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IMMUNOMODULATORY EFFECTS OF VITAMIN D AND ITS STATUS IN PATIENTS WITH AUTOIMMUNE DISEASES

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ABSTRACT

The incidence of autoimmune diseases is increasing year by year, especially in Western societies. Many factors, both genetic and environmental, are involved, and vitamin D (vD, 25(OH)D3) deficiency is considered to be one of the key factors. However, the precise etiopathogenesis of autoimmune disorders is still not fully understood, which is also reflected in the limitation of therapeutic possibilities. Recently, there has been a growing interest in the role of vitamin D in alleviating autoimmunological processes, as vD has the ability to stimulate or inhibit virtually every stage of the immune response through its vitamin D receptor (VDR), expressed on immune cells. Innate and adaptive immune system and endothelial membrane stability. This allows us to define this vitamin as a strong immunomodulator in terms of both innate and acquired immunity. The aim of this paper is to present the pathophysiology of selected autoimmune diseases and to demonstrate the modifying properties of vitamin D on the immune system. Our review also demonstrates the scale of deficiency, both in the general population and among individuals diagnosed with autoimmune disease.

KEYWORDS

Vitamin D, Vitamin D Receptor, Autoimmunity, Immunomodulation, Autoimmune Disorders

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Introduction

There is a growing interest in the role of vitamin D in autoimmune and allergic diseases due to its confirmed influence on the course of such diseases. It is also important to note that the number of patients suffering from autoimmune diseases is increasing, especially in western countries (1). VD has a wide range of functions in the context of their pathogenesis. It is a well-known immunomodulator and has anti-inflammatory, antioxidant, and anti-fibrotic properties that may influence the occurrence and course of immune-mediated diseases. It has been confirmed in studies that vitamin D levels within the normal range in childhood and adolescence has the ability to limit the development of autoimmune diseases such as multiple sclerosis, rheumatoid arthritis and type 1 diabetes (2). The decreased serum level of vitamin D is regarded as a significant factor of many other diseases, ex. hypertension, cardiovascular and metabolic diseases. A proper 25(OH)D3 concentration is also considered a protective factor in the case of neoplasms such as: breast, lung, prostate cancer and non-Hodgkin's lymphoma (3).

Epidemiology of vitamin D deficiency in a healthy population.

Vitamin D deficiency is a global problem that may affect as many as one billion people, especially chronically ill and elderly persons, worldwide. According to the US Institute of Medicine VD deficiency occurs when the level is below 30 nmol/L (12ng/mL) (which was determined based on its contribution to metabolic bone diseases); concentration in the range of 30-50 nmol/L (12-20 ng/mL) is considered insufficient, and ≥50 nmol/l (≥20 ng/mL) is regarded as sufficient. The Endocrine Society, however, considers a concentration below 50 nmol/L (20 ng/mL) to be a deficiency, then an insufficiency is in the range of 50-75 nmol/L (20- 30 ng/mL) and a proper level ≥75 nmol/L (≥30 ng/mL). The concentration reflects both dermal synthesis and oral intake as well (4,5).

Data from a large observational study have shown that this problem may affect up to 40% of people in Europe (6,7). The range of the deficit has varied depending on the age group and has been the highest among teenagers of 15-18 years old, reaching up to 40%. In the remaining age groups, i.e. among adults, older adults aged >61 years and children, this indicator has shown respectively 9-24%, 1-8% and 4-7%. Overall, the deficit affects 13% of the European population. (6).

Insight into the physiology of vitamin D.

The main source of vitamin D in human organisms is the skin.. The first step of the vitamin D bioactivation is a photolytic conversion of 7-dehydrocholesterol in subcutaneous fat under the influence of ultraviolet B (UV-B) of wavelength 290 to 315 nm exposure to pro-vitamin D and then a thermal isomerization to still inactive vitamin D3 (cholecalciferol) and D2 (ergocalciferol) (8,9,10).

Hydroxylases essential to 25(OH)D3 (calcifediol) and to 1, 25 (OH)2 D3 (calcitriol) synthesis are present mainly in the liver and in the proximal tubular cells of the kidneys, respectively (9). A few other tissues, including intestines and kidneys, are known to show the gene expression of 25-hydroxylases which enables them to produce calcifediol, but it has been reported that 1-hydroxylase occurs mostly in kidneys (8, 10).

The epidermis cells, especially keratinocytes, also show the gene expression of both hydroxylases which enables them to produce a fully active 1,25 (OH)2 D3 (10).

Widespread functions of vitamin D.

Calcitriol acts in metabolic pathways through the highly prevalent 1,25(OH)2D3 receptor (VDR), which works as a ligand-dependent transcription factor by vitamin D response elements in promoter regions of more than 200 genes (8, 11, 12). The heterodimer created by VDR and retinoid X receptor (RXR) mediates in 1,25 (OH)2D3 action at nuclear level and it is reported to be highly involved in proliferation, differentiation, immunomodulation, responsiveness and apoptosis of various cells (11). Apart from its key role in calcium metabolism, such as increasing calcium and phosphate absorption in intestines, bone mineralization and parathormone inhibition, it has a vasoprotective function by increasing NO production, improves hematopoiesis and alleviates the course of autoimmune diseases (8, 13, 14). VD receptors can be found in nearly all immune cells, especially in antigen-presenting cells (APC), such as macrophages and dendritic cells and in activated T cells, which explains a strong immunomodulatory effect of vitamin D (15).

Table 1. Some functions of 25(OH)D3 within the immune system (16, 17).

Cell subpopulation	Function of 25(OH)D3
Antigen presenting cells (APC): dendritic cells, macrophages, monocytes	↓MHC class II expression ↓CD40, CD80, CD83, CD86 expression ↓TNF-α, IL-1β, IL-6, IL-12 production ↓dendritic cells differentiation, maturation, and immunostimulatory capacity ↓auto-Ag presentation
T Lymphocytes	↓Th1-cells proliferation, secretion of cytokines ↓IL-2, IL-6, IL-12, INF-γ production ↓surface CLA expression ↑IL-4, IL-5, IL-10 production ↑VDR expression ↑Th2-cells functions ↑T-reg development, differentiation, activity
B Lymphocytes	↓IgE and auto-Ab production ↓plasma cells differentiation ↓B-cells proliferation ↑VDR expression
NK cells	↓INF-γ production

The immunomodulatory effect of vitamin D on the selected autoimmune diseases.

Rheumatoid arthritis

It is known that vitamin D deficiency contributes directly to both the development of rheumatoid arthritis (RA) itself and the course of the disease (18). It is debatable whether it is also involved in the very onset of the disease (19). The activity in RA is negatively correlated with vD serum level. It has also been observed to contribute to the relief of musculoskeletal pain occurring in the course of RA (18).

The complex and not fully understood etiopathogenesis of rheumatoid arthritis means that the direct mechanism of action of vitamin D in this disease has not been established either (18). It is currently known that both innate and adaptive immunity are involved in the development of this disease (20). The special role in the pathogenesis of RA is supported by the fact that this disease occurs more frequently at high latitudes than around the equator (19, 21). A similar relationship may be observed in other rheumatoid diseases, such as ankylosing spondylitis, psoriatic arthritis, undifferentiated connective tissue disease and systemic sclerosis (SSc). It is also observed in osteoarthritis (20).

It is currently assumed that vitamin D has a strong immunomodulatory effect, which can increase the body's immunotolerance (18). Its immunomodulatory effects occur at every stage of the immune response, beginning with antigen presentation by antigen-presenting cells (APC), such as macrophages and dendritic cells (18, 22, 21). The participation of APC cells in the etiopathogenesis of RA involves the presentation of autoantigens, which include collagen, fibrin, fibrinogen, or immunoglobulin G, to Th lymphocytes. The process leads to the formation of autoreactive T and B lymphocytes (20, 23). Vitamin D may counteract this phenomenon through reducing the expression of MHC II receptors on their surface.

Additionally, vD is a great inhibitor of dendritic cell differentiation (21). Various lymphocyte subpopulations have also been shown to have vitamin D receptors on their surface, which enable vD to influence the proliferation and activity of T-/B-cells. (22, 24). Under the influence of vitamin D, Th1 lymphocytes show reduced activity, which inhibits their pro-inflammatory effect and tissue damage. T helper cells are the source of RANKL, which is responsible for the activation of osteoclasts leading to joint destruction (25). The production of major pro-inflammatory cytokines such as TNF-α, IL-1β and IL-6 by macrophages is suppressed as well (20, 26). Studies have shown that IL-1 is a direct cause of joint damage in RA. It is also an inducer of another cytokine, IL-6, whose concentration in synovial fluid is closely linked to damage in the surrounding tissues. Furthermore, TNF-α inhibits the immune-limiting response of Treg lymphocytes and stimulates metalloproteinases (MMPs) to subsequent tissue destruction (20, 27). The involvement of macrophages in the local and systemic inflammatory process as amplifiers is well-established, but there is no consensus on their role in the initiation of the process itself (28).

B lymphocytes play a special role in the pathogenesis of the disease by producing antibodies such as rheumatoid factor (RF) and anti-cyclic citrullinated peptide (anti-CCP) antibodies, whose presence correlates

with tissue damage (20, 29). It is currently believed that B-cells are also a source of IL-6 and TNF-α, and are capable of synthesizing lymphotoxins and IL-10 as well. IL-10 is a cytokine that stimulates follicular dendritic cells and other B cells, thereby causing mutual stimulation of these cells (29). Studies have shown a significantly reduced production of autoantibodies by B-cells due to vitamin D supplementation (21).

At the same time, the production of cytokines, such as IL-10, by the Treg and Th2 lymphocyte subpopulation is enhanced (20, 21, 22). Thus, IL-10 acts in a dual manner, being both a pro-inflammatory factor and an immunomodulator limiting the extent of inflammation (29). Another proposed element of the response in autoimmune diseases is Th17 lymphocytes, which have the ability to produce pro-inflammatory cytokines such as IL-17, which acts as a mediator in some inflammatory reactions (22). Under the influence of vitamin D, their proliferation and migration towards the central nervous system is inhibited (20). Thus, it is estimated that the effect on T lymphocytes is the main target of the immunomodulatory action of vitamin D (21).

Researchers on this subject reported statistically significant differences in deficiency or insufficiency of vitamin levels in affected patients compared to the control group (30, 31, 32). Narendra et al. reported in their study that the vD in the serum of RA patients were significantly lower (mean value of 21.05 ± 10.02 ng/ml) compared to the healthy participants (mean value of 32.87 ± 14.16 ng/ml). (30). Similar findings were shown in the research by Cen et al. - in these studies the difference was 35.99 ± 12.59 nmol/L in the study group to 54.35 ± 8.20 nmol/L in the control group (32). Also in the study conducted by Rajeev et al., a clear difference was observed between sick and healthy people: 43.00±26.85 nmol/l (17. 20 ± 10.74 ng/ml) and 55.97±35.07 nmol/l (22.39 ± 14.03 ng/ml) (31)

Thus, vitamin D status in RA patients is not clear. In individuals with low disease activity, levels may not differ from that in healthy controls. However, it was found that the severe course of the disease, which may be reflected by the Disease Activity Score Calculator (DAS28) value, correlates inversely proportionally with the level of vitamin in the blood (19, 30). In some studies, the relationship between vitamin D concentration and DAS 28 score is questioned. Mansour et al. in their research did not find a strong relationship between 25(OH)D levels in patients and DAS28, Erythrocyte Sedimentation Rate (ESR), pain sensation described in Visual Analogue Scale (VAS), swollen and tender joints number (36). This implies the need for further exploration of the impact and use of vitamin D in rheumatoid arthritis.

Animal studies have shown that the additional supply of vitamin D has had a mitigating effect on the course of the disease even in individuals with normal concentrations of the vitamin in the blood serum (19).

Systemic lupus erythematosus

As with other rheumatological diseases, systemic lupus erythematosus (SLE) is characterized by a complex, not fully understood etiopathogenesis. SLE is a multifactorial and multisystemic connective tissue disease (CTD) characterized by highly diverse clinical presentation, course and prognosis as well (34). In its complex pathogenesis, a special place is taken by autoreactive B lymphocytes producing antinuclear antibodies (ANA), such as anti-dsDNA.

Anti-dsDNA antibodies are detected in 43-92% of SLE cases and are one of the criteria for diagnosing the disease, in both ACR and SLICC classification. It is assumed that their concentration correlates with the course of the disease (34, 35). The anti-nucleosome autoantibodies (AAbs) are other antinuclear antibodies that are observed in 59, to 61,9% of patients. Its IgG3 type correlated with SLE activity. It is noteworthy that they may appear in the serum before other ANAs (34).

Other antibodies involved in this disease include anti-Sm Aabs, anti-Ro and anti-La Aabs (in Sjögren disease), anti-histone Aabs (corresponding to drug-induced SLE), anticardiolipin Aabs, and anti-phospholipid antibodies (34, 35).

As with other autoimmune diseases, genetic factors, familial predisposition and trigger factors play a role in the development of the disease. Factors that have been confirmed to contribute to the etiology of lupus include exposure to estrogens, smoking, and viral infections such as herpesvirus infections. The role of pesticides, air pollution, UV exposure and alcohol consumption is also postulated (36). Female sex hormones are a strong predisposing factor to the development of lupus, and this is confirmed by the fact that women constitute 90% of patients with lupus (36). The influence of genetic factors on the development of SLE is debatable. Studies have shown that the BsmI B allele is a potential genetic factor associated with the development of this disease in Asians. For other alleles studied, such as the FokI F allele, such a clear association has not been demonstrated. More research in this area is recommended to clearly determine the influence of genetic factors on the development of the disease (37).

Table 2. Autoantibodies in systemic lupus erythematosus (34).

AAb	Meaning
Anti-ds-DNA	Correlation with SLE activity
Anti-Sm	Specificity 98-100%
Anti-histone	Drug-related SLE
Anti-Ro	Congenital heart block
Anti-La	Congenital heart block, SLE in newborns
Anti-C1q	Glomerulonephritis
Anti-nucleosome	Correlation with SLE activity
Anti-ribosomal P	Neuropsychiatric symptoms

The Th1 to Th2 ratio shows an imbalance in favor of Th1 lymphocytes. This contributes to the overproduction of cytokines such as Il2 and INF gamma, which translates into increased disease activity, as the concentration of anti-inflammatory cytokines IL-4 and IL-10 produced by Th2 is reduced (38). The phenomenon of increased cytokine production by Th1 is probably secondary to an imbalance in the production of increased IL-10 and decreased IL-12 by monocytes (39).

Mok et al. showed that patients suffering from systemic lupus erythematosus had deficiency ($25(OH)D_3$ < 15 ng/ml) or insufficiency (<30 ng/ml) in serum vitamin D concentration. The study also found an inverse correlation with Physical Global Assessment (PGA). 40). In a study by Bonakdar et al. involving patients with newly diagnosed SLE, varying serum vitamin D levels were obtained. Severe deficiency occurred in 12.5% (<12,5nmol/L) of the samples tested.

Moderate (12.5-24.9 nmol/L) and mild (25-39.9 nmol/L) deficiency were found in 62.5%, and 17.5% of the cases, respectively (41).

Autoimmune hepatitis

Autoimmune hepatitis (AIH) is a chronic disease of unclear etiology that can lead to cirrhosis of this organ (42, 43). As it is a disease resulting from the overactivity of the immune system, in this case also there is an imbalance between the subpopulations of lymphocytes, with the predominance of Th1 cells and the IL-2 over Th2 with its IL-10 and Treg lymphocytes (42). In this case, too, attention has recently been drawn to the role of the Th17 lymphocyte subpopulation. It is currently assumed that the interleukins they synthesize, such as IL-17, IL-21, and IL-22, play pivotal roles in tissue damage. Transformation of naive T cells into Th17 cells is induced by interleukin IL-6 (44). The importance of genetic factors in causing AIH is currently limited to demonstrating the influence of the FOK polymorphism of the Vd receptor on the development of the disease (42). Insufficiency is estimated to occur in 17-23% of people with AIH, while deficiency is reported in as many as 51-92% of patients, which is associated with poor prognosis (45, 46, 47). The inverse correlation of vitamin D levels with both the MELD and Child-Pugh scores has been demonstrated in numerous studies. This correlation was observed in liver dysfunction regardless of its etiology. Generally, studies have shown that its vD concentration decreases with increasing degree of liver fibrosis (48). Furthermore, both the MELD score and low vitamin D levels are confirmed predictors of mortality (11). In the case of liver diseases, regardless of the etiology, ex. viral hepatitis, alcoholic liver disease and NASH (48), vitamin D, in addition to its strictly immunomodulatory effect, slows down the process of fatty degeneration and fibrosis of the liver, prevents the formation of reactive oxygen species (ROS), and even stimulates liver cell regeneration. Vitamin D also enhances immunosuppressive glucocorticoid therapy (49). Due to its function in the context of activating vitamin D through its hydroxylation, this action is disturbed, contributing to the creation of a vicious circle, as active vitamin D supporting liver function cannot be produced.

Type 1 diabetes

According to the data, up to 25% of youth diagnosed with type 1 diabetes do not have sufficient vitamin D levels in their blood serum (50).

It is assumed that the immunological cause of the development of diabetes is the escape of autoreactive lymphocytes from the mechanisms of central, in the thymus and bone marrow, and peripheral selection and elimination but, as with all autoimmune diseases, its exact etiopathogenesis has not been well established (51). The basic immunological phenomenon in type 1 diabetes is the production of autoantibodies targeting pancreatic islets of Langerhans (52). These antibodies are detected many years, even decades, before symptoms appear, making them a reliable prognostic factor (53, 54). It has been estimated that of the four main types of antibodies ([pro]insulin, IA-2, GAD65 and ZnT8), at least one of them is present in the blood in 94% of patients at clinical onset (54). Unfortunately, by the time clinical onset occurs, 80% of the beta cells of the pancreas are destroyed (53). Another postulated property of vitamin D is a direct effect on insulin sensitivity by stimulating the synthesis of the insulin receptor and by activating peroxisome proliferator-activated receptors (PPAR-γ), involved in the metabolism of fatty acids (55). By influencing calcium metabolism, it indirectly regulates insulin sensitivity through the concentration and flow of calcium through the cell membranes of pancreatic beta cells, as well as those cells that are the target of insulin (55).

The gene detected so far contributing to the development of central tolerance is the AIRE gene located on chromosome 21. Its mutation is a causative factor of autoimmune polyendocrine syndrome 2 (APS 2). It is a syndrome that mainly includes type 1 diabetes, but also autoimmune thyroid diseases, celiac disease, alopecia and vitiligo as well (51).

In vivo studies using nonobese diabetic (NOD) mice, an animal model for human type 1 diabetes, have shown a preventive effect of vitamin D on the development of this disease in supplemented individuals (52). The results showed a reduction in insulitis and cumulative diabetes incidence in the group of mice supplemented with vitamin D, compared to the control group, which received no treatment. The severity of inflammation within the pancreatic islets was also highly limited, as assessed by histopathological examination by measuring lymphocyte infiltration (52).

The other research using NOD mice by Giulietti et al. showed that even slight vD deficiency early in life contributes to a development of a more aggressive manifestation of type 1 diabetes. Additionally, the earlier onset of symptoms and the frequency of the disease itself were found (56).

The results obtained in the in vivo animal model were confirmed in a case-control study using data from 820 patients diagnosed with type 1 diabetes and 2335 control participants.

Based on questionnaire, the collected data showed a relationship between vD supplementation in infancy and decreased risk of disease development (57).

Multiple sclerosis

Multiple sclerosis is regarded as a model example of a disease whose course is modified by the action of vitamin D. Much research has been devoted to the pathogenesis of this disease, yet it is still not fully understood and all factors remain unknown (58).

Postulated environmental factors in the development of multiple sclerosis are viral agents, such as herpesviruses and retroviruses, smoking and poor UV exposure (59, 60).

The influence of vitamin D deficiency on the development of this disease is indicated by its higher frequency of occurrence with increasing distance to the north and south from the equator. Italy and Sweden are exceptions to this rule, which can be explained by certain genetic factors as well as lifestyle (61). It is believed that the first step in disease development is the interaction between antigen-presenting cells (APCs) and CD4+ lymphocytes (62). During the course of the disease, there is an imbalance between T helper lymphocytes, in favor of Th1 lymphocytes over Th2 lymphocytes and their anti-inflammation properties (62). Stimulated lymphocytes Th1 produce proinflammatory cytokines, such as IL-2, IL-6, and TNFα, which play a pivotal role in the development of inflammation within the central nervous system (62, 63). Some studies also indicate the involvement of other cytokines, such as INF-γ and IL-12 (63, 64). Another subpopulation implicated in the development of MS are Th17 lymphocytes, which produce pro-inflammatory cytokines, including IL-17, IL-21, IL-22 and IL-26 (62).

A special place in immunopathogenesis is occupied by B lymphocytes, which produce autoreactive antibodies directed against elements of the myelin sheaths of nerves, which include myelin basic proteins (MBP), myelin-associated glycoprotein (MAG), myelin oligodendrocyte glycoprotein (MOG) and proteolipid protein (PLP) (65). Detecting their presence in the cerebrospinal fluid is one of the diagnostic elements of multiple sclerosis, although it is not sufficient to make the diagnosis (66).

Inflammation and the proinflammatory cytokines produced as a result have the ability to stimulate osteoclasts responsible for bone turnover in the course of MS (67).

The best-known genetic factor in the development of MS is the HLA DRB1*1501 polymorphism, which is a strong prognostic factor for the development of this disease. Along with environmental factors such as vitamin D deficiency, they may exacerbate each other's impact on the development of the disease (68)

Some studies found an effect of Taq-I and Bsm-I polymorphisms of the vD receptor gene, while other studies ruled out their relationship and correlation with MS risk (69).

Assessment of vitamin D concentration in the serum of patients suffering from multiple sclerosis is important because it strongly correlates with fractures and their degree of disability, which is caused by the disease itself (70).

Also, when assessing the concentration of cholecalciferol in blood, it is customary to use the terms 'insufficiency'/'suboptimal level' (value in the range 20-30 ng/ml) and 'deficiency'/'reduced level' (value <20 ng/ml).

Scientific studies assessing vitamin D status, and calcium and phosphate metabolism, in MS patients do not provide a clear picture, as there are many factors that interfere with the concentration of this hormone. There are discrepancies in the results of studies on 25(OH)D3, 1,25(OH)2D3 or PTH concentrations. In general, most researchers found a reduction in these parameters in the diseased participants compared to the control group(71, 72, 73 74). However, some results indicate no such difference between the two groups (76). Thus, deficient or insufficient levels are obtained in patients from the very beginning of the disease (76) and longer duration of the disease contributes to the deepening of the deficiency of this vitamin (77). It may occur in up to 95% of MS patients (78). Vitamin D levels strongly correlate with the occurrence of osteopenia, especially in patients with its deficiency compared to insufficiency. Osteoporosis is also observed more frequently than in the general population, but is not as prevalent as osteopenia (79). Osteopenia is diagnosed at the time of diagnosis of multiple sclerosis in 80% of patients (80).

In their study, Nieves et al. demonstrated reduced BMD in the lumbar spine and femoral neck in 52 female participants. The difference increased proportionally with disease severity and vitamin D deficiency (81).

Intestinal bowel diseases

Deficiency in people with IBS is accelerated by additional factors resulting from the nature of the disease itself. Diseases such as ulcerative colitis (UC) or Crohn's disease (CD) involve reduced absorption of nutrients and impaired bile salt circulation. Additionally, dietary intake is often restricted (82, 83). Therefore, it is not fully known whether vitamin D deficiency is the cause or consequence of intestinal disease, although deficiencies are observed from the very beginning of the disease (84). It can be assumed that vitamin D deficiency and inflammatory diseases create a vicious cycle, with one element fueling the other.

The putative target of vitamin D in inflammatory bowel diseases is the suppression of Th1 and Th17 lymphocyte subpopulations with simultaneous activation of Th2 and Treg lymphocytes (82). This reduces inflammation in the intestines, allowing the mucosa to regenerate through the synthesis of new junction proteins and the rebuilding of the microbiota, which plays a key role in maintaining homeostasis in the digestive system (1, 82).

In a study of 72,719 female patients, Ashwin et al. demonstrated an inverse correlation between patients with adequate 25(OH)D3 concentration, with a proper dietary intake or supplementation, and UC risk. In terms of CD, a nonsignificant reduction in incidence was observed (84). Data show that for individuals who never experienced vitamin D deficiency, the frequency of surgical intervention was significantly reduced compared to deficient or insufficient patients. This also applies to the need for hospitalization (82).

Discussion

In autoimmune diseases, the prevalence of insufficient or deficient serum vitamin D concentrations is evident. However, it is unclear whether deficiencies act as a causative factor or a consequence of the disease. It can be assumed that 25(OH)D3 performs both functions.

Many studies have confirmed the role of vitamin D and its metabolites as immunomodulators. It can effectively suppress or stimulate at any stage of the immune response through its ubiquitous VDR receptor.

There is no clear consensus on the optimal concentration of vitamin D in blood serum. This applies to both healthy and sick individuals. It is assumed that a level sufficient to prevent the development of osteoporosis is 75 nmol/l (30 ng/mL). Inhabitants of countries located far from the equator, need to take oral supplementation to achieve this concentration (85). For people with autoimmune disease, the recommended dose is not clearly established and is a subject to ongoing debate (1). There are too many confounding factors

associated with 25(OH)D3 concentrations to establish a single, specific dose for all subgroups. Even among healthy individuals, circumstances can alter the need for this vitamin, including physiological conditions such as pregnancy, lactation, advanced age, and dark skin. The situation varies for individuals with chronic illnesses, obesity, avoiding sun exposure, with limited physical activity, impaired cholecalciferol metabolism, immune deficiencies, or allergies. However, it is assumed that 100 IU of calcidiol increases its level in blood serum by 1 ng/mL (1). Factors interfering with the production or absorption of this vitamin should also be controlled.

Conclusions

It seems to be reasonable to individually adjust and establish the threshold dose depending on the measured serum 25(OH)D3 concentration. Vitamin D supply has to be a component of a treatment for patients with an autoimmune disease, while there is indisputable evidence that the shortage of this vitamin contributes to accelerated disease course – regardless of the exact disease etiology. It is not without significance that its appropriate concentration in blood serum leads directly into therapeutic success.

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