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The Relationship Between Low Vitamin D Levels and the Development of Autoimmune Endocrine Diseases.

Zależność między niskim poziomem witaminy D a rozwojem endokrynologicznych chorób autoimmunizacyjnych.

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Abstrakt

Witamina D jest niezbędnym składnikiem odżywczym odgrywającym ważną rolę w promowaniu ogólnego zdrowia i dobrego samopoczucia. Niedobory składników odżywczych, takich jak witamina D, często występują wu pacjentów z chorobami autoimmunologicznymi. Częstotliwość występowania tych schorzeń stale rośnie. W związku z tym pacjenci są narażeni na ciężkie objawy oraz dyskomfort w codziennym funkcjonowaniu. Przyczyny, a także objawy i powikłania, które powodują, są różnorodne, co utrudnia diagnozę i leczenie. Dlatego podczas opieki klinicznej nad pacjentami z AID należy wziąć pod uwagę możliwe niedobory mikroelementów i jeśli zostaną zaobserwowane, należy je leczyć poprzez kontrolowaną suplementację. Celem artykułu był przegląd literatury na temat wpływu niskiego poziomu witaminy D na rozwój chorób autoimmunologicznych w dziedzinie endokrynologii.

Słowa klucze: witamina D, dieta, odżywianie, styl życia, choroby autoimmunologiczne, endokrynologia, hormony

Abstract

Vitamin D is an essential nutrient that plays an important role in promoting overall health and well-being. Deficiencies of nutrients such as vitamin D are common in patients with autoimmune diseases. The incidence of these conditions is constantly increasing. As a result, patients are exposed to severe symptoms and discomfort in daily functioning. The causes, as well as the symptoms and complications they cause, are diverse, making diagnosis and treatment difficult. Therefore, during the clinical care of patients with AID, possible micronutrient deficiencies should be taken into account and, if observed, they should be treated with controlled supplementation. The aim of this article was to review the literature on the impact of low vitamin D status on the development of autoimmune diseases in the field of endocrinology.

Keywords: vitamin D, diet, nutrition, lifestyle, autoimmune disease, endocrinology, hormones

Introduction

Vitamin D is a prohormone that plays a crucial role in regulating skeletal and mineral ion homeostasis, protecting against the development of rickets and osteomalacia [1,2]. It also influences cell proliferation and differentiation and is key in various immune system processes. Its involvement in immune functions is partly due to the presence of vitamin D receptors (VDR) in T and B lymphocytes, monocytes, macrophages, dendritic cells and NK cells [3,4]. Vitamin D can be obtained through the consumption of vitamin D-rich foods or dietary supplements. It is also synthesized in the skin upon exposure to UV-B radiation. Since it can be produced endogenously and its intake is not necessary for those with adequate sun exposure, referring to it as a vitamin is somewhat misleading [1,2].

Vitamin D (calciferol) exists in two forms: D2 (ergocalciferol) and D3 (cholecalciferol). Cholecalciferol is produced in the skin under UV-B exposure from the precursor 7-dehydrocholesterol. Whether obtained through diet or synthesized, most vitamin D is transported via binding proteins to the liver, where it is converted into 25-hydroxyvitamin D (25(OH)D), an inactive intermediate form. It then travels primarily to the kidneys, but also to various other tissues (e.g., skin, bone cells, immune cells, placenta), where it is converted into 1,25-dihydroxyvitamin D (1,25(OH)2D3, calcitriol), the active form that remains in the circulating blood. Vitamin D metabolites exert their effects through interactions with VDRs present in most body tissues. One of VDR's primary functions is to promote intestinal calcium absorption, thereby impacting calcium homeostasis and bone health [1,2]. Vitamin D conserves calcium in the intestines, bones, parathyroid glands and kidneys [5]. Additionally, calcitriol, by binding with the VDR complex, regulates the transcription of about 300 genes, enhancing innate immunity and inhibiting adaptive responses, thus significantly influencing the immune system [3]. Vitamin D also affects hematopoiesis, as VDR promotes myeloid differentiation towards monocytes and granulocytes. This process is particularly important for the body's antibacterial response [5]. Studies suggest that vitamin D, acting as a selective immune modulator, likely prevents the development of autoimmune diseases [3]. There is also epidemiological evidence suggesting a possible link between low vitamin D levels and the development of musculoskeletal, metabolic, oncological, infectious and cardiovascular diseases [1,5]. Unfortunately, many cross-sectional and observational studies contained errors and biases, making it difficult to establish a definitive relationship between serum vitamin D deficiency and the development of such disorders [1].

In clinical practice, the parameter used to diagnose and determine vitamin D levels is the measurement of 25(OH)D concentration, as its conversion process is not strictly regulated and is independent of whether the vitamin was obtained through diet or synthesized in the skin [1,2,3]. A deficiency in vitamin D is indicated by 25(OH)D levels < 20 ng/mL (< 50 nmol/L), suboptimal levels are between 20-30 ng/mL (50-75 nmol/L), and optimal levels are within the range of 30-50 ng/mL (75-125 nmol/L) [6].

The aim of this article was to review the literature on the impact of low vitamin D levels on the development of autoimmune diseases within the field of endocrinology. The identification of relevant studies was conducted using the electronic PubMed/MEDLINE search engine, seeking publications that present the latest knowledge in this field.

Vitamin D and Endocrine Autoimmune Diseases

Vitamin D supplementation plays a significant role in autoimmune diseases (AID) due to its immunomodulatory effects [2]. Observational and epidemiological studies have shown an inverse relationship between vitamin D levels and the risk of developing many chronic diseases, including autoimmune disorders. Controlled clinical trials have also demonstrated that supplementation with vitamin D at a dose of 2000 IU per day reduces the incidence of autoimmune thyroid diseases by up to 22% [3]. As mentioned earlier, due to numerous confounding factors, there is currently a lack of randomized trials and debates continue on how to eliminate biases and errors from them [1,7].

Autoimmune Thyroid Diseases

Autoimmune thyroid diseases (AITD) include Hashimoto's thyroiditis (HT) and Graves' disease (GD), which are the most common autoimmune diseases in the general population. The etiology of AITD is complex and involves the interaction of genetic and environmental factors. Both diseases are characterized by lymphocytic infiltration of the thyroid gland [3,5]. In HT, there is damage to follicular cells, leading to hypothyroidism, and the presence of thyroid peroxidase antibodies (anti-TPO) and thyroglobulin antibodies (anti-Tg). In GD, there is hyperplasia of the thyroid and hyperthyroidism due to the presence of circulating thyroid-stimulating hormone

receptor antibodies (TRAb), which stimulate the thyroid to produce hormones [3,4,5]. Although promising results from studies on mice with HT have shown that calcitriol can reduce thyroid inflammation and limit damage, evidence in humans remains inconclusive. Observational studies have found that patients with HT more frequently have low vitamin D levels and have indicated an inverse relationship between vitamin D levels and thyroid antibody levels. However, other studies have reported conflicting results. Randomized studies have demonstrated that cholecalciferol reduces anti-TPO and anti-Tg antibody levels in HT patients with both sufficient and insufficient vitamin D levels, and significantly lowers TSH levels [3,5,8]. The probable beneficial effect of vitamin D is attributed to its anti-inflammatory and immunomodulatory properties [8,9].

In studies involving mice with GD, vitamin D has been found to likely have a significant impact on thyroid function and structure, with deficiency potentially leading to persistent overproduction of thyroid hormones. Other studies in GD patients have shown that the combined use of methimazole and calcitriol resulted in a greater reduction in thyroid hormones compared to methimazole alone [3,4,5,10]. Calcitriol also helps maintain normal cytokine and autoantibody levels [5]. Meta-analyses have shown that serum vitamin D levels are lower in GD patients, and low levels may increase the risk of developing the disease [4,11]. Studies have reported insufficient serum vitamin D levels in AITD patients and an inverse relationship between vitamin D levels and thyroid antibody levels. This suggests that vitamin D deficiency may be involved in the pathogenesis of these diseases. However, it remains unclear whether inadequate vitamin D levels precede or result from AITD, and further research is needed to clarify this relationship [8,12,13]. Scientists suggest monitoring serum vitamin D levels in AITD patients and correcting deficiencies through diet and supplementation, as cholecalciferol appears to have a positive effect on thyroid autoimmunity [3]. Confirmation of the impact of supplementation on clinical outcomes in AITD patients requires further multicenter studies [5,8].

Type 1 Diabetes

Type 1 diabetes (T1D) is one of the most common autoimmune diseases affecting the population [14]. The etiology of the disease is unknown, likely involving a combination of genetic and environmental factors [5]. The disease involves the production of autoantibodies

and autoreactive Th1 lymphocytes, leading to the destruction of pancreatic beta cells, which produce insulin. As a result, lifelong exogenous insulin administration is necessary. Animal studies have suggested that calcitriol administration, which stimulates Treg lymphocytes and inhibits Th1 cells, leads to a decreased incidence of the disease. Additionally, vitamin D binding to VDR can stimulate insulin secretion in pancreatic beta cells, often improving glycemic control and reducing the daily insulin dose needed by patients. Some studies also report an increase in C-peptide levels with vitamin D administration, although this was not confirmed in an open-label randomized study where patients received calcitriol or nicotinamide for 12 months [2,5]

T1D is more frequently encountered in countries with low sunlight exposure. Limited UV-B radiation leads to vitamin D deficiencies [2]. A meta-analysis found an inverse relationship between 25-hydroxyvitamin D (25(OH)D) levels and the risk of developing type 1 diabetes. Similar conclusions were drawn from a multicenter study, which demonstrated a reduced risk of developing the disease in patients supplementing with vitamin D in any dose. However, another randomized study yielded differing, contradictory results [2,5,8]. Nonetheless, it is evident that vitamin D supplementation has a beneficial impact on disease activity and its intake in early childhood may serve as a protective measure against future disease development [2,8]. Further randomized clinical trials and meta-analyses are needed to determine the specific effects of vitamin D on type 1 diabetes treatment and the appropriate doses for various demographic groups [8,9].

Addison’s disease

Addison's disease (AD) is a rare disease characterized by autoimmune selective destruction of the adrenal cortex, which can be isolated (40% of patients) or associated with autoimmune polyendocrine syndromes (APS) types 1, 2 or 4 (60% of patients) [15]. AD is a rare endocrine disorder with an incidence ranging from 60 to 140 per million [16]. Interestingly, autoimmune Addison's disease (AAD) has a remarkable tendency to combine with other autoimmune diseases, exceeding 60% of AAD cases and causing autoimmune polyendocrine syndromes [17]. Vitamin D deficiency is very common in patients with AAD. Genetic factors may influence vitamin D status in AAD, suggesting individual vitamin D requirements throughout the year [18]. At present the evidence for the association of vitamin D and AD is largely based on a few observational studies. These preliminary results suggest that vitamin D may influence

genetic susceptibility to AD by modifying the immune response. However, further studies are needed to confirm or refute the correlation between vitamin D status and Addison's disease [19, 20, 21].

Autoimmune Polyglandular Syndromes

Autoimmune polyglandular syndrome (APS) is a group of autoimmune diseases characterized by the co-occurrence of the activity of several endocrine glands. It contains many differences of this classification, often but distinct: polyglandular autoimmune syndrome type 1 (APS1) - rarer, already manifesting in children and polyglandular autoimmune syndrome type 2 (APS2) - more common, occurring in adults. Various authors also distinguish: polyglandular autoimmune syndrome type 3 (APS3) - a variant of APS2, diagnosed in the case of coexistence of autoimmune diseases with autoaggressive endocrinopathies other than Addison's disease and polyglandular autoimmune syndrome type 4 (APS4) - a sentence when the constellation of coexisting autoimmune endocrine diseases does not meet the criteria of APS1, APS2 or APS3, e.g. in the case of coexistence of Addison's disease with autoimmune oophoritis. The appearance of each component that can be revealed over time, as well as an additional risk that will be introduced in the event of the occurrence of the disease. This can occur in the case of the need to change the diagnosis: the disease is automatically diagnosed, the diagnosis is changed from APS4 to APS2 and Addison's disease - from APS3 to APS2. Autoaggression usually causes hypofunction of the affected gland, exclusion is hyperfunction of the social (Graves-Basedow's disease). However, only one study has assessed whether the association of APS affects vitamin D status [22]. This study showed that a higher prevalence of low vitamin D status was observed in individuals with APS-3. Furthermore, lower vitamin D concentrations were found in patients with a single autoimmune disease, such as T1DM or with APS including T1DM, compared with control subjects. This finding suggests that the type of autoimmune disease, rather than the association of several autoimmune diseases, as is the case in APS, may negatively affect vitamin D status in affected patients, possibly in relation to impaired absorption or metabolic steps of this vitamin at the level of the skin, liver or kidney. Further prospective studies are needed to clarify whether impaired vitamin D status is a causal factor in the pathogenesis of APS or its consequence.

Fertility

More than 10% of couples experience infertility, which is one of the world's greatest public health challenges. Vitamin D supplementation during pregnancy has been associated with a reduced risk of preterm birth and low birth weight [23]. Vitamin D has immunomodulatory effects, which may contribute to embryo implantation, placental implantation and pregnancy success. In the study population, mean 25(OH)D levels were lower in women who had two or more miscarriages than in those who had one or no miscarriage. Previous results have been inconsistent regarding a possible association between miscarriages and 25(OH)D, but the problem with these observations is that the study groups were small, so the results should be interpreted with caution. Nevertheless, future studies are warranted to assess the association between miscarriages and 25(OH)D [24]. Polycystic ovary syndrome (PCOS) is responsible for anovulatory infertility in about 15% of women of reproductive age. The etiopathogenesis and clinical symptoms of PCOS are significantly influenced by macronutrients and micronutrients, especially vitamin D [25]. It is already well documented that patients with PCOS have lower serum vitamin D levels compared to the general population [25]. These data suggest a possible association between serum vitamin D levels and PCOS. Furthermore, low serum vitamin D levels may increase the risk of cardiovascular disease (CVD) in women with PCOS and negatively affect disease symptoms, including insulin resistance, ovulation disorders, infertility, menstrual irregularities, hyperandrogenism and obesity [26]. There is ample evidence to support the importance of vitamin D for fertility in both women and men. In cases of infertility, treatment with vitamin D alone may not solve the problem, but vitamin D supplementation may have a beneficial effect on fertility. We emphasize the importance of further research on vitamin D supplementation and its effects on sperm quality, fertility, and conception rates.

Conclusions

Vitamin D3 appears to be an important immunomodulatory factor, potentially involved in autoimmune diseases. Its nuclear receptors are widely distributed in the immune system and the vitamin itself has been found to increase the synthesis of anti-inflammatory cytokines (TGF beta-1, Il-4) and reduce the secretion of Il-2 and IFN-gamma, the main mediators of autoimmune tissue damage [27]. The incidence of AID is increasing, which means that many people suffer from diseases that are difficult to treat. As a result, patients are at risk of severe

symptoms and death. In general, the predisposition to AID cannot be simply related to one factor, such as limited sunlight and therefore vitamin D deficiency or being a vegan and therefore at risk of zinc deficiency. In addition, not every person with vitamin D or zinc deficiency will develop AID, as genetics and general lifestyle also play a role. However, deficiencies of nutrients such as zinc and vitamin D are common in patients with AID. Their origins, as well as the symptoms and complications they cause, are diverse, making diagnosis and treatment difficult. Therefore, possible micronutrient deficiencies should be taken into account during the clinical care of patients with AID and, if observed, should be treated with controlled supplementation of the deficient element(s). Therefore, more research focusing on nutrient interactions is clearly warranted to optimize treatment strategies for AID patients and stem the increasing disease burden using simple and cost-effective nutritional approaches.

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Author contributions

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