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Emerging role of vitamin D in autoimmune diseases: an update on evidence and therapeutic implications

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Abstract

Vitamin D plays a key role in in calcium homeostasis and, thus, provides an important support in bone growth by aiding in the mineralization of the collagen matrix. However, vitamin D performs various immunomodulatory, anti-inflammatory, antioxidant and anti-fibrotic actions. Autoimmune diseases result from an aberrant activation of the immune system, whereby the immune response is directed against harmless self-antigens. Does vitamin D play a role in the pathophysiology of autoimmune diseases? And, if so, what is its role? In the last decade, researchers' interest in vitamin D and its correlations with autoimmune diseases has considerably increased. We conducted a literature review, covering the period January 1, 2009 through March 30, 2019, in PubMed. We analyzed more than 130 studies in order to find a correlation between vitamin D levels and its effect upon several autoimmune diseases. The analysis demonstrated an inverse association between vitamin D and the development of several autoimmune diseases, such as SLE, thyrotoxicosis, type 1 DM, MS, iridocyclitis, Crohn's disease, ulcerative colitis, psoriasis vulgaris, seropositive RA, polymyalgia rheumatica. International multicenter study could allow us to confirm the data already present in the literature in the single clinical studies and to evaluate when to effectively supplement vitamin D in patients who do not take corticosteroids.

Keywords: vitamin D, autoimmunity, vitamin D receptor, autoimmune disease, vitamin D deficiency, immunomodulation.

1. Introduction

Activated vitamin D promotes the calcium absorption in the small intestine by binding to calcium transporting proteins [1,2], the stimulation of osteoclastic maturation resulting in an increase in bone resorption and the release of calcium into the blood [3] and provides an important support in bone growth by aiding in the mineralization of the collagen matrix [4]. For these reasons, vitamin D deficiency classically results in rickets in children and osteomalacia in adults. However, vitamin D executes many other functions apart from the role in calcium homeostasis. Indeed, vitamin D performs various immunomodulatory, anti-inflammatory, antioxidant and anti-fibrotic actions [5-12], and, thus, it may be involved in regulatory pathways that help preventing or ameliorating inflammatory and immune-mediated tissue injury. Autoimmune diseases result from an aberrant activation of the immune system, whereby the immune response is directed against harmless self-antigens. The introduction into the therapeutic armament of the so-called biologics, like tumor necrosis factor (TNF)-α inhibitors, has improved the prognosis and quality of life of patients with autoimmune diseases [13,14]. However, the immunomodulatory effects of vitamin D provide opportunities to improve the treatment of autoimmune diseases. First, given the high prevalence of vitamin D deficiency in patients suffering from autoimmune diseases, vitamin D supplementation can reduce disease severity or improve the therapeutic response to specific immunosuppressive treatment. Second, knowing the molecular mechanisms underlying the immunomodulatory effects could lead to the discovery of new potential therapeutic targets. Therefore, this review discusses the role of vitamin D in the pathogenesis of various autoimmune diseases and the validity of therapeutic supplementation.

2. Vitamin D structure, signalling and function

Vitamin D is a secosteroid hormone with two forms, D2 (ergocalciferol) and D3 (cholecalciferol). The latter is produced from the precursor protein 7-dehydrocholesterol sited in the skin after exposure to ultraviolet B light. In fact, vitamin D supply derives mainly from the skin, and only a

small amount is obtained from the diet. Vitamin D is transported mainly by D-binding protein (DBP), while albumin and lipoproteins transport the remaining 10–15% by low affinity binding. The inactive form is then transported to the liver and converted to the intermediate inactive form of 25-hydroxyvitamin D. The conversion requires 25-hydroxylase, which is encoded in the liver by the *CYP2R1* allele [15]. The 25-hydroxyvitamin D is then re-bound to DBP in the circulation, and transported to the kidney, where it is converted to the active form, also called calcitriol, by the 1α-hydroxylase. This enzyme is encoded by the *CYP27B1* allele, and its activity is tightly regulated by the parathyroid hormone (PTH) [15]. In fact, PTH and phosphate levels closely control hydroxylation in the kidney [1]. Thanks to its steroidal nature, 1,25-hydroxyvitamin D passes through the cell membrane targeting citoplasmic vitamin D receptor (VDR). The 1,25-hydroxyvitamin D–VDR complex is then translocated into the nucleus to modulate gene expression by acting as a transcriptional factor [1]. As a result, calcium homeostasis is achieved, modulating calcium intestinal absorption. However, in the presence of low 1,25-hydroxyvitamin D levels, calcium will be mobilized from the bone rather than the intestine. If these conditions are prolonged, this may lead to osteomalacia and rickets, both well-known clinical signs of vitamin D deficiency [8]. Recent findings found that VDR is expressed by several human cells, including lymphocytes and dendritic cells, suggesting that vitamin D may have pleiotropic effects. Nowadays, many studies focused on the role of vitamin D upon different conditions as, for example, tumors, cardiovascular diseases and autoimmune disorders. Several works conducted on autoimmune and inflammatory disease confirmed that vitamin D exerts effects both on the innate and adaptive immune response [1,2,4,6,8,10,12,15].

3. Vitamin D effects on innate immune system

1,25-dihydroxyvitamin D regulates the effects of all the major players of the innate immune system. Kamen et al. [2] analyzed vitamin D effects upon macrophages. They found that VDRs expression is regulated by toll-like receptors (TLRs) activation. Bacterial stimuli lead to TLRs activation, thus

increasing VDRs expression and 25-hydroxyvitamin D-1α-hydroxylase activity. The latter stimulates cathelicidins, which bind to microbes to kill them. On the other hand, many studies demonstrated that low vitamin D levels are associated with an increased risk of infections (i.e. tuberculosis) and autoimmune diseases due to cross-mimicry mechanisms [16]. Cholecalciferol has positive effects also on dendritic cells activity, thus inhibiting monocytes differentiation into dendritic cells and decreasing IL-12 production [1,17]. Ota et al. [18] investigated the effects of vitamin D upon natural killers (NK) cells. The authors conducted a study on women with recurrent pregnancy loss. They found that 1,25 dehydroxivitamin D has immune regulatory effects on NK cell cytotoxicity, cytokine secretion and degranulation process as well as TLR4 expression, which was down-regulated by high cholecalciferol levels. These results may also explain the protective role of vitamin D on tumors occurrence.

4. Vitamin D effects on adaptive immune system

Several studies demonstrated that vitamin D and VDR have effects on both B and T lymphocytes [2,15,19]. However, Vitamin D may influence B-cell function inhibiting their differentiation and proliferation, promoting their apoptosis and, finally, decreasing immunoglobulin production, including auto-antibodies. Vitamin D may also influence T-cell function reducing T helper (Th) cell proliferation and differentiation and promoting a shift from a pro-inflammatory to a more tolerogenic immune status. Indeed, vitamin D inhibits the secretion of proinflammatory Th1 (IL2, interferon-γ, tumor necrosis factor α), Th9 (IL9) and Th22 (IL22) cytokines and promotes the production of more anti-inflammatory Th2 cytokines (IL3, IL4, IL5, IL10). These findings may explain the protective effect of vitamin D upon the risk of developing autoimmune diseases [20].

5. Vitamin D and autoimmune diseases: preventive or triggering factor?

Several clinical studies have been conducted to determine an association between vitamin D levels and autoimmune diseases [1, 21-23]. Autoimmune diseases express the organism's tendency to react

against self-components, thus involving several mechanisms, including increased inflammatory response, oxidative stress, pro-fibrotic effects and glucocorticoid response. Vitamin D is mainly synthesized in the skin after exposure to UVB and only a small part is derived from food intake [19]. Which is the link between vitamin D levels and the onset of autoimmune diseases? Antico et al. [24] conducted a systematic review, which demonstrated that hypovitaminosis D in genetically predisposed subjects can impair self-tolerance by compromising the regulation of dendritic cells, regulatory T-lymphocytes and Th1 cells. Vitamin D deficiency is also frequent in healthy population. Indeed, vitamin D deficiency occurs commonly among healthy European infants, children, and adolescents, especially in certain risk groups, including breastfed infants not adhering to the present recommendation for vitamin D supplementation, children and adolescents with dark skin living in Northern countries, children and adolescents without an adequate sun exposure and, finally, obese children [25]. However, the high incidence of autoimmune diseases, such as multiple sclerosis (MS), in northern countries is related to low levels of vitamin D resulting from low sun exposure and reduced food intake. Moreover, An et al. [26] conducted a meta-analysis which demonstrated that SSc patients, especially those with diffused type, have lower vitamin D levels; this was hypothesized to be mainly due to the skin- thickening of SSc patients, thus reducing vitamin D production. During the last years, several studies demonstrated an association between VDR polymorphism and autoimmune diseases. Indeed, VDR activation plays a central role in modulating the immunological response. Bizzaro et al. [27] found a statistically significant association between specific polymorphisms of VDR, single nucleotides, and autoimmune diseases. Some polymorphism associations have been identified with the onset of specific immune-mediated diseases: BsmI or TaqI polymorphisms with autoimmune thyroid disease, BsmI and FokI polymorphisms with systemic lupus erythematosus (SLE), FokI polymorphism with diabetic nephropathy and, finally, ApaI, BsmI and TaqI polymorphisms with rheumatoid arthritis (RA) [27-34]. Notably, VDR polymorphisms lead to functional changes reducing vitamin D regulatory effects on the immune response. Although the majority of the studies confirmed the favorable effects of

vitamin D on immune disorders, recent studies investigated the possible role of vitamin D as a trigger of immune-mediated diseases. Nowadays, several works dealt with the role of vitamin D in the onset of cardiovascular involvement in immune-mediated diseases showing controversial results [35, 36]. Sarkar et al [37], conducted a study on rheumatic heart disease (RHD) and hypothesized that vitamin D and vascular endothelial growth factor (VEGF) homeostasis may have plausible roles on endothelial cells function in heart valve injury during RHD pathogenesis. This finding confirmed that certain changes in the heart valve endothelium due to leukocyte endothelial transmigration or increased expression of adhesion molecules may result in the progression of valvular damage in RHD [36,38,39]. There are evidences that vitamin D status affects the normal function of endothelial cells through the alteration of VEGF production [40,41]. Up-regulation of VDR enhances the production of vitamin D analogues, which reduces the cytokine-mediated expression of adhesion molecules and prevents the formation of advanced glycation products in in-vivo animal models [42]. Furthermore, vitamin D is crucial for the VEGF homeostasis and to maintain the normal function of valve endothelial cells. Indeed, it has been demonstrated that vitamin D in high doses improves the function of endothelial cells and local valvular stiffness in vitamin D-deficient patients suffering from chronic kidney disease [43]. Vitamin D has the potential to maintain the concentration of VEGF in the circulation and induce the function of endothelial cells. Finally, vitamin D and VEGF homeostasis can alter the function of endothelial cells, which may subsequently trigger the valvular remodeling or even damage the heart valves during the progression of RHD pathogenesis.

6. Materials and Methods

Under such premises, we conducted a literature review, covering the period January 1, 2009 through March 30, 2019 in PubMed. The search strategy was as follows: ((“vitamin d”[MeSH Terms]) AND (“autoimmune disease”[MeSH Terms]) OR “autoimmunity”[MeSH Terms]). The results were sorted by relevance and the most important works dealing with the specific topic were

included in the review. We analyzed more than 130 studies in order to find a correlation between vitamin D levels and its effect upon several autoimmune diseases. All the studies analyzed in this study are listed in Table 1 .

7. Results and discussion

7.*1 Vitamin D and autoimmune neurological diseases*

MS is a demyelinating chronic neurological disease characterized by inflammation and neuroaxonal damage within the central nervous system (CNS), leading to high morbidity and negative social and economic effects [44]. It is a multifactorial disorder involving both genetic and environmental factors. To date, several studies demonstrated that vitamin D plays a key role on different aspects of MS including pathogenesis, disease activity and drug response. However, results are still controversial. Many studies found that high vitamin D levels correlate with a decrease in MS risk of incidence [45]. These results were also confirmed by pediatric studies. Indeed, Gianfrancesco et al. [46] found that decreased vitamin D levels correlated to susceptibility to pediatric-onset MS. On the other hand, Fragoso et al. [47] conducted a study on a large population living in the area of the Capricorn showing that there were no significant differences in serum levels of vitamin D between patients and controls. Regarding disease activity, several studies showed absence of correlation between vitamin D levels and MS. Rito el al [48] found no correlation between vitamin D levels and Expanded Disability Status Scale (EDSS) scores. Muris et al [49], in the SOLARIUM study, focused on the immune regulatory effect of vitamin D on MS. The authors analyzed the cytokine patterns of 30 patients suffering from relapsing remitting MS (RRMS) undergoing vitamin D supplementation and 23 patients on placebo during a period of 48 weeks. They demonstrated that vitamin D3 supplementation did not increase lymphocytes with a regulatory phenotype. Moreover, IL4+ Th cells decreased in the placebo but not in the vitamin D3 group. Holmøy et al [50] conducted a study on RRMS patients in order to compare neurofilament light chain (NFL), a

sensitive marker of axonal degeneration, and vitamin D levels. The authors excluded that weekly supplementation with 20000IU vitamin D3 did not affect NFL levels in RRMS patients, with the possible exception for patients not treated with disease-modifying drugs (DMARDs). Finally, a recent update of a previously published Cochrane review by Jagannath et al. [51] concluded that, to date, very low-quality evidence suggests no benefit of vitamin D for patient-important outcomes among people with MS. Vitamin D appears to have no effect on recurrence of relapse, worsening of disability measured by the EDSS, and magnetic resonance imaging (MRI) lesions. Effects on health-related quality of life and fatigue are unclear. Vitamin D_3 at the doses and treatment durations used in the included trials appears to be safe, although available data are limited. The effect of Vitamin D has also been evaluated upon peripheral nervous system diseases, such as myasthenia gravis (MG), chronic inflammatory demyelinating polyneuropathy (CIDP) and Guillain-Barré syndrome (GBS). MG is a chronic autoimmune neuromuscular disease characterized by the presence of autoantibodies directed against the neuromuscular plaque, leading to early muscle exhaustion. Two studies, respectively conducted on Asian and Caucasian patients, found lower serum 25(OH) vitamin D levels in patients with MG compared with healthy controls [52,53]. On the other hand, Chroni et al. [54] conducted a study among Greek MG and CIDP/GBS patients and found low plasma 25(OH) vitamin D levels in all groups without any statistically significant difference between patients and healthy controls.

7.2 Vitamin D and autoimmune thyroid diseases

Autoimmune thyroid diseases (AITD) are common T cell-mediated organ-specific autoimmune disorders often affecting women between 30–50 years of age. This immune dysregulation can lead both to hypothyroidism (autoimmune thyroiditis known Hashimoto's thyroiditis; AT) or hyperthyroidism (Graves' Disease; GD). Genetic, environmental and endogenous factors are responsible for breaking down immunological tolerance leading to disease development. Recent studies have shown the importance of cytokines and chemokines in the pathogenesis of AT and GD.

In thyroid tissue, recruited T helper 1 (Th1) lymphocytes may be responsible for enhanced IFN-γ and TNF-α production, which in turn stimulates CXCL10 (the prototype of the IFN-γ-inducible Th1 chemokines) secretion from the thyroid cells, therefore creating an amplification feedback loop, initiating and perpetuating the autoimmune process. As a result, anti-thyroid peroxidase (TPO) antibodies and anti-thyroglobulin (TG) antibodies develop [55-57]. Several studies investigated the correlation between vitamin D levels and thyroid autoimmunity. In 2015, Wang et al. [58] published a meta-analysis, which confirmed a strong association between vitamin D deficiency and AITD incidence. Further studies confirmed these results. In fact, Muscogiuri et al. [59,60] found a significant relationship between low levels of 25(OH) vitamin D and AITD both in women with polycystic ovary syndrome (PCOS) and in the elderly population. The same results were also confirmed in an AIT pediatric population. Metwalley et al. [61] conducted a study on 56 Egyptian AITD children concluding that low serum vitamin D was significantly associated with AITD. Moreover, the authors noticed that vitamin D level was not an independent risk for AITD progression to overt hypothyroidism. In AITD, as well as in other autoimmune disorders, FOXP3 plays a critical role in the establishment of peripheral tolerance. As mentioned above, vitamin D can regulate Treg cells function. Based on this concept, Şıklar et al. [62] measured FOXP3 expression in 32 children with chronic AT and 24 healthy subjects before and after vitamin D replacement therapy finding that FOXP3 was underrepresented in AT patients. Furthermore, FOXP3 molecule expression significantly increased in those who were given vitamin D replacement, suggesting that vitamin D can play a role in enhancing natural Treg cell functions. Regarding epigenetic factors, many studies found that polymorphism in VDR genes (specifically BsmI and TaqI) were significantly associated with AITD [1], whereas ultrasonography is a marker of histopathological change during the course of the AITD. Nalbant et al. [63] conducted an original study to investigate the relationship between vitamin D levels and thyroid hemodynamic indices in patients with AT, concluding that vitamin D insufficiency/deficiency might lead to severe parenchymal injury.

7.3 Vitamin D and connective tissue disease

a. Systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is a chronic, multisystem, autoimmune inflammatory disease that occurs predominantly in young women. The association between SLE and low vitamin D levels has been established [64-70]. Recently, Wang et al. [71] conducted a meta-analysis, which confirmed that SLE patients had lower concentration of vitamin D as compared with healthy controls. Regarding SLE complications, Willis et al. [72] found that low vitamin D is a predictor of pregnancy morbidity. Moreover, Salman-Monte et al. [73] found that vitamin D deficiency is often associated with low bone mineral density (BMD) in SLE patients. However, they did not find any association of vitamin D with pro-inflammatory cytokines. Evidence regarding the effect on vitamin D upon disease activity is still debated. Indeed, while the majority of the studies found a correlation between low vitamin D and higher disease activity, two studies noticed that vitamin D did not affect disease activity nor SLE serology [74,75]. Vitamin D levels also appears to be related to the risk of developing the disease in genetically predisposed individuals. Young et al. [76] conducted a study on 436 individuals who reported having a relative with SLE but did not have any clinical manifestation. They were evaluated at baseline and 6 years later. They found that vitamin D status and CYP24A1 might have a combined role in the transition to SLE in individuals at increased genetic risk for SLE. Regarding SLE and VDRL polymorphisms, many studies have been conducted. Mahto et al. [77] found that *Fok*I and *Taq*I variants are significantly associated with SLE in an eastern Indian cohort; however, further studies are needed to eventually confirm these results. To sum up, as Shoenfeld et al. [78] highlighted, although vitamin D seems to play an

important role on SLE patients, a common consent regarding ideal vitamin D target dose or its target levels is still lacking

b. Systemic sclerosis

Systemic sclerosis (SSc) is an immune-mediated disease characterized by vasculopathy and fibrosis, which may involve skin and/or internal organs such as lungs, heart and kidneys, leading to multi-organ damage [78, 79]. Several studies demonstrated that SSc patients have lower vitamin D levels compared with healthy subjects [80-83]. These results were recently confirmed by An et al. and Gupta et al. [84, 85], demonstrating that clinical manifestations were not associated with the degree of vitamin D deficiency. Notably, Gupta et al. [85] found that serum vitamin D levels did not even correlate with age, gender, disease duration or its variants, type of auto-antibodies, presence of digital ulceration, or systemic involvement, but have an inverse correlation with skin sclerosis. During the last years, authors focused on the molecular mechanisms related to Ssc. Although several molecular pathways seem to be involved in Ssc pathogenesis, the myofibroblast remains the key effector cell in SSc. The transition from fibroblast to activated myofibroblast is a crucial event and involves multiple pathways including well-known signaling cascades, such as TGF-β signaling, as well as the involvement of epigenetic reprogramming and a number of more recently defined cellular pathways [86, 87]. On this background, hypotheses regarding vitamin D effect upon fibrosis grew up. Zerr et al. [88] reported that impaired VDR signalling with reduced expression of VDR and decreased levels of its ligand may contribute to hyperactive TGF-β signalling and aberrant fibroblast activation in SSc. Recently, Kotyla et al. [89] conducted a study on 48 SSc patients and 23 healthy controls and analyzed vitamin D levels and two of its major regulators: α-Klotho and FGF23 in order to find a relationship between those parameters and disease activity. The authors noticed that FGF23/α-Klotho index was significantly reduced in SSc patients and its $\log_{10}$ significantly correlated with disease activity score (Eular2017).

c. Rheumatoid arthritis

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease that mainly affects the joints, leading to cartilage and bone damage, as well as disability. It can also involve other organs and systems such as the lung, serosa, eye, skin and vessels. It mainly affects women between 40 and 50 years. RA pathogenesis is complex and several pathways are involved [100]. Early diagnosis is key to optimal therapeutic success, particularly in patients with well-characterized risk factors for poor outcomes such as high disease activity, presence of autoantibodies, and early joint damage [101]. Nowadays, the majority of studies demonstrated low vitamin D levels in RA patients [92-95]. However, the effect of vitamin D upon disease activity is still controversial. Herein, Pakchotanon et al. [96] conducted a study on 239 RA patients finding no associations of serum vitamin D levels with disease activity or functional status in RA. More recently, Gopal et al. [97] confirmed in a group of Malaysian RA patients that vitamin D is not associated with disease activity or serum IL-6 levels but it may have a role in functional disability in RA patients. Same results, independently of population ethnicity, were also observed by previous studies [98-104]. Recently, Brink et al. [105] enrolled 515 RA patients and 267 controls and demonstrated that vitamin D was not associated with the future risk of RA, although increasing levels of vitamin D binding protein (DBP) were associated with an increased risk of disease in females carrying the minor allele of a DBP encoding SNP. On the other hand, beneficial effect of vitamin D upon RA have been described [106-113]. Zhou et al. [114] investigated, in murine RA models, the molecular pathways that underlie RA development. They found that VD treatment ameliorates collagen-induced arthritis (CIA) suppressing Th17 cells and increasing Tregs. Chandrashekara and Patted [106] confirmed, in 150 patients, that VD supplementation improved RA disease activity within a short duration period. Moreover, Lourdudoss et al. [107] demonstrated, in a large population of 727 RA patients, that higher intake of vitamin D during the year preceding DMARD initiation was associated with better

treatment results in early RA patients. As pain is one of the crucial symptoms described by RA patients, two studies demonstrated the positive effect of vitamin D on this aspect [115-116].

d. Miscellanea

The antiphospholipid syndrome (APS) is a rare multisystem autoimmune disease characterized by a chronic state of hypercoagulability, which may conduct to recurrent fetal loss and thromboembolic events associated with the presence of elevated titres of antiphospholipid antibodies (aPL) [117,118]. Current evidence suggests that APS patients had low vitamin D levels compared to healthy subjects [119-123]. These data were also recently confirmed by a meta-analysis by Riancho-Zarrabeitia [124]. Moreover, at least two studies demonstrated that VD deficiency in APS patients is associated with clinically-defined thrombotic events, although low-dose VD supplementation seems to be ineffective [119,123]. Type 1 diabetes mellitus (T1DM) is an early-onset autoimmune chronic disease characterized by the destruction of beta pancreatic cells by auto-antibodies. Although recent studies demonstrated that vitamin D might have a protective role on this condition [125-129], few authors found different results. Nandi-Munshi et al. [130] performed a study on 938 patients with T1DM and 8789 controls without reporting any association between serum VD and albuminuria in either non-diabetic youth or those with T1DM. Moreover, Cadario et al. [131] found no association between vitamin D levels at birth and risk of T1DM up to 10 years of age among Italian patients. The role of vitamin D upon the risk of developing T1DM was also studied by Sørensen et al. [132], who found that lower vitamin D concentration, particularly in the third trimester of pregnancy, was associated with T1DM of the offspring. Immunoglobulin A nephropathy (IgAN) is the most prevalent primary form of glomerulopathy in the western world. It is a multi-factorial disease involving autoimmune mechanisms, genetics and environmental as well as nutritional factors. It still represents one of the major causes of renal impairment and proper treatment is necessary to avoid irreversible damage [133,135]. To date, an association between

vitamin D and IgAN was found. Indeed, Li et al. [135] conducted a study on 105 patients reporting that vitamin D deficiency correlated with poorer clinical outcomes and more severe renal pathological features; and low levels of vitamin D at baseline associated with increased risk of renal progression. Further studies are needed in order to confirm these results. The role of vitamin D upon dermatologic immune-mediated diseases was also studies. Moravvej et al. [136] reported that vitamin D deficiency was common in patients and controls; however, lower vitamin D levels were noticed in patients with more severe disease. Controversial results were also reported regarding pemphigus. In fact, Karagüzel et al did not find any significantly difference of vitamin D levels in patients suffering from pemphigus compared to healthy controls [137,138]. Low vitamin D levels were also observed among Sjögren syndrome (SS) patients. In fact, Garcia-Carrasco et al [139] hypothesized that vitamin D may play a role in the SS pathogenesis, demonstrating an association between low vitamin D levels and extra-glandular manifestations, such as lymphoma or neuropathy. Moreover, vitamin D effects were also studied upon hematologic diseases such as immune thrombocytopenic purpura, primary autoimmune hemolytic anemia, Evans' syndrome and chronic idiopathic neutropenia. In fact, Fattizzo B et al [140] found that vitamin D is reduced in autoimmune cytopenias and correlate with disease severity, supporting its possible protective role against the development of autoimmunity.

8. Statistics

Statistics at a glance for the different groups of diseases are reported in Table 2. Regarding vitamin D plasma levels among AIT patients, we did not found any statistically significant difference. In fact, 50% of patients showed normal vitamin D levels, while the other 50% had low levels (37.5% had vitamin D deficiency and 12.5% vitamin D insufficiency). On the other hand, we noticed that vitamin D had a significant effect on AIT (88.9% Vs 11.3%) . In fact, Metwalley et al. [61] reported

that vitamin D was lower in patients with overt hypothyroidism than those with subclinical hypothyroidism ($p< 0.01$). Similarly, Kim et al [141] conducted a study on 369 patients with AIT and 407 controls, concluding that among HT (Hashimoto's thyroiditis) cases, vitamin D deficiency prevalence comparing to hypothyroidism, euthyroidism, subclinical hypothyroidism and no-AITD respectively were: 60.4% vs. 44.1% vs. 21.7% vs. 37.1% ($p <0.001$). Focusing on autoimmune neuromuscular diseases, low vitamin D levels were reported among 66.7% of patients. Among them 44.4% had vitamin D deficiency, while 22.3% of patients were insufficient. Considering vitamin D effect on these conditions, data demonstrated that, in 87.2% of cases, vitamin D had a favorable role. Herein, Jelinek et al. [142] studied vitamin D effect on 2466 patients with MS reporting significant associations between deliberate sun exposure, vitamin D supplementation and health outcomes ($p< 0.001$). Moreover, studies on cytokines response to vitamin D supplementation were conducted. Toghianifar et al. [143] reported that IL-17 levels showed significant change in RRMS patients after receiving high dose of vitamin D for 12 weeks compared to placebo arm. In fact, IL-17 serum levels at baseline were 56.75 ± 28.72 pg/ml in the intervention group vs. 30.31 ± 75.85 pg/ml in the placebo arm. IL-17 levels were re-assessed after 12 weeks: 58.93 ± 67.93 pg/ml was reported in the intervention group compared to 46.13 ± 94.70 pg/ml among the placebo arm. In conclusion, vitamin D consumption was associated with the logarithm of IL-17 measures adjusted by EDSS ($\beta = 1.719$; $p = 0.002$, $R^2 = 0.91$). Concerning connective tissue diseases, normal vitamin D levels were reported only in 20% of cases. In fact the majority of patients (80%) presented with low vitamin D levels. As far as it concerns SLE, for example, Gao et al. [144] reported that vitamin D deficiency is prevalent in SLE. Indeed, vitamin D insufficiency was found in 62.81% and severe deficiency in 34.71% of patients. Our analysis also demonstrated that vitamin D was found to a have a significant effect upon these conditions in 76.5% of cases. Regarding RA patients, Azzeh and Kensara et al. [111] found lower vitamin D in RA patients with high disease activity. They reported an inverse correlation between serum vitamin D and DAS28 ($r = -0.277$, $p = 0.014$). ROC curves showed that vitamin D< 12.3 ng/mL predicted high disease activity, while vitamin D> 17.9

ng/mL predicted low disease activity. As far it concerns SLE, Lin et al. [145] reported that serum vitamin D levels inversely correlated with SLE disease activity at both active and inactive disease status and with the presence of LN at active disease stage. Differences between vitamin D levels among active and inactive SLE patients were respectively: 12.0±7.2 ng/mL (active SLE) vs. 15.4±7.4 ng/mL (inactive SLE) ($p=0.005$). The same results were also obtained from the mixed conditions groups. Savastio et al [128], for example, reported that, among type 1DM children, vitamin D deficiency impacted on the metabolic status and glycemic homeostasis and that vitamin D supplementation improved glycemic control. In this study, the authors demonstrated that vitamin D insufficiency was present in 26.6% of subjects, vitamin D deficiency in 40.6% and severe deficiency in 23.4%. Moreover, vitamin D levels were inversely related to diabetic keto-acidosis severity ($p<0.05$). To sum up, there are no differences between pathology groups, either as regards the effect of the variation of vitamin D on the pathologies (Kruskal-Wallis Test: H= 2.352, p= 0.503) (see Figure 1), nor as concerns the prevalence of insufficiency/deficiency of vitamin D among different conditions: vitamin D Deficiency (Kruskal-Wallis Test: H= 0.765, p= 0.858), vitamin D Insufficiency (Kruskal-Wallis Test: H= 3.550, p= 0.314) (see Figure 2). In fact, regardless of the specific disease, all these groups were found to be associated with low vitamin D levels. Moreover, any statistically significant difference was found to be related to vitamin D effect among different groups, as it was demonstrated to have a favorable effect upon all conditions. Our results are in line with Skaaby et al.'s study [146], who analyzed several autoimmune disease such as thyrotoxicosis, type 1 DM, MS, iridocyclitis, Crohn's disease, ulcerative colitis, psoriasis vulgaris, seropositive RA, polymyalgia rheumatica, demonstrating an inverse association between vitamin D and the development of any autoimmune disease. In the last decade, researchers' interest in vitamin D and its correlations with autoimmune diseases has considerably increased. Vitamin D plasma level and its correlation to the occurrence of autoimmune disorders are controversial. Moreover, it is not clear if vitamin D has a favorable role upon all kinds of immune-mediated conditions. Our research aims to provide to the reader an updated and complete review about

vitamin D effect upon different autoimmune conditions. Autoimmune diseases are multifactorial diseases in which several factors are involved, including genetic ones. Low vitamin D levels are often reported in both affected patients and healthy controls. Further studies are needed to explore the effect of vitamin D upon immune-mediated disorders; however, recent findings demonstrated that vitamin D has an effect upon these conditions.

9. Perspectives

As shown in figure 3 vitamin D plays an important role on different aspects of the immune system. Understanding the effect of vitamin D upon immune-mediated diseases is thrilling and represents a significant future scientific perspective. It is now established that immune-modulatory effects of vitamin D can improve autoimmune diseases treatment. Thus, it is necessary to integrate vitamin D in autoimmune patients, especially those who are taking corticosteroids. However, the immediate prospect would be to program an international multicenter study aimed to confirm data published in the literature. Furthermore, specific studies could be useful to assess at what level vitamin D could play a role in the development of an autoimmune disease and, finally, international multicenter studies could allow us to evaluate when to effectively supplement vitamin D in patients who do not take corticosteroids.

Table 1. Effect of VD (up) and prevalence of normal VD, insufficient VD and deficient VD (bottom) per group of diseases.

VD effect on groups of diseases		
Disease group	**Significant VD effect**	**No significant VD effect**
Connective Tissue Diseases	76.5%	23.5%
Autoimmune Thyroiditis	88.9%	11.1%
Autoimmune Neuromuscular Diseases	87.2%	12.8%
Other Diseases	78.3%	21.7%

Prevalence of normal VD, VD insufficiency and VD deficiency per group of diseases			
Disease group	**Normal VD**	**VD insufficiency**	**VD deficiency**
Connective Tissue Diseases	20.0%	27.4%	52.6%
Autoimmune Thyroiditis	50.0%	12.5%	37.5%
Autoimmune Neuromuscular Diseases	33.3%	22.3%	44.4%
Other Diseases	33.3%	16.7%	50.0%

Table 2. Effect of VD (up) and prevalence of normal VD, insufficient VD and deficient VD (bottom) per group of diseases.

VD effect on groups of diseases			
Disease group	**Significant VD effect**	**No significant VD effect**	
Connective Tissue Diseases	76.5%	23.5%	
Autoimmune Thyroiditis	88.9%	11.1%	
Autoimmune Neuromuscular Diseases	87.2%	12.8%	
Other Diseases	78.3%	21.7%	
Prevalence of normal VD, VD insufficiency and VD deficiency per group of diseases			
Disease group	**Normal VD**	**VD insufficiency**	**VD deficiency**
Connective Tissue Diseases	20.0%	27.4%	52.6%
Autoimmune Thyroiditis	50.0%	12.5%	37.5%
Autoimmune Neuromuscular Diseases	33.3%	22.3%	44.4%
Other Diseases	33.3%	16.7%	50.0%

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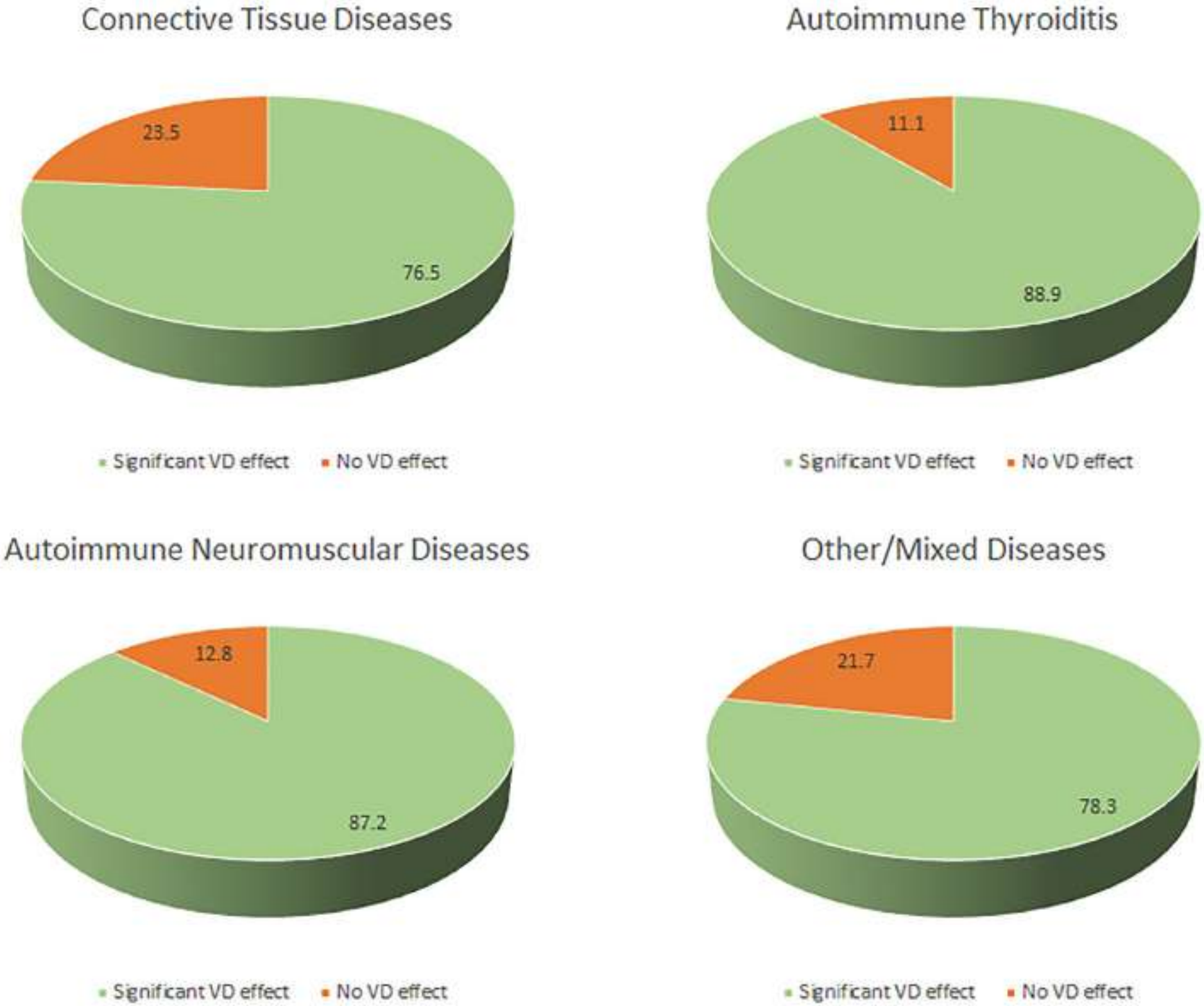
Figure 1

Figure 2

Figure 3


Connective Tissue Diseases
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76.5
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No VD effect
Autoimmune Thyroiditis
11.1
88.9
Significant VD effect
No VD effect
Autoimmune Neuromuscular Diseases
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Other/Mixed Diseases
21.7
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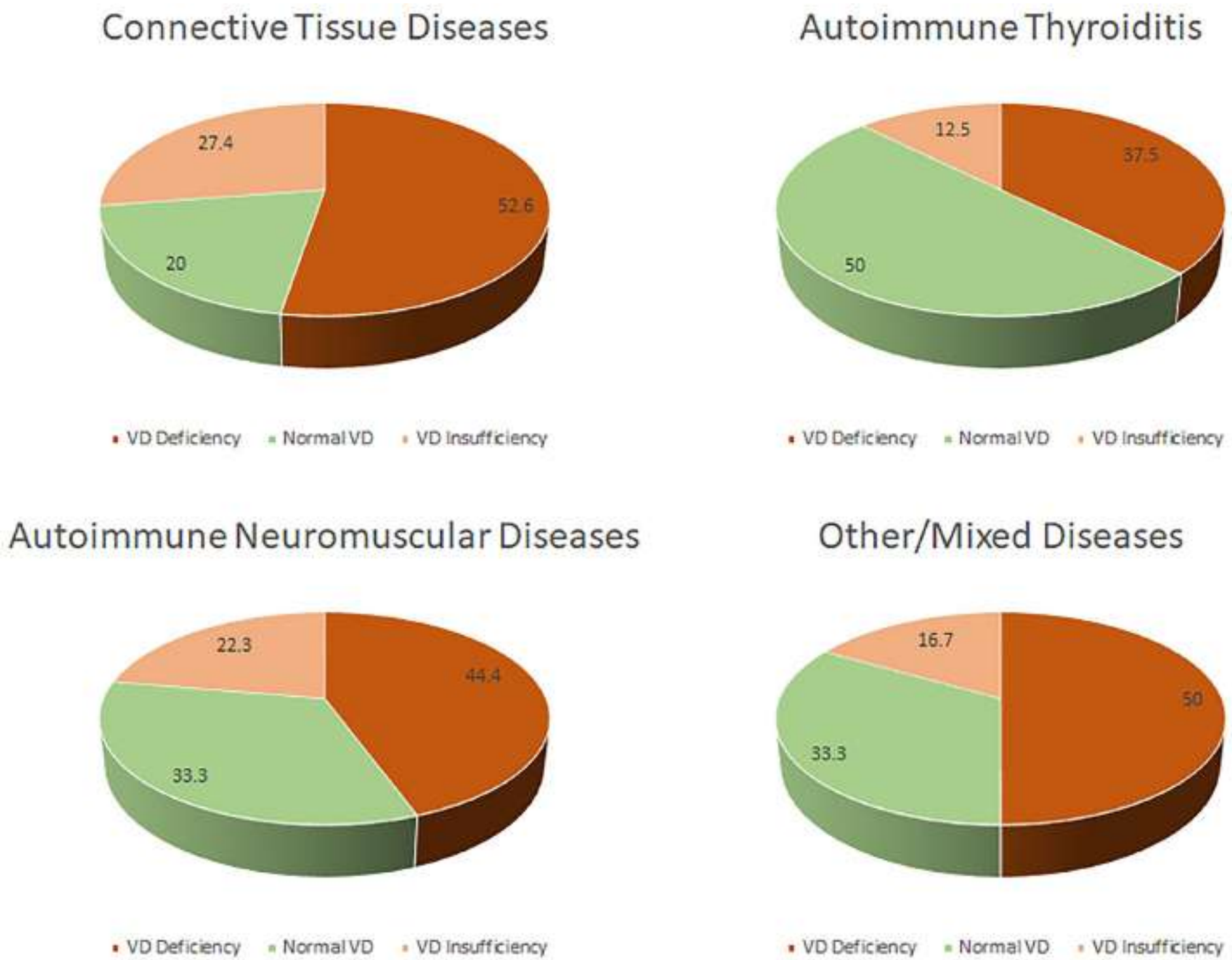
Significant VD effect
No VD effect

Figure 1


Connective Tissue Diseases
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52.6
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Normal VD
VD Insufficiency
Autoimmune Thyroiditis
12.5
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VD Deficiency
Normal VD
VD Insufficiency
Autoimmune Neuromuscular Diseases
22.3
44.4
33.3
VD Deficiency
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VD Insufficiency
Other/Mixed Diseases
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VD Deficiency
Normal VD
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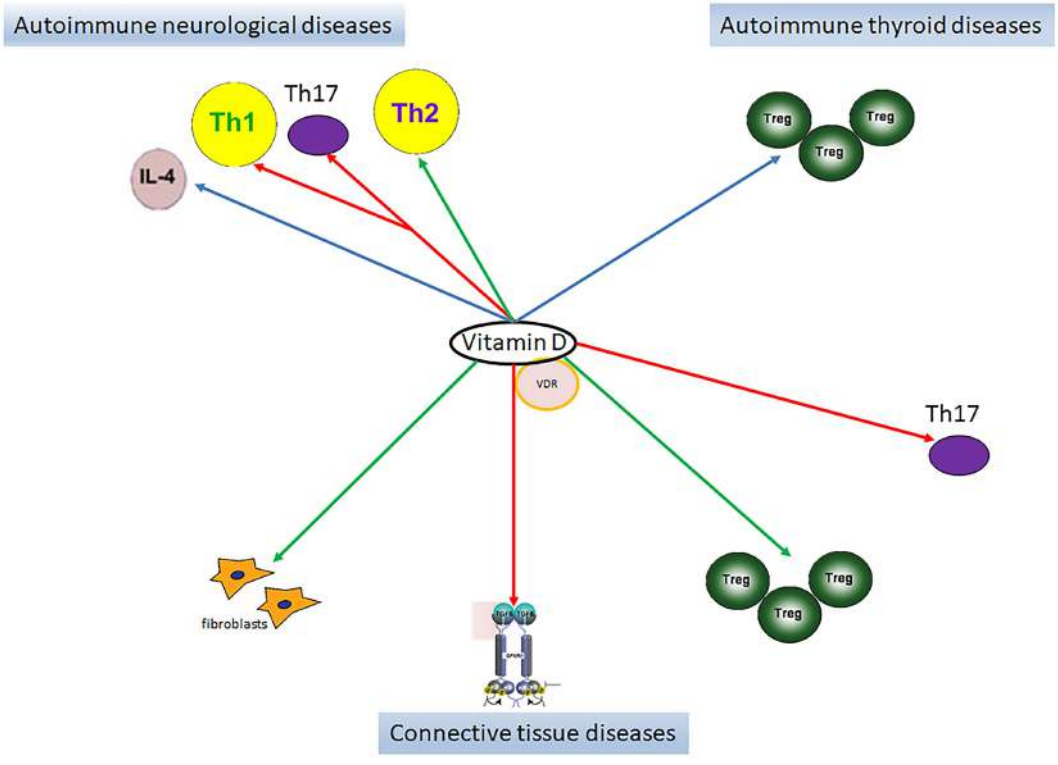
Figure 2


Autoimmune neurological diseases
Autoimmune thyroid diseases
Th1
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IL-4
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Vitamin D
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fibroblasts
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Treg
Connective tissue diseases

Figure 3