Pleiotropic Effects of Vitamin D in Inflammatory-Based Diseases

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Numerous pleiotropic effects have been reported for vitamin D (vit D) since its discovery a century ago. Today it is well known that in addition to its pivotal role in calcium homeostasis and bone metabolism, vit D has antibacterial, anti-proliferative, immunomodulatory, and anti-inflammatory actions, among other beneficial properties. In the context of inflammatory-based diseases, vit D and its receptor VDR might fulfil their roles as gene regulators through direct gene regulation and epigenetic mechanisms.

vitamin D | genetic | genomic | epigenetic | inflammatory diseases

1. The Role of Vitamin D in Inflammation at the Cardiovascular Level

Vit D deficiency is associated with an increase in serum levels of pro-inflammatory mediators, including IL-6 and tumor necrosis factor-alpha (TNF-α), which are related to both the development and progression of some vascular inflammatory pathologies [14,15,24,25]. In addition, a study carried out on obese patients revealed that reduced serum 25(OH)D concentrations were usually related to increased levels of other biomarkers of vascular inflammation such as high-sensitivity C reactive protein (hCRP) and fibrinogen [26]. Similar conclusions were informed for severely obese children [27,28]. The 25(OH)D levels below 20 ng/mL were associated with increased markers of oxidative/nitrosative stress, inflammation and endothelial activation, all of them indicators of cardiovascular risk. Moreover, in obese people, hyperleptidemia is usually observed. This disorder provokes vascular inflammation [29]. The 1,25(OH)2D3 pretreatment of cultured human umbilical vein-derived endothelial cells exposed to high concentrations of leptin with 1,25(OH)2D3 prevented the rise in the expression of vascular pro-inflammatory mediators caused by leptin, including CCL2, VCAM-1, and transforming growth factor β (TGF-β) [30]. Furthermore, Oma et al. [31] observed a higher presence of mononuclear cell infiltrates in the aortic adventitia of patients with coronary artery disease and vit D deficiency as compared with those with suiTable 25(OH)D levels. The adhesion of monocytes to endothelial cells represents an early stage in atherosclerosis development, thus, vit D supplementation would be a helpful tool in the prevention and treatment of atherosclerosis and other vascular inflammatory diseases [32]. Furthermore, it has also been suggested that vit D deficiency and the down-regulation of its receptor could be involved in aggravating vascular inflammation in pregnant women during preeclampsia (pregnancy hypertension). Interestingly, vit D supplementation reversed the inflammatory process in these patients [33]. These findings along with the significant number of VDR located in vascular smooth muscle cells (VSMCs) and endothelial cells indicates a crucial role of this endogenous compound in the regulation of inflammation, especially at the vascular level [34].

The location of VDR in VSMCs is of particular interest since these cells represent the majority of cell population in the blood vessel walls' levels and they have a vital role in the advance of vascular inflammatory disease. New technologies have shown that VSMCs may switch their contractile phenotype to a macrophage-like phenotype, proving the plasticity of these cells. Thus, there is interplay among VSMCs, immune cells, and endothelial cells during the convoluted

process of vascular inflammation where VSMCs can control, interact with, and influence the behavior of other cellular components of the blood vessel wall [35]. In this context, a study carried out using an in vitro model of endothelial inflammation (primary cultured human umbilical vein endothelial cells exposed to TNF-α) showed that the treatment with paricalcitol (a vit D analog) inhibited the increased expression of the intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), and fractalkine (a chemoattractant cytokine) in these cells [36]. Furthermore, in a clinical model of vascular inflammation (patients with an abdominal aneurysm), paricalcitol reduced the CD4+ T-helper and the T-cell (CD3+) content in aneurysm wall samples from these patients. Paricalcitol also prevented the rise in the levels of pro-inflammatory cytokines (IL-1β, IL-6, IL-8, and TNF-α) in cultured human aortic smooth muscle cells exposed to elevated concentrations of phosphate, indicating that active vit D derivatives have anti-inflammatory effects at the vascular level [37].

Likewise, VDRs also modulate the RAAS, inflammation, and fibrosis. Thus, their activation counteracts myocardial hypertrophy and hypertension [38]. In this regard, it is proposed that the activation of VDRs associated with Hsp70 (as a chaperone protein) could favor physiological cardiac remodeling after a myocardial infarction and reduce progression to heart failure [39].

In SHR rats, treatment with vit D analogs ameliorates left ventricular hypertrophy and improves left ventricular diastolic measures. Mizobuchi et al. [40] showed that combined therapy with enalapril and paricalcitol significantly decreased proteinuria, glomerulo-sclerotic index, and tubulointerstitial volume in uremic rats [41].

In addition, experimental studies suggest that active vit D analogues at low doses ameliorate myocardial renin overexpression and lower blood pressure, protect against aortic calcification and prevent cardiac/vascular remodeling [42].

Moreover, our previous work [38] in rats with a ureteral obstruction showed a reduction in myocardial VDR expression, and this fact, might be related to myocardial remodeling associated with an increase in arrhythmogenesis. Important to note, that paricalcitol protects against these changes by restoring myocardial VDR levels [38].

For its part, vit D deficiency at the cellular level produces a higher oxidative stress, inflammatory markers, and mitochondrial damage. Serum 25(OH)D concentrations below 25 ng/mL were related to an increase in vascular tone mediated by smooth muscle contraction, either through direct effects on vascular smooth muscle cells, up-regulation of the RAAS, and/or through modulation of calcium metabolism with secondary hyperparathyroidism; which predisposes patients to develop hypertrophy of the left ventricle and of the vascular wall, causing hypertension. The VDR plays a role at the mitochondrial level and the regulation of the respiratory chain, which would influence arterial remodeling, since its activation would reduce oxidative damage and preserve cell life. Such data implicates that maintaining adequate levels of vit D is important for protection against cardiovascular disease [42].

Several studies assessed the effect of calcitriol administration as an anti-inflammatory agent. On an apoE (−/−) mouse model of abdominal aneurysm induced by angiotensin-II (Ang-II) infusion, the oral treatment with calcitriol reduced the aneurysm formation and all altered parameters observed during abdominal aneurysm were decreased, including macrophages infiltration, expression of vascular endothelial growth factor (VEGF), angiogenesis, monocyte chemoattractant protein 1 (CCL2), CCL5, and CXCL1 chemokines and synthesis of matrix metalloproteinase-2 and 9 (MMP-2 and 9) [43]. In an in vitro model of human endothelial cells, the treatment caused inhibition of leukocyte-endothelial cell interactions induced by Ang-II, morphogenesis, and synthesis of endothelial pro-inflammatory and angiogenic chemokines mediated by VDRs [43,44].

In addition, vit D administration decreases the expression of pro-inflammatory and proatherogenic cytokines such as IL-2 and interferon-gamma (IFN-ɣ), which are responsible for the T-helper-1 cells activation and vascular inflammation [45]. Accordingly, clinical studies showed that vit D supplementation was able to reduce central blood pressure parameters in individuals with vit D deficiency, but not in individuals with adequate vit D status. It was also reported to improve arterial stiffness in overweight African Americans patients with vit D deficiency and to improve microvascular responses in African Americans, mitigating or preventing the development of cardiovascular dysfunction in this population [46].

2. Anti-Inflammatory Role of Vitamin D in the Gastrointestinal System

Vit D helps the intestine absorb calcium and phosphate and its deficiency is correlated with increased mucosal inflammation, leading to inflammatory bowel disease (IBD) [2]. However, administration of the vit D at a dose that raises and maintains a 25(OH)D of 30 ng/mL, may have the ability to reduce the disease. Moreover, VDR has been linked to the gut microbiota and its metabolites and its expression is down-regulated in Crohn's disease (CD) and ulcerative colitis [2].

VDR is regulated by miRNAs, which are a class of small non-coding RNA (17–22 nucleotides) that regulates gene expression post-transcriptionally. It also inhibits transcription of ZO-1, claudin-5, and occludin genes and increases the tight junction protein claudin-2 which enhance intestinal permeability. Thus, lacking intestinal epithelial VDR regulation in inflamed intestine leads to hyperfunction of Claudin-2 and exaggerates the inflammatory responses in the intestines [47].

3. Vitamin D Role in Renal Protection

Several animal models have suggested a role for active vit D in albuminuria and kidney fibrosis. In fact, vit D analogues are able to affect blood pressure, proteinuria, and inflammation. A study carried out on VDR knockout mice reveals a rise in renin consequent to loss of normal suppression of the renin-angiotensin aldosterone system (RAAS) by vit D [48]. Thus, RAAS have been shown to play an important role in the progression of chronic kidney disease (CKD) and low levels of 25(OH)D and 1,25 (OH)2D were correlated to be predictors of disease progression and death in patients with CKD and End Stage Renal Disease [49].

In this regard, in previous investigations, the expression of VDR and genes associated with nephrogenesis in spontaneous hypertension rats (SHR) from week 0 to 8 of life were analyzed. Hypertension in these rats is known to develop at about 6 weeks of age [50]. We observed a decrease in the expression of the nephrogenic gene, wt-1, and VDR by week 4, before the establishment of arterial hypertension, suggesting that the alteration in the kidney occurs previous to the increase in blood pressure [51].

Moreover, our group has found in adult SHR rats that the induction of VDR modulates an increase in Hsp70 levels, with a decrease in the angiotensin II receptor, type 1 (AT1) expression, providing renal protection [41]. Of interest, Hsp70 effects on the VDR may also accentuate repressive anti-inflammatory signaling [52].

4. The Role of Vitamin D in the Nervous System

As early as the early 1980s, attempts were made to find a relationship between the nervous system and vit D, starting with the question of whether vit D was able to cross the blood-brain barrier [53]. Today the questions revolve around the relationship of vit D status and its interaction with antioxidant mechanisms, complex immunomodulatory systems, and neurotrophic factors among others [19,54]. As a result, vit D has a key part in the process of neuro-inflammation,

cognitive decline, and neurodegeneration [55]. In line with this, it has recently been reported that vit D has a neuroprotective function in aging cognitive decline [56]. This is one of the reasons why many human dietary supplements include vit D alone or in combination with other compounds that have antioxidant effects. A closer look into the different cell types of the nervous system, VDR are found in neurons, astrocytes, and microglia in the central nervous system [54]. Furthermore, using the 25-hydroxyvitamin D-1alpha-hydroxylase (CYP27B1) and 25-hydroxyvitamin D-24-hydroxylase (CYP24A1) enzymes, some of these cells may synthesize and catabolize 1,25(OH)2D. The unequal distribution of 1,25(OH)2D and 25(OH) D in different parts of the brain shows that vit D and its metabolism in the CNS might either function in a paracrine or autocrine manner [57].

Many studies have discovered that appropriate amounts of vit D reduce oxidative stress and brain inflammation, resulting in diverse neuroprotective benefits [58]. The VDR is also implicated in the neuroprotective effects of neurosteroids. Furthermore, calcitriol has been shown to stimulate VDR expression, down-regulate NOX2, and inhibit cellular death rate [59], suggesting that VDR-activated ERK1/2 activation may contribute to neuronal apoptosis prevention [60]. On the other hand, findings show that vit D shortage causes significant changes in microglia, implying that these cells may play a role in the sensory dysfunctions associated with hypovitaminosis D [61].

The human brain produces 1,25(OH)2D3, which affects a variety of brain areas, including the prefrontal cortex, hippocampus, cingulate gyrus, thalamus, hypothalamus, and substantia nigra. The 1,25(OH)2D3 lowers oxidative stress, inhibits inflammation, offers neuroprotection, down-regulates inflammatory mediators, and up-regulates neurotrophins in neurons [62].

The Klotho gene, which was initially discovered as an ‘aging suppressor’ in mice, encodes the antiaging protein Klotho. Klotho deficiency is linked to early mortality and rapid aging, but its overexpression is linked to longevity. Klotho protein is involved in the control of a number of biological processes, including calcium-phosphate balance, PTH, and vit D metabolism [63]. The precise chemical pathways through which 1,25(OH)2D3 and Klotho protein exerts its activities in the brain are yet unknown; however, the relationship between them might be both genomic and non-genomic, but the interplay processes are mainly unknown [63].

For all the above reasons, we could hypothesize that the therapeutic use of 1,25(OH)2D3 or similar agonists may have considerable promise due to its documented function in neuroinflammation, neurodegenerative diseases, and neuropsychiatric disorders.

Depression is a frequent mental illness in the elderly that lowers quality of life and increases morbidity and death. Vit D may play a role in the onset and treatment of depression as a neuro-steroid hormone [64]. One of the proposed mechanisms by which this neurohormone exerts its action is its relationship with serotonin and dopamine levels in the brain [65].

5. The Role of Vitamin D in Autoimmunity

Clinical studies have suggested that VDR polymorphisms and vit D deficiency is related to the development and progression of several autoimmune diseases, such as rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis, and autoimmune endocrine disorders (e.g., Hashimoto thyroiditis, type-1 diabetes mellitus (T1DM), Addison’s disease, and Graves’ disease) [66]. As mentioned, due to its great ability to bind to VDR and act as a transcriptional factor, vit D may modulate gene expression and, consequently, exert immunomodulatory effects on immune cells. Vit D has the capability to inhibit the production of Th17 cytokine, improve Treg activity, stimulate NKT cell functions, inhibit Th1, and induce the production of Th2 cytokine, and thereby shift T cells toward Th2 profile [67]. However, the role of vit D supplementation in the improvement of autoimmune diseases remains unclear. Therefore, additional studies are needed to know the potential underlying mechanisms involved [68]. Of note, all the clinical studies

performed so far, only demonstrate correlations. Thus, it is difficult to establish whether the low 25(OH)D3 level is the cause or the consequence of autoimmune diseases [69]. Despite several studies having demonstrated a beneficial effect of vit D supplementation in autoimmune diseases, there are also some studies that did not show any effect on the main parameters of this kind of diseases. This could be due to differences in the supplementation strategy or the individual characteristics of the subjects included in the study, which are aspects that should be addressed in a properly way at the moment of designing multicenter clinical trials [70,71].

6. Remarks

It is common to associate vit D with skeletal homeostasis. However, new roles are constantly emerging for vit D with closer investigations. VDR is linking at hundreds of
sites in the genome and is associated with the regulation of more than 60 genes. Moreover, vit D (and its active derivatives) not only play a role in the genetic regulation of many genes, but also in the epigenetic regulation. In fact, the epigenetic machinery can be altered by vit D, acting through multiple genetic mechanisms. Gene expression can be modified by numerous miRNAs working as epigenetic modulators of VDR, also by methylation and histone acetylation/deacetylation [2].
Vit D is involved in processes related to the development and progression of some inflammatory diseases, and has the ability to alter serum levels of both proinflammatory
and anti-inflammatory mediators. Beyond the known intimate relationship between vit D and the gastrointestinal tract, we can highlight a bidirectional communication between the VDR and the intestinal microbiota. Both participate in an autoregulation in which different types of post-transcriptional mechanisms and their relationship with intestinal permeability are also involved.

Moreover, vitD has protective effects in CKD and hypertension, and one of themechanisms by which it carries out this function is through the alteration of the RAAS system.
On the other hand, with new research findings, more insight is being obtained about the relationship between vit D and different pathologies of the nervous system. Most
of these are focused on vit D and its relationship with oxidative stress. We know that oxidative stress is one of the best-known starting points of different neuroinflammatory,
neurodegenerative, and neuropsychiatric processes. It is clear that vit D has implications in general health and this fact invites researchers to continue looking for functions and delving into the study of other physiological actions and how its deficiency is associated with numerous pathologies beyond those explained here, such as diabetes, obesity, and cancer.

Thus, yesterday vit D was considered a calciotropic vitamin; however, today, we may be affirmative about it as a hormone with multisystemic action.