]. An actual study reported beneficial effects of supplementation of vitamin D_3 in combination with probiotics in schizophrenia patients [175]. Addressing the underlying molecular mechanism, vitamin D could perform its suggested beneficial actions via modulation of immune system and inflammation processes since it was reported that patients with chronic schizophrenia have significantly elevated levels of TNF-α and IL-6 [176]. Furthermore, it could be shown that the expression of genes involved in the metabolism of vitamin D_3 (*VDR*, *CYP27B1*, *CYP24A1)* is significantly elevated in peripheral blood of schizophrenic patients [177], indicating a potential causal relationship between vitamin D_3 and schizophrenia, which should be the aim of future research.

9. Conclusion

In summary, in the current literature, several lines of evidence suggest a tight link between vitamin D_3 and neurodegenerative diseases (see **Table 1**). Besides epidemiological studies, vitamin D deficiency influences several pathways associated with neurodegenerative diseases, which also indicates a causal link of hypovitaminosis D and AD, MS, and PD. As a consequence, vitamin D hypovitaminosis is broadly assumed to be a risk factor for these diseases. In addition, recent literature underlines a potential link between prion diseases, ALS, HD, and neuropsychiatric

	Alzheimer's disease	Parkinson's disease	Multiple sclerosis	Prion disease	Amyotrophic lateral sclerosis	Huntington's disease
Epidemiological and clinical studies	Vit. D levels ↓ [39, 40] Risk factor [41, 43–48] Causal link [51–56]	Vit. D levels ↓ [76–79] Severity of PD [80–81, 83] Genetic link [85–86]	Risk factor [96, 103] Genetic predisposition [99–101] Causal link [109–111]	/	Non-consistent findings [132, 133, 136] Evidence of genetic link [137]	Vit. D levels ↓ [148]
Animal and cell culture studies	Causal link [63] Transcription [62]	Causal relationship [63]	Regulatory T cells ↑ [112]	Vit. D2 as suitable therapeutic candidate [128]	Potential role of the VDR [138] Benefits after supplementation [139, 140]	Vit. D supplementation ↓ prolonged lifespan [149] Epigenomic action on *HTT* gene [150]
Molecular mechanisms	APP homeostasis [64–69] Neurotrophins [71–73] Inflammation [74] Ca^{2+} homeostasis [6]	Dopamine homeostasis [89] Antioxidative properties [91] Ca^{2+} homeostasis [92]	Immunomodulatory effects [113] Ca^{2+} homeostasis [114]	Reduced oligomerization of prions [128]	Inflammation [141] Ca^{2+} homeostasis [142]	Potential transcriptional regulation of *HTT* gene [150]
Intervention studies	Beneficial [58]	Beneficial in dependence of genotype [87]	Beneficial [115–118] Vit. D as genetic and environmental risk factor [124]	/	Variable outcomes [131, 134]	/

Vit. D, vitamin D; APP, amyloid precursor protein; Ca^{2+}, calcium; PD, Parkinson's disease; VDR, vitamin D receptor; ↓ reduced.

Table 1.
Summary of the current research findings about the influence of vitamin D on selected neurodegenerative diseases Alzheimer's disease, Parkinson's disease, multiple sclerosis, prion disease, amyotrophic lateral sclerosis, and Huntington's disease in respect to epidemiological and clinical, animal and cell culture studies, identified molecular mechanisms, and intervention studies.

diseases and reduced Vitamin D level; however, it has to be emphasized that many aspects of vitamin D remain obscure in these diseases. Therefore, further studies to clarify and judge a potential beneficial effect of vitamin D_3 are needed to unravel the exact role of vitamin D in brain metabolism and neurodegenerative diseases. Especially determination of the individual serum 25(OH)D_3 levels by appropriate methods like mass spectrometry and taking the individual patient's competence to metabolize or form active vitamin D_3 into consideration will help to avoid ambiguous results. The fact that several prospective studies investigate a mixture of several different nutritional components makes it hard to trace the observed effects back to vitamin D in particular at the moment.

Interestingly some European countries, like Finland, already supplement vitamin D in general in food to prevent hypovitaminosis in the elderly population, and an optimal intake of 2000–4000 IU vitamin D or 10–20 min sunlight exposure per day is already recommended by experts, for example, at the Joint International Symposium Vitamin D in Prevention and Therapy and Biologic Effects of Light (2019). Further studies will help to validate the beneficial effects of these recommendations.

Conflict of interest

The authors declare no conflict of interest.

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