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VITAMIN D IN NEUROLOGICAL DISEASES:

A RATIONALE FOR A PATHOGENIC IMPACT

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Abstract

It is widely known that vitamin D receptors have been found in neurons and glial cells and their highest expression is in the hippocampus, hypothalamus, thalamus and subcortical grey nuclei, and *substantia nigra*. The vitamin D helps the regulation of neurotrophin, neural differentiation and maturation, through the control operation of growing factors synthesis (ie NGF and GDNF), the trafficking of the septo-hyppocampal pathway, and the control of the synthesis process of different neuromodulators (such as Ach, DA, and GABA).

Based on these assumptions, we have written this review in order to summarize the potential role of vitamin D in neurological pathologies. The work could be titanic, and might result very fuzzy and even incoherent, if we would not have conjectured to taper our first intentions and devoted our interests towards three mainstreams: demyelinating pathologies, vascular syndromes and neurodegeneration.

Due to the lack of effective therapeutic options, a part from the disease modifying strategies, the role of different risk factors should be investigated in neurology, as far as their correction may lead to the improvement of the cerebral conditions.

We have explored the relationships between the gene-environmental influence and long term vitamin D deficiency, as a risk factor for the development of different types of neurological disorders, along with the role and the rationale of therapeutic trials with vitamin D implementation.

Key words: neuro-degeneration, MS, demyelination, vascular disease, stroke, AD, vitamin D-OH 25, VDR, VDH, calcium.

SEARCH STRATEGY AND SELECTION CRITERIA

We searched MEDLINE using the search terms: “vitamin D central nervous system” , both “vitamin D” and “central nervous system”; “vitamin D immune system/response”, both “vitamin D” and “immune system” or “immune response”; “vitamin D multiple sclerosis risk”, both “vitamin D” and “multiple sclerosis risk”; “vitamin D multiple sclerosis relapse”, both “vitamin D” and “multiple sclerosis relapse”; “vitamin D multiple sclerosis magnetic resonance imaging”, both “vitamin D” and “multiple sclerosis magnetic resonance imaging”; “vitamin D multiple sclerosis disability”, both “vitamin D” and “multiple sclerosis disability”; “vitamin D supplementation/therapy/treatment multiple sclerosis”, both “vitamin D supplementation” or “vitamin D therapy” or “vitamin D treatment” and “multiple sclerosis”; “vascular dementia”, both as –vascular- and –dementia-, “subcortical vascular dementia”, both as –subcortical- and –dementia-, “Alzheimer’s disease”, “pathogenesis neurodegeneration” “amyloid”, “cholinergic afferents”, “arteriolosclerosis”, “cerebral flow regulation”, “stroke”. Publications were selected mostly form the past 20 years, but did not exclude frequently referenced and highly regarded older publications. Researchers have been extended to EMBASE, with the same strings, to COCHRANE LIBRAY, to LILACS. All searchers were done from January 1st 1993 up to May 31st 2018. We have considered papers published in English, French, German and Italian. Secondary searching was performed using the bibliography of the most relevant articles (in accordance with PRISMA statement, 2009) [65]. Congress abstracts and isolated case reports were not considered. We searched the reference lists of articles identified by this search strategy and selected those we judged relevant. Review articles and book chapters are cited to provide with additional details. A total of 7876 studies showed up and appropriate studies (n=282) were included. All the eligible articles were carefully read by the authors.

Introduction

Low levels of vitamin D, considering serum 25-hydroxy-vitamin D (25(OH)D), have been recognized as a widespread health problem, affecting approximately 1 billion people worldwide [1]. Latitude, season, cultural norms, religious practices, low awareness, low knowledge/health literacy, indoor lifestyles, urban living, skin pigmentation, malnutrition, diet, co-morbidities like tuberculosis, and drugs may contribute to vitamin D deficiency especially in the in the developing world, moreover, blacks tend to have lower levels of 25(OH)D compared to whites [2, 3]. It has been widely demonstrated that Vitamin D is also involved in different non-skeletal functions, including hypertension, diabetes, multiple sclerosis, Alzheimer's disease, Parkinson's disease, and Stroke [4,5,6,7].

Methabolism and biological actions of Vitamin D

Vitamin D is a lipid-soluble vitamin, which can be synthesized and acts like a hormone [8]. The active form of vitamin D, $1,25(OH)_2D$, known as calcitriol, has chemical similarities to typical hormones such as testosterone, estrogen, and cortisol. The vitamin D receptors (VDR) are found in almost all human tissues, participating in the classic actions of vitamin D in the bone, gut, and kidney, but also are involved in immune functions, hormone secretion, and cellular proliferation and differentiation [9].

The presence of Vitamin D receptors (VDR) in the hippocampus, hypothalamus, thalamus, cortex, and subcortex and substantia nigra [10] induced many studies, on the possible determinant role of vitamin D, in different neurological conditions [11-12]. Calcitriol is a fundamental actor in the neuronal differentiation and in the neural maturation [13]. Vitamin D normalizes the trafficking of the septo-hippocampal pathways, mainly *via* NGF; moreover, it is a strong controller of the genetic regulation of the synthesis of acetylcholine, dopamine, serotonin and gamma aminobutiric [14-16].

The knock-out model of VDR-/- has an accelerated aging process in all the organs, and in the brain [17-18], with a significant in-brain decrease of NGF [19] and of other neurotransmitters, such as acetylcholine [20-24]. Congenital deficiency of vitamin D significantly reduces the activity of glutamic acid decarboxylase (GAD) 65/67 (key enzymes in GABAergic inter-neurons) and the levels of glutamate and glutamine in brain tissue [25].

Vitamin D deficiency and multiple sclerosis: role in the susceptibility, activity and treatment of the disease

Immunological researches make two major observations to explain the link between vitamin D and the immune system. First, most immune cells, both the innate and adaptive immune system, expresses the vitamin D receptor (VDR) [26-28]. Moreover, such immune cells exhibit an active vitamin D metabolism, with the expression of the rate-limiting enzyme for vitamin D synthesis, 1α-hydroxylase (CYP27B1) [29]. Immune cells are, therefore, able to synthesize and secrete Vitamin D in both an autocrine and paracrine way [29-30]. Immune cell types targeted by vitamin D include

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monocytes and macrophages, dendritic cells (DCs), T and B cells [31]. 1,25(OH)$_2$ vitamin D induces monocytes proliferation and differentiation into macrophages [32], expression of interleukin-1 (IL-1) and antimicrobial peptides (cathelicidin, β-defensin-2, hepcidin) [33]. Vitamin D inhibits DC differentiation and maturation, their expression of major histocompatibility complex (MHC) class II, CD40, CD80, CD86 and IL-12 (whereas inducing the production of IL-10), leading to reduced T-cell stimulatory capacity [34-36]; it decreases the production of nitric oxide (NO), via downregulation of inducible nitric oxide synthase (iNOS) expression [37]. Moreover, it stimulates the development of natural killer T (NKT) cells, and it increases IL-4 and IFN-γ production by NKT cells [38]; it attenuates the proliferation of CD8+ T cells and their cytotoxic activity, by reducing the production of IL-2, IL-17 and IFN-γ; it exerts its immunomodulatory effects on T lymphocytes by inhibiting the production of pro-inflammatory Th1 cytokines (IL-1, IL-2, IL-6, IL-12, IFN-γ, TNF-α, TNF-β), and stimulating the production of anti-inflammatory regulatory Th2 cytokines (IL-4, IL-5 and IL-10) [39-40]. Thus, Vitamin D potentiates the innate immune system and regulate the adaptive immune system, particularly by inducing polarization to Th2 and T_{reg} over Th1 and Th17 lymphocytes differentiation [41], via direct and indirect actions on naive CD4+ cells, with an overall effect of switching from a pro-inflammatory autoimmune to an anti-inflammatory tolerogenic immunological profile.

In Multiple Sclerosis (MS) patients, the blood level of 25(OH)D or 1,25(OH)$_2$D has been correlated with the suppressive activity of Regulatory T-cells (Tregs) [42-43], and the number of Tregs has been correlated with the serum levels of 25(OH)D or 1,25(OH)$_2$D (Royal, 2010). Tregs are increased in MS patients supplemented with vitamin D [44-45].

Little is known about the role of vitamin D in remyelination. According to many studies, vitamin D may have an impact on the balance between the inflammatory and anti-inflammatory mechanisms involved in remyelination. Vitamin D increases microglial activation, promoting the clearance of myelin debris, and consequently remyelination [46]. In OPC cell cultures, vitamin D upregulates the transcription of VDR and neurotrophic growth factor (NGF) mRNA, but not of myelin basic protein (MBP). Oligodendrocytes express VDR, and 1,25(OH)$_2$D depletion results in reduced differentiation into oligodendrocytes and demyelination [47]; vitamin D and VDR therefore positively regulate oligodendrocytes progenitor culture (OPC) differentiation. VDR expression has been observed in OPCs in MS tissue cultures [48-49]. In vitro studies show that blocking VDR reduces OPC differentiation, myelination, and remyelination, whereas activating VDR via vitamin D increases differentiation [50]. Likewise, neural stem cells (NSC) express VDR and 1,25(OH)$_2$D. The latter increases NCS proliferation and differentiation into neurons and oligodendrocytes, reducing astrogliosis [51]. Vitamin D promotes NCS proliferation in murine models of MS [52]. Moreover, vitamin D-induced microglial activation promotes phagocytosis of amyloid-β peptides (Aβ), thus preventing axon damage: Aβ expression

is increased in demyelinating plaques [53-55], which may cause toxicity at later stages. Remyelination of demyelinated lesions has been observed in the early stages of MS [56-58], and it has been supported by neuroimaging findings [59-65]. However, remyelination is incomplete [66] and eventually ceases [67], perhaps due to the inability of OPC to migrate and reach the site of demyelination [68], or to a lack of suitable conditions for differentiation [69]. An inflammatory microenvironment prevents OPC maturation and differentiation into oligodendrocytes, and subsequent prevents axon remyelination. This is relevant for MS treatment, since current treatments are effective only in controlling immune mechanisms (i.e., in the early stages of the disease), but have no effect on remyelination.

Since vitamin D deficiency was proposed as an important risk factor in MS development since the 1970s, most epidemiologic observational studies have suggested that adequate vitamin D levels may reduce the risk of MS onset and modify the course of the disease. MS is a disease that is essentially unknown at the equator, and the prevalence of the disease increases in populations that live farther away from the equator [70]. Prevalence of MS is greater at higher latitudes and tends to peak in areas with the lowest exposure to ultraviolet (UV) light [71-77]; however, in these areas, diets rich in Vitamin D-containing oily fish may offset this risk to some degree [71-72, 78]. Moreover, the risk of MS has been found to decrease among people who migrate from higher to lower latitudes [79]. This latitudinal finding has been declining in recent decades, instead of an associated increasing trend towards avoiding sun exposure by staying indoors for longer periods of the day, even in warmer climates [80-81]. In fact, higher levels of sun exposure (past, recent, and cumulative) was independently associated with higher levels of vitamin D and with a significant reduced risk of developing demyelinating events [82]. Sunlight seems to have an immunosuppressive effect and, therefore, the effects of sunlight on MS risk could be related to sunlight itself, or to an increase of vitamin D [83]. The association between calculated vitamin D intake from diet or supplements and the risk of developing MS, has been prospectively evaluated in two large cohorts involving more than 187,000 women [84]. Woman who had a higher intake of dietary vitamin D (approximately 700 IU/day) had a 33% lower incidence of MS compared with those with lower intake. Moreover, women who used vitamin D supplements (more than 400 UI/day) had a 41% reduced risk of developing MS compared to non-users. Higher levels of 25(OH)D (independently from dietary vitamin D intake) also seem to predict a lower risk of MS onset. A longitudinal study evaluated serum vitamin D levels derived from blood samples of seven million US military personnel [85]. Those with 25(OH)D levels superior to 40 ng/mL had a 62% lower chance of developing MS. A more recent prospective study confirmed these findings and reported that levels of vitamin D over 30 ng/mL were associated with a decreased MS risk [86]. Adiposity has been associated with lower vitamin D levels [87-88], and higher body mass index (BMI) has been associated with higher incidence of MS in adolescent women, but not in adult women [89].

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A crucial question related to a primary prevention trial or to a all-encompassing recommendations from vitamin D supplementation in MS, is the relevant age of exposure, which can range from in utero, till to adolescence and to adulthood [90]. Mirzaei et al. studied a large cohort and analyzed the association between maternal dietary vitamin D intake, and predicted maternal serum 25(OH)D during pregnancy and their daughters' risk of developing MS [91]. The study showed that the relative risk of MS was significantly lower in women whose mothers had high vitamin D intake during pregnancy than in women born to low-intake mothers. A diminished in utero exposure to vitamin D, coupled to the solar cycle and latitudinal differences, may be an environmental risk factor for the development of MS. Similarly, albeit not statistically significant, a reduced MS risk was reported among women reporting increased vitamin D intake from supplements in adolescence [92]. These results suggest that MS risk is related not only to recent vitamin D levels, but it might be also related on its levels during childhood or even in utero. Several studies including a meta-analysis demonstrated that spring-borns have a significant higher lifetime MS risk than autumn-borns, which has been attributed at least in part to an insufficient in utero vitamin D levels because of low maternal serum vitamin D levels during winter [93-94]. In a large population-based case-control study [95], children born with 25(OH)D levels <10 ng/mL seemed to be at a high risk of developing MS. Likewise, the level of sun exposure in childhood and adolescence, e.g. by outdoor leisure activities which may serve as a proxy for vitamin D supply in early life, has been inversely linked to the risk of MS in adulthood [96-99]. In a recent longitudinal Canadian study of 302 children with acute demyelinating syndrome, low vitamin D levels were significantly associated with MS risk in the subsequent three years [100]. One report showed that children with higher serum 25(OH)D concentrations at presentation with an acquired demyelinating syndrome had a lower risk of early MS diagnosis [101]. Gender- and sex-related immunological differences may have an influence on the association between vitamin D and MS. The disproportional increase in the incidence of MS in women is likely to be caused by sex-specific exposure or susceptibility to environmental factors [102]. Data supporting an interaction between female sex, possibly mediated by oestrogen, and vitamin D in MS risk are accumulating. A protective effect of sun exposure was only observed in female monozygotic twins [103], and the association of sun sensitive skin types with disability was only found in untreated female MS patients [104]. In vitro studies of MBP-specific T cell proliferation have shown sex differences in the metabolism of vitamin D that were confirmed by treating male MBP-specific T cells with 17β-estradiol in the assay [105]. In one animal study, vitamin D resulted in fewer clinical, histopathologic, and immunologic signs of EAE in female mice compared with ovariectomized females and intact or castrated males [106].

It has been assessed the eventual role of vitamin D in MS disease progression: it has been hypothesized that 25(OH)D levels can predict later development of MS in acute optic neuritis (ON) [107], but result are unconclusive.

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A discrete quantity of studies demonstrated that vitamin D levels affect clinical relapses and MS disease activity. In a retrospective study of 110 patients with pediatric-onset MS, the authors found that each increase of 10 ng/mL in 25(OH)D level was associated with a 34% decrease in relapse risk [108]. Similar findings were seen in a prospective cohort study, whose authors concluded that raising 25(OH)D by 20 ng/mL could decrease the hazard of a relapse by up to 50% [109]. In a prospective longitudinal study, relapse risk was significantly reduced in those patients with medium (20-40 ng/mL) and high (>40 ng/mL) serum vitamin D levels compared to those with low levels (<20 ng/mL) [110]. Moreover, the same authors found that for each doubling of serum vitamin D concentration from baseline of 10, 20, 30 ng/ml MS relapse risk decreased by 27%. In another study lower vitamin D levels predicted conversion from CIS to clinically definite MS [111-112]. In the study by Embry et al., low serum 25(OH)D levels predicted an increased likehood of Gd+ lesions in MRI scans performed in the subsequent 2-months period [113]. In the EPIC study [114], the authors concluded that individuals with CIS/RRMS with higher vitamin D levels have lower risk of subsequent development of new T2 lesions and of gadolinium-enhancing (Gd+) lesions on brain MRI, even after accounting for potential confounding factors. Moreover, an increment of 10 ng/mL of 25(OH)D was associated with a 15% lower risk of new T2 lesions and a 32% lower risk of Gd+ lesions [114]. In a post-hoc analysis including up to 2 years of follow-up of participants treated with interferon beta (IFNB)-1b in the BENEFIT trial [115], Gd+ lesions development was inversely associated with 25(OH)D levels; those patients whose 25(OH)D levels were >20 ng/mL had a 39% lower risk of new Gd+ lesions. Unfortunately, across all analyses, associations with lower vitamin D were generally stronger for MRI, than for clinical outcomes. Moreover, the participants of the BEYOND study [116], treated with IFNB-1b, with higher serum 25(OH)D levels, had lower numbers of new T2 and Gd+ lesions during the first 12 months of follow-up. Moreover, a 20 ng/mL higher serum 25(OH)D level was associated with a 31% lower rate of new lesions, and the patients with 25(OH)D ≥40 ng/mL showed 47% lower rate of new T2 lesions and new Gd+ lesions, when compared to patients who had serum levels of 20-32 ng/mL. Vitamin D and disease-modifying therapies (DMTs) may positively influence each other, and produce an additive, or even synergistic, effect on MS disease activity. In an observational cohort study, which included 178 patients with MS [117], patients who were treated by IFN had significantly higher 25(OH)D levels, than those who did not. Interestingly, IFN treatment was protective only against relapses among patients with higher vitamin D levels. The authors hypothesized that treatment with IFNB may increase serum vitamin D levels, through enhanced responsiveness to sun exposure [117]. The same authors did not find similar associations for glatiramer acetate (GA) therapy and vitamin D. More recently, Mowry et al. [118] found that higher vitamin D levels in CIS may slow neurodegeneration evaluated by brain volume measures. In fact, they found that each 10 ng/mL increase in 25(OH)D was significantly associated with 7,8 mL higher gray matter volume [118]. Variations in the relapse rate and number of MRI brain lesions have shown a seasonal pattern that can be related to variation in UVR exposure and

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vitamin D status [119-124] with some exceptions [125-126]. Most cross-sectional studies have concluded a negative correlation between 25(OH)D level and disability [114, 127-135], and, interestingly, even a direct correlation between 25(OH)D level and poorer memory performance [136], however causality is considered uncertain, at the moment.

Given the previous reviewed findings, the assessment of vitamin D supplementation for a possible disease-modifying course of MS, is obviously of key interest. Unfortunately, current evidence does not offer a definite consensus for the supplementation. Kimball et al. [137] performed a 6-month safety study with escalating doses of vitamin D and they found a significant reduction in the mean number of Gd+ lesions, at the end of the study. In an open-label randomized trial, patients randomized to a vitamin D supplementation had an annualized relapse rate (ARR) significantly lower in the treatment, with prolonged relapse free time and with a persistent reduction in T-cell proliferation [44]. In a 1-year double-blind randomized placebo-controlled trial with vitamin D3 as add-on treatment to IFNB-1b, MRI T2 lesion burden, as well as new/enlarging T2 lesions, tended to increase more in the placebo group than in the vitamin D group, however without statistical significance [138]. A preliminary Iranian study assessed the safety and efficacy of high-dose vitamin D supplementation during pregnancy in women with MS [139]. The women in the vitamin D group had significantly fewer relapses during pregnancy, a tendency for fewer relapses up 6 months after delivery, and a more stable EDSS than those without supplementation [139]. In a longitudinal study [140], in which 170 natalizumab-treated patients were followed for 1 year between two winter seasons, patients with insufficient serum 25(OH)D levels at baseline (<20 ng/mL) were advised to take vitamin D supplements and a significant inverse relationship with the ARR was found, since for each nmol/L increase in 25(OH)D, a 0,014 decrease in ARR was observed. The double-blind, multicentre, 48-week SOLAR study of high-dose oral vitamin D3 has been the largest study to date [141]. An insignificant trend toward lower ARR in the treatment group was found (0,28 in vitamin D group versus 0,41 in placebo), and no statistically significant differences in disease activity was found between the two groups. Vitamin D3 was associated with a statistically significant reduction in combined unique lesions (secondary endpoint). The CHOLINE study investigated the addition of vitamin D3 to IFNB-1a over 96 weeks [142] did not show a significant trend toward a lower ARR (primary endpoint) among those patients receiving vitamin D treatment, which became statistically significant when the analysis was restricted to those who completed the study. Among completers, there were also significantly fewer new T2 lesions in the vitamin D group. It is unclear whether findings of these trials are related to insufficient power or other issues leading to inability to detect a treatment effect for all outcomes.

Larger RCTs are currently underway to reveal the role of vitamin D supplementation as an add-on to IFNB therapy in the treatment of RR MS, and even CIS, patients: VITADEM study in Spain, EVIDIMS study in Germany, PrevANZ study in Australia, D-Lay-MS study in France, the VIDAMS trial in the US. One study investigated cognitive effects of

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vitamin D supplementation on patients with MS treated with IFNB [143] and after the follow-up period they scored better on the Brief Visuospatial Memory test (BVMT) delayed recall.

In conclusion, numerous studies suggest that vitamin D supplementation may benefit MS patients, although larger RCTs are needed to establish this supplementation as a standard of care in MS. Moreover, there is no consensus on the definition of "sufficient" vitamin D levels in MS, and many physicians question whether people with MS should empirically be supplemented, while awaiting for more conclusive results of vitamin D clinical trials. In the view of the IOM (Institute of Medicine), 25(OH)D levels greater than 20 ng/mL (50 nmol/L) are sufficient. The Endocrine Society, considering skeletal and non-skeletal health, argues for levels of almost 30 ng/mL (75 nmol/L). In the MS field, numerous studies suggest that serum 25(OH)D levels of approximately 40 ng/mL (100 nmol/L) are the lower limit for controlling MRI and clinical activity. Some experts favour maintaining 25(OH)D levels between 30 and 50 ng/mL in MS patients, as immunomodulatory effects have been observed in these ranges in experimental studies. Longitudinal RCTs are needed to establish the recommended levels of vitamin D supplementation necessary to reduce the risk of MS onset and MS pathological activity. According to other authors [144], for individuals with CIS or MS and vitamin D deficiency (<20 ng/mL), an "attack" supplementation with 50,000 IU/week of vitamin D2 (ergocalciferol) for 8 weeks and subsequent evaluation of serum level is recommended. Continuation of this therapy until serum 25(OH)D is greater than 30 ng/dL may be necessary. A maintenance supplementation with vitamin D3 (colecalciferol) at 1000 to 2000 IU/day may be started when the deficiency has been corrected, and at once in case of vitamin D insufficiency (20-29 ng/mL). Since current evidence also suggests both obstetric and pediatric benefit from vitamin D against the risk of developing MS, vitamin D supplementation in children and pregnant women at risk of developing or being affected by MS should be considered [144]. According to other authors, since a general aim is to goal 25(OH)D levels between 40 and 60 ng/mL, most patients should take a dose which arise from 2000 to 5000 IU/day vitamin D3 [145].

Vitamin D deficiency and ischemic stroke

Stroke is a main cause of major long-term disability all over the world and is an enormous source of global disease burden. Ischemic stroke recognize a heterogeneous etiology, caused by not modifiable risk factors (genetic, age, sex), and modifiable risk factors, like hypertension, diabetes mellitus (DM), dyslipidemia, sedentary lifestyle, and smoking [146].

Vitamin D deficiency is associated with an increased risk of vascular disease and ischemic stroke in healthy subjects, the risk is higher for ischemic stroke than for hemorrhagic ones. Moreover, vitamin D deficiency is associated with other contributing factors for ischemic stroke, i.e. hypertension, hyperlipidemia, diabetes mellitus and ischemic heart disease. In stroke, vitamin D deficiency might relate with higher disease severity and adverse outcomes including death,

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moreover, hypovitaminosis D is independently associated with larger ischemic infarct volume [147]; finally, vitamin D deficiency relates with slower recovery after stroke. Moreover, recently, Suzanne et al. [148] found that lower concentrations of 25(OH)D were associated with higher risk of incident stroke in models adjusted for age, race, age and race interaction, and sex. The magnitude and strength of the associations were unchanged after the adjustment for season of blood draw, systolic blood pressure, BMI, diabetes, current cigarette smoking, atrial fibrillation, and use of anti-hypertensive medications, aspirin and statins. In their work no statistically significant differences in the association of lower 25 (OH) D with higher risk of incident stroke were observed in blacks when compared to white subjects. Vitamin D can inhibit the development of thrombosis, which may provide a rational explanation for the relationship between vitamin D and ischemic stroke. Nevertheless, vitamin D might induce hemorrhagic stroke through other mechanisms, such as inflammation and endothelium shear stress. Even less is known regarding the relationship between Vitamin D deficiency and other cerebrovascular disease, like vessel dissection. In one study the clear relationship between low level of Vitamin D and acute aortic dissection (AAD) was not found, Vianello et al. [149] reported that in AAD hypovitaminosis D is not associated to changes in bone-related metabolic pathways, but is inversely related to Osteocalcin which could be an interesting molecule able to mediate the effect of inadequate 25(OH)D level at vascular level.

Moderate to strong associations between lower serum 25(OH)D concentrations and stroke were identified in different analytic approaches, even after controlling for traditional demographic and lifestyle covariates. Such associations were mostly evident among young females younger than 50 years. The mechanisms behind the associations between vitamin D and cerebrovascular and cardiological profiles have been widely examined in both animal and human studies. Accumulating evidence has shown negative regulatory effects of vitamin D on the renin-angiotensin system. Renin expression was significantly increased among vitamin D receptor knockout mice and suppressed among wild-type mice after injected with 1,25- dihydroxyvitamin D.7 Treatment of vitamin D in rats may lead to increased endothelium-dependent vascular relaxation, and inhibition of vascular smooth muscle cell growth and proliferation. Vitamin D supplementation in human subjects may contribute to improved insulin sensitivity and beta-cell function, and lower levels of inflammatory markers [150-153].

Moreover, vitamin D deficiency has been shown in several pathology related to higher incidence of stroke. Shah Sanket et al. reported that Vitamin D deficiency was observed in significant number of patients with Chronic obstructive pulmonary disease (COPD) and in more than half of the study subjects, there is an increasing frequency across combined COPD class of cardiovascular and cerebrovascular disease [154]. Moreover, stroke patients with enough vitamin D had more favorable outcomes, including improved muscle strength and bone density. Navid Manouchehri et al. [155] showed that Vitamin D deficiency had an increased risk of ischemic stroke by nearly 7-fold compared to

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controls. They reported an increase by 13-fold increase in the risk of large vessel stroke, and 4.37-folded increase for the small vessel stroke was observed. The risk of stroke increases with concomitant deficit of vitamin D, vitamin B12 and homocysteine. Serum homocysteine, vitamin B12, and vitamin D levels are associated with baseline first-ever stroke severity, but also contribute to some extent to is prognosis in early period after stroke. Early detection and management of these laboratory parameters may contribute both to primary and to secondary stroke prevention. Hyperhomocysteinemia increases the likelihood of stroke and is mostly dependent on folic acid (vitamin B9), vitamin B12, and vitamin B6 serum levels. Vitamin B12 deficiency can be detected in 10–40% of the general population and may contribute to stroke and cognitive decline. Status of homocysteine, vitamin B12, and vitamin D and go further to assess the importance of these correctable factors during the functional recovery after stroke.

Patients with a low level of serum vitamin D at the onset of the stroke showed more severe disability [147]. Qiu et al. [156] reported also a strict association between lower serum levels of 25(OH) D and the stroke recurrence, and stroke mortality at 24 months. Also, the inverse association between serum 25 (OH) D levels and functional outcome in patients with acute ischemic stroke had been reported. Mortality in stroke patients is higher for those subjects <75 years old with a low serum 25(OH) D level at stroke onset [156-158]. Few studies have also reported vitamin D deficiency after a stroke. Kiyoung Kim et al. [159] reported that the mean level of 25(OH)D was lower in subacute and chronic patients than in healthy controls; in addition, the level of 25(OH)D was lower in patients with a longer duration of illness after stroke for 1 month. These data suggest that it might be explained by an exhaustion of vitamin D, stored prior to stroke onset and insufficient synthesis after stroke. Finally, patients with an independent gait have higher levels of vitamin D, than immobilized patients. Restricted outdoor activity may have affected the synthesis of vitamin D after the stroke and resulted in a VDD.

Pathophysiology of stroke is quite complex and still not completely understood. Cerebral ischemic damage is due to the activation of several inflammatory events, including the infiltration of circulating immune cells and activation of microglia, astrocytes, and endothelial cells [160]. In stroke individuals, the mechanism involved in vessel disease mediated by vitamin D deficit might consist of a release of atherogenic pro-inflammatory cytokines, that foster atherosclerotic vascular changes, and might induce plaque instability [161-162]. Vitamin D plays an additional role for the regulation of inflammation process, through prostaglandin inhibition, reduction of mitogen-activated protein kinase (MAPK) and reducing the expression of the nuclear factor kappa B (NF-κB) pathways [163-165]. Moreover, down regulation of pro-inflammatory cytokines, such as tumor necrosis factor (TNF)-α, interleukin (IL)-6, IL-12, and interferon (IFN)-γ, and up regulation of anti-inflammatory T regulatory (Treg) and Th2 cells and their cytokines have been reported [166-168]. Thus, the deficit of vitamin D is responsible of endothelial dysfunction [169], and is considered an independent risk factor for the occurrence of acute ischemic stroke [170-171]. As previously reported,

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VDD is strictly associated to higher levels of high sensitivity C-reactive protein (hsCRP), remarking the anti-inflammatory activities of vitamin D, including the inhibition of IL-6 synthesis by monocytes. CRP acts on endothelial cells inducing tissue factor expression and promotes smooth muscle and endothelial cell proliferation [172]. Moreover, CRP increases plasminogen activator inhibitor–1 expression [173], and induces several inflammatory genes via NF-κB activation in endothelial human cells [174]. Usually, Vitamin D deficiency in stroke patients preceded stroke and prevalence of vitamin D deficiency is more evident in stroke patients than general medical patients. On the other side, Vitamin D supplementation in post stroke patients may play a role in prevention of recurrent stroke and improves functional outcome after stroke [159, 175-177].

Zhao-Nan Wei reported that vitamin D deficiency is associated with a 3.2-fold increased risk of poor functional outcome events. Adjustment for established cardiovascular risk factors, including glucose level, age, and NIHSS score, did not attenuate this association. For vitamin D deficiency, the adjusted risk of mortality increased by 290% [178]. High dose oral vitamin D supplementation produced short-term improvement in endothelial function in stroke patients, with a better management of blood hypertension. Moreover, it has been proposed a possible cardiovascular protective role of vitamin D, reducing mortality risk both in patients with renal failure.

A meta-analysis of 50 RCTs of supplemental vitamin D, administered for a median of 2 years, involving predominantly elderly women who were mainly in institutions and dependent care, showed that vitamin D decreased mortality [179], moreover, vitamin D3 (cholecalciferol) has been shown to decreased mortality significantly. Anu Gupta et al. [180] in a randomized controlled open-label trial, found that patients with acute ischaemic stroke that received vitamin D and calcium supplementation, along with usual care, compared to those receiving usual care alone, presented a greater probability of survival, achieving a better outcome at 6 months compared to controls. Concerning Stroke, the VITamin D and OmegA-3 triaL (VITAL) studied the effect of supplementation on total cancer and major cardiovascular events (a composite of myocardial stroke, and death due to cardiovascular events), thus reporting significant effects only on reduction of bone fractures [181-182]. Similarly, the benefit of vitamin D supplementation for stroke related depressive symptoms is still debated [183]. If vitamin D really contributes to post-stroke recovery by pathophysiological mechanisms that should still be elucidated (some could be related to a reduction in the volume of the cerebral infarct, and neuroprotective properties), in which case, vitamin D supplementation could bring the hope of a benefit is not known jet.

In summary, the precise relationship between vitamin D and stroke is still unclear, a revision from data suggest that vitamin D status is associated with ischemic stroke and with the injury volume. Vitamin D levels should be measured in all stroke patients and should be consider an independent stroke risk factor. Supplementation of vitamin D could be considered as a fundamental part of stroke therapy, but new studies should be done.

Vitamin D deficiency and neurodegenerative diseases

Different important studies have implicated amyloid beta accumulation, hyperphosphorilation of tau, oxidative stress, mythocondrial dysfunction and inflammation as the major responsible factors for neurodegenerative process, which underlies Alzheimer's Disease [184-187]. Nevertheless, calcium excito-toxic hypothesis and glutamate currents theories can support and amplify the Alzheimer's cascade of events [186-187]. Moreover, many doubts still merge, especially for sporadic AD cases pathogenesis. It has been established that the etiology of sporadic AD might involve multiple gene-environment relationships, and probably many epigenetic mechanisms [187-189]. The most debated aspects are those concerning the reasons of abeta accumulation and taupathy consequences in the ageing brain, being seriously possible a relationship between their accumulation and various environmental risk factors, which the brain gathers life long. Epigenetic modifications can act as first hits, with a consequence which remains latent for many years, until a second hit (probably determined by metabolic factors, ie. altered nutrition, pro-inflammatory cytokines, ageing by itself) can promote the degenerative progression [190]. Due to these premises, VDR, the major effector of vitamin D, polymorphisms have been studied in AD [191]. Some surprising results have been obtained: it has been demonstrated a link between altered gene expression of VDR and of 1,25 MARRS (membrane associated rapid response steroid-binding); this association endorses a less efficient employment of vitamin D inside neurons, and let them to be more prone to degeneration [191-193]. Brewer et al [194] recognized that cultured hippocampal cells treated with adequate concentrations of VDH (1-100 nM) were protected against excitotoxic insults, probably due to a modulation of L-type voltage-sensitive calcium channels, whose increase has been documented in hippocampus aged cells [195] and in the aged long-term cultured hippocampus cells [196]. VDH down-regulates mRNA expression for different subunits of L-type voltage sensitive calcium channels. Consequently, VDH has a fundamental role in the homeostasis of calcium mediated activities [194], such as neuronal death and apoptosis. The VDR-/- knock-out model shows a higher sensitivity to neuro-degeneration, with a rapid increase of calcium currents and neural death [197]. Many different VDR polymorphisms have been described as increasing the susceptibility to AD [198], mainly due to altered expression of neurotrophins. Genome analyses, transcriptomics and proteomics have pointed the role of VDR polymorphism in late onset AD susceptibility [191]. In fact, even in animal models, vitamin D seems to interfere with cognitive functions even in other ways, probably through its different polymorphic gene expression of VDR [199]. It seems, for instance, that Bsm I and Taq I altered carriers are more prone to manifest memory and cognitive dysfunctions, as well as vitamin D defect; on the contrary, the APA-I haplotype is associated with an increased risk of fractures, but not memory alterations [200]. Therefore, in line with Buell and Dawson-Hughes [201], calcium concentrations are not likely to vary in the different haplotypes, indicating a protective effect on the brain, beyond the calcium homeostasis. Thus, in Alzheimer disease culture models, VDH stimulates amyloid plaques [202], supporting the phagocitosis induced by macrophages of soluble

amyloid beta protein [203] and reduces the inflammation response, induced by amyloid deposition [16]. Lipopolysaccharide-induced levels of mRNA encoding for macrophage colony stimulating factors and tumor necrosis factor in cultured astrocytes are partially reduced after vitamin D treatment [16]. Additionally, vitamin D has neuroprotective properties against glutamate toxicity [204]. It inhibits the synthesis of inducible nitric oxid synthase and regulates the gammaglutamyl transpeptidase, fundamental in the metabolism of glutathione [205]. Furthermore, vitamin D enhances the protein phosphatase 2A activity, modulating the redox state, and thus reducing age-related tau hyperphosphorilation, limiting the cascade of neuronal dying back and the promotions of collateral inflammatory potentiation [206]. To summarize, it can be said that vitamin D acts in the brain, through a regulation of NGF and neurotransmitters, regulating calcium homeostasis, promoting anti-inflammatory responses, interfering with amyloid beta metabolism, and implementing brain oxidative response. On the contrary, clinical practice does not give univocal results. Vitamin D deficit has been widely detected in frail old population [207-212] and calcium homeostasis is heavily lowered in neurodegenerative pathologies, such as Alzheimer disease [210-212]. In a mild cognitive impairment population, not already Alzheimer disease, low level of vitamin D was reported [213]. Nevertheless, vitamin D implementation in clinical practice does not give univocal results. A 7-year follow-up study confirmed that a huger intake of vitamin D has been linked to a lower risk of developing AD in normal ageing women [214-216]. Some recent works put in evidence that the combined effect of vitamin D and docosahexaenoic acid can enhance the neural protection towards the different effects of beta amyloid deposition [217], and a 6-month trial determined that there are better, even limited effects, when memantine was prescribed in association with vitamin D, rather than alone in AD patients [218]. On the other hand, two studies showed the opposite results [219-221]. Even though may different studies should be needed in order to demonstrate a definite role in real clinical practice of supplementation of vitamin D, many questions remain without a proper answer:

1. When should the implementation begin?
2. Is it a possible preventive therapy for reducing the cascade of events of AD?
3. Should it be considered as one of the multifactor agents (along with folate, vitamin B12 and antioxidant substances)which can procrastinate the AD second hit process?

Emergent evidence from experimental and clinical studies suggests that vitamin D may be linked to atherosclerotic pathology [222]. Some studies link the vitamin defect to an increased risk of hypertension, diabetes, congestive heart failure, myocardial infarction and stroke [223]. Moreover, some very recent studies link it to small vessel disease and vascular dementia too [224-226]. Vitamin D receptors are hugely expressed by the endothelial cells and their activation induce the promotion towards maturation of immature cells, via VEGF [227]. Vitamin D receptor gene is up-regulated during inflammation in endothelial cells [228-229] and vitamin D analogues protect against advanced glycation products

derived insults [230]. Enriched vitamin D diet models promote anti-lymphoproliferative effect for the endothelium and a diminished response to inflammatory cytokines [231-233]. Moreover, as previously described, vitamin D regulates the expression of 74 genes and 36 proteins, connected with the correct development of the cytoskeleton and exerting a regulation on post-transcriptional controls for L-type voltage sensitive calcium channels [234-236]. All the effects of vitamin D on the vascular system link it to vascular dementia, in many different ways: epidemiological [225], based on vascular pressure control [228], based on biological properties of vitamin D, above described [194, 237], or simply considering vitamin D deficiency as a risk-modifiable factor [201, 223, 230, 238-239]. It seems quite interesting that the three works which link vitamin D defect to small vessel disease-related dementia [224-226] stand on two biological axiomatic properties: the antioxidative capacity of vitamin D (therefore a loss of protection against ROS, whenever it lacks), and the control of smooth vessel, which is fundamental for auto-regulation in brain circulation. It is widely known that there is an excess of superoxide by NADPH oxidase in small vessel disease [240]. That causes an increase of ROS, indirectly evidenced by an hyperexpression of the NOX 2 and NOX 4 oxidase isoforms [240-241]; ROS induced damage is one of the trigger for apoptosis. *In vitro*, vitamin D down-regulates the activity of NF-KBETA activity [242] and stimulates anti-inflammatory cytokines [239, 243]. Additionally, vitamin D-binding proteins are more evident in proximity to endothelium injury [244], inhibiting the expression of MMP-2, MMP-9 and of the endothelium growth factor [245]; they probably diminish the activity of platelet derived growth factor, conversely up-regulating thrombomodulin [246-247]. The second study, entirely dedicated to small vessel disease and vitamin D [224] lights some shadows in a fascinating problem: it presents a well-known association between bone small vessel disease and osteoporosis. Authors hypothesize a common way of alteration, in the peripheral autonomous nervous system, which deteriorates small-bone vessels as well as brain vessels [248]. The first and the third study on the topic [225-226], starting from two different perspectives have some common points. Chung et al (225) demonstrate that vitamin D is inversely associated with lacunes, white matter hyperintensites and deep microbleeding, in profound white matter, not elsewhere, suggesting a high impact on small vessel disease. Moretti et al (226) hypothesize that vitamin D might act on the altered control of CBF [249-254] and in the distorted neurovascular coupling system [255-256], both heavily impaired in small vessel dementia. Intracerebral calcium, intimately regulated by vitamin D, interferes with vessel activation. Vessel relaxation is heavily influenced by ATP-sensitive potassium channels (delayed rectifier and inward rectifier potassium channel) but also by calcium-activated potassium channels [257-258]. Mediated by cAMP, calcium activated- potassium channels seem to be involved in the negative “feedback system to regulate vascular tone” [257]. It seems that in atherosclerosis models, there is a major impairment of calcium-activated potassium channels in mainstream vessels [259]. On the other hand, the neurovascular coupling system (vascular smooth cells, neurons and astrocytes) seems to be intimately regulate by vitamin D, which is determinant for the glutamate release. Glutamate pass from the

synapse, activating NMDAR in the neurons and metabotropic glutamate receptors in the astrocytes [256]. Moreover, by interfering with calcium influx, vitamin D indirectly mediates the neural nitric oxid synthase. NO activates phospholipase A2 in the astrocytes, enabling the prostaglandine cascade, which widen arteries [256]. The presence of vitamin D increases, moreover, acetylcholine, and VIP which potentiate the mechanism [256]. Low levels of vitamin D might therefore interfere with smooth cells control, with NO and neuropeptides synthesis and with neurovascular defective coupling, leading towards some aspects of small vessel disease. Being so few the studies on the topic, there are any study concerning vitamin D supplementation in vascular dementia.

A significant concentration of vitamin D receptors was found in the hippocampus, in the prefrontal cortex–brain and in the substantia nigra [260]. There is evidence of low-levels of vitamin D, and increased bone turnover markers, such as bone alkaline phosphatase compared to controls [261]. Being that all the non-genomic role of vitamin D above described, as regulating calcium inside the neurons and astrocytes, regulating L-type voltage sensitive calcium channels, inducing and promoting NGF and other growth factors, down-regulating MMP and other inflammatory activity, down-regulating prostaglandins and COX -2 activity and acting as a redactor of oxidative stress, reducing also the NO production by lipopolysaccharide stimulated macrophages, are validated in PD cells and animal models as well (see data and literature in [262]), we intend to proceed to describe the genomic factors associated with vitamin D in PD. It is well accepted that increased levels of MHC class II expressions were detected in the monocytes of the cerebrospinal fluid of PD patients [263], together with HLA-DR positive reactive microglia, found in substantia nigra and in nigrostriatal tract of PD patients [264]. Recent evidence demonstrated that vitamin D suppresses MHC class II antigens [265] and IFN-gamma induced HLA-DR antigen expression in human cells [266]. Additionally, Cytochrome P450 (CYP), and in particular CYP2D6, which has polymorphic expression, and which is expressed in neurons and in the gut has a different expression in PD patients, where it has been found preponderantly as CYP2D6*4 allele [267] CYP2D6 acts as a 25-hydroxylase, which is able to convert vitamin D3 into 25OHD, being the key enzyme to determine a deficiency of vitamin D. In mouse MPTP treated model (inducing PD phenotype), Singh et al. [268] reported the strong expression of the animal ortholog of CYP2D6, CYP2D22. Very interestingly, CYP2D loci are located on chromosome 22 where many genes related to PD are segregated [269-271]. It seems surprising that deletion of chromosome 22q11 was reported to be associated to PD [271] but also with a reduced serum calcium and a reduced level of vitamin D [272]. According with cytoprotection, there are three more links, between vitamin D and PD. The first one is the so-called S1 transcription factor, a DNA binding protein, that mediates accurate response to oxidative stress in neurons [273], controls the expression of the dopamine transporter gene, and of the dopamine receptor gene [274-275]. The link between vitamin D and Sp is represented by the fact that binding sites for transcription factors for Sp have been determined by hormones: in fact, two vitamin D-responsive elements (which acts by inducing the expression of CYP24 genes, previously described ad 25-OHD-24

hydroxylase) are helped by the synergic activation of Sp1 [276]. The second genomic link factor between vitamin D and PD is represented by Heme-Oxygenase, a stress protein with anti-oxidant properties. In the normal brain, its expression is limited to neuroglia [277] whereas it is overexpressed in PD brain, but not in AD patients [278]. In PD brains, Heme Oxygenase 1 is overexpressed in astrocytes within the substantia nigra and in the deteriorated dopaminergic neurons [279]. Quite unpredicted, calcitriol seems able to delay the effect of Heme oxygenase, reducing the glial fibrillary immunoreactivity [280]. Finally, vitamin D seems to interfere the activity of Poly (ADP-Ribose) Polymerase-1, also called PARP1. It is a stress protein, which can, however, promote neuronal death. In fact, there is an overexpression of PARP1 in the substantia nigra of PD patients [281]; increased levels of vitamin D down regulate PARP-1 expression, probably mediated by a diminishment of microglial activation [282]. All these aspects considered, clinical trials on vitamin D supplementation in Parkinson's disease have been carried out [283]. Although some data demonstrated that low levels of vitamin D may influence the speed of the disease [283], the supplementation of vitamin D did not modify the disease outcomes. That conclusion probably lies on clinical time of supplementation, far from the initial ones of labs models.

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