ANALYSIS OF LITERATURE DATA ON THE RELATIONSHIP BETWEEN VITAMIN D DEFICIENCY AND TYPE 1 DIABETES MELLITUS

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Type 1 diabetes mellitus is a chronic autoimmune disease in which genetic predisposition and environmental factors play a major role. Vitamin D deficiency is becoming a pandemic in the world and is observed in type 1 diabetes mellitus.

The aim*. Analytical review of available literature data on the relationship of vitamin D deficiency with the development and course of type 1 diabetes mellitus.*

Materials and methods*. Analysis of open sources of scientific literature.*

Results and discussion*. Clinical observations and experimental studies show that vitamin D deficiency is one of the risk factors for the development of type 1 diabetes, and is a consequence of this disease. The status of vitamin D in the body is determined not only by the intake of vitamin from the outside, but also by the activity of tissue transport and metabolism systems, which have a high degree of polymorphism. Numerous studies show the positive effect of the use of vitamin D preparations in the prevention and treatment of type 1 diabetes mellitus. However, there are works in which there is no protective effect.*

Conclusions*. Thus, the optimization of the status of vitamin D in the body is a promising measure to prevent the development of type 1 diabetes and facilitate its course, but requires further research.*

Keywords*: vitamin D, type 1 diabetes mellitus, immunomodulatory and anti-inflammatory activity, pancreatic β cells*

1. Introduction

Type 1 diabetes mellitus (DM1) is a chronic endocrine-metabolic disease caused by insulin deficiency due to immune-mediated destruction of β-cells of the pancreas (β-cells), which leads to the need for insulin therapy [1]. It develops most often in childhood or adolescence and is one of the most common chronic diseases in childhood. Diabetes mellitus accounts for 10–15 % of the total number of cases of diabetes [2]. In Ukraine, about 100 thousand patients with this type of diabetes, of which more than 8 thousand – children under 18 years [3].

DM1 is considered a multifactorial disease in which genetic predisposition and environmental factors interact to trigger autoimmune responses to β-cells. More than 40 individual genes determine predisposition to autoimmune DM1 type [4]. Among the external factors that provoke the development of islet autoimmunity, viral infections, chemical factors, reduced diversity of the intestinal microbiota, as well as dietary factors are particularly actively discussed [5]. Autoantigens of islet cells are recognized by autoantibodies and autoreactive effector T-lymphocytes, i.e. both humoral and cellular parts of the immune system are activated [6]. DM1 is also accompanied by dysregulation of the balance of T-helpers of type 1 (Thl) and T-helpers of type 2 (Th2) by the type of relationship of counterregulation. Thl activity predominates, so proinflammatory cytokines, cytotoxic enzymes (perforin and granzyme) and other compounds, including free radicals that they produce, have a dominant effect on the development of the autoimmune process and the destruction of β-cells [7].

Studies in recent decades have shown that one of the risk factors for DM1 is vitamin D deficiency [8, 9]. In addition, impaired metabolism of vitamin D is observed as a consequence of diabetes [10]. Therefore, the optimization of vitamin D status is seen as a preventive measure to prevent development and as a therapeutic mechanism to reduce the severity of the disease.

The aim of the study was to conduct an analytical review of the available literature on the relationship between vitamin D deficiency and the development and course of type 1 diabetes.

3. Materials and methods

Analysis of open sources of scientific literature. The following electronic open access resources were used to search for scientific papers: PubMed, Elsevier, electronic resources of the National Library named after V. I. Vernadsky.

4. Research results

4. 1. Vitamin D deficiency as a risk factor for DM1.

The relationship between DM1 and vitamin D status is quite complex because it is determined not only by the intake of the vitamin from food, the use of food supplements or the formation of ultraviolet radiation in the skin, but also the polymorphism of genes involved in the transport and metabolism of vitamin D, in particular vitamin D receptor (VDR) [11, 12], vitamin D-binding protein (VDBP), 25-hydroxylase (CYP2R1) [13] and 1α-hydroxylase (CYP27B1).

Vitamin D receptors have been found in at least 38 organs and tissues of the human body, including β-cells [14]. The genomic pathway of calcitriol is realized through the intracellular vitamin D receptor (VDR), affecting the expression of about 3 % of genes. Vitamin D exerts rapid non-genomic effects through plasma receptors with the help of calcium ions, MAP-kinase cascade and phosphoinositol system [15].

The main function of vitamin D is to regulate, but is not limited to, calcium and phosphorus metabolism. Vitamin D is involved in the regulation of proliferation and differentiation of all organs and tissues, regulates metabolism, including the synthesis of receptors for many hormones, regulates ATP formation, promotes oxidation and phosphorylation, affects the structural and functional activity of cell membranes, weakens adaptive immunity and promotes congenital, inhibits neoplastic processes, has anti-inflammatory effects, etc. [16].

Today, vitamin D deficiency is a national and global problem. More than one billion children and adults worldwide suffer from vitamin D deficiency [17]. The majority of the population of Ukraine (81.8 %) also has a severe vitamin deficiency (<20 ng/ml). Vitamin D deficiency (20–30 ng/ml) is registered in another 13.6 % of respondents, only 4.6 % of residents have a level of 25 (OH) D in the serum within normal limits [18].

Numerous epidemiological data and research results indicate that vitamin D deficiency accompanies the development of DM1, but it is not always clear whether this is the cause or consequence of pathology [19, 20]. Indirect evidence of the involvement of this vitamin deficiency in DM1 is that the disease is most common in the regions furthest from the equator, i.e. with the least amount of solar radiation [1]. Vitamin D levels have been shown to be lower in children with multiple islet autoantibodies and in children with DM1 than in children without autoantibodies. However, vitamin D deficiency has not been associated with faster DM1 progression in children with multiple islet autoantibodies [21]. Experimental studies show that keeping animals on a D-vitamin diet is accompanied by an increase in glucose levels by more than 2 times and a decrease in insulin content by 30 %. The addition of vitamin D to the diet almost completely restores these indicators [15].

The results of meta-analyzes demonstrate a protective dose-dependent effect of vitamin D intake in infants on the development of DM1. However, no association between low vitamin D levels and DM1 development was found in older children. In addition, there is insufficient evidence of a link between maternal vitamin D intake during pregnancy and the risk of developing DM1 in offspring [22]. However, another study showed that higher levels of maternal vitamin D binding protein during childbirth were associated with a lower risk of DM1 in offspring [23]. The same study reliably demonstrated a reduction in the risk of DM1 in children who had higher levels of 25 (OH) D at birth in combination with the VDR rs11568820 G / G genotype. The most interesting were the results of a study [24] – a significant reduction in the risk of DM1 recorded in infants who received vitamin D from 7 to 12 months of life than in children of the first 6 months of life, which suggests participation in these processes acquired immunity.

The established antidiabetic effect of vitamin D is associated with its anti-inflammatory and immunomodulatory properties [9]. The immunomodulatory effect of calcitriol is the ability to modify the transcription of certain genes. From the point of view of autoimmune diseases, the most important role of vitamin D is its ability to suppress acquired immunity and induce immunological tolerance, as well as cause anti-inflammatory effect, which together prevents the development of autoimmune pathologies, including DM1. Calcitriol accelerates the maturation of monocytes into macrophages, but at the same time reduces their ability to present antigens to T cells, reducing the expression of the surface histocompatibility complex. It also disrupts the maturation of dendritic cells, which leads to the formation of tolerogenic dendritic cells that are unable to represent the antigen [25]. In addition, calcitriol promotes the differentiation of CD4+T cells into Th2 and regulatory T cells, reduces the production of Th1 and Th17 cells, resulting in reduced Th1/Th2 ratio, reduced production of pro-inflammatory cytokines and increased release of anti-inflammatory cytokines [26]. Moreover, calcitriol enhances immune tolerance also by maintaining B-cell homeostasis (prevents B-cell proliferation, plasma cell differentiation, memory B-cell formation, and immunoglobulin production, including autoantibodies) [27]. In general, these actions correspond to a decrease in autoimmunity without compromising immune protection against pathogenic microorganisms [28].

It is also known that vitamin D binds to mature β-cells and developing cells, which is consistent with the participation of calcitriol in the proliferation and differentiation of these cells, and in the regulation of their functional activity [29]. Vitamin D has been shown to directly induce insulin secretion by increasing intracellular calcium levels through nonselective potential-dependent calcium channels. Another mechanism may be the indirect activation of calcium-dependent β-cell endopeptidase, which converts proinsulin to active insulin [30]. Calcitriol has been shown to reduce inflammation, reduce the level of calcium and reactive oxygen species in β-cells, preventing their destruction. Vitamin D also plays a very important role in maintaining the epigenome. Epigenetic changes are a feature of diabetes in which many genes associated with diabetes are inactivated by hypermethylation. Vitamin D prevents such hypermethylation by increasing the expression of DNA demethylases [31]. In addition, vitamin D prevents the development of insulin resistance, as it stimulates the secretion of receptors to the hormone, and affects the functional activity of the membranes of most cells of the body [32].

4. 2. Disorders of vitamin D metabolism in DM1 condition

On the other hand, vitamin D deficiency develops because of DM1 disease. As insulin regulates the activity of 25- and 1α-hydroxylases, its absence reduces the activity of these enzymes [33, 34]. However, there is a report of no insulin therapy for vitamin D levels in the long-term follow-up [35]. The authors suggest that over time there is an adaptation of enzyme activities. It is believed that insulin affects the activity of hydroxylase enzymes indirectly, through the regulation of intracellular calcium levels due to stimulation of Ca^{2+}, Mg^{2+}-ATPase activity, as well as by changing the sensitivity of these enzymes to phosphorus [36]. In addition, it has been found that the reasons for the decrease in vitamin D levels in diabetes mellitus are reduced absorption of the vitamin in the small intestinal mucosa, decreased absorption by the liver, and impaired transport to hepatocytes from reticulocytes due to destructive changes in this organ by DM1. Another reason for the decrease in vitamin D levels by DM1 may be its loss in combination with binding protein in the presence of albuminuria, which is confirmed by a number of studies [37, 38].

4. 3. The use of vitamin D drugs in the treatment of DM1

The use of vitamin D not only reduces the risk of DM1, as mentioned above, but also has a positive clinical effect on the preservation of residual β-cell function, as evidenced by increased regulatory T cells, C-peptide levels and reduced insulin requirements in patients [39]. Moreover, increasing the level of vitamin D improves glycemia in adult patients with DM1 (increased glucose tolerance, decreased concentration of glycosylated hemoglobin, etc.) [40]. Including the continuous monitoring of glucose levels, the use of vitamin D supplements improved glycemic variability, reduced insulin requirements and reduced the incidence of hypoglycemia in patients with DM1 [41]. In one intervention study, vitamin D administration significantly improved endothelial function and significantly reduced the amount of inflammatory cytokines in the urine [42]. However, in adolescents, 6-month replenishment of vitamin D did not affect glycemia and the level of markers of inflammation [43]. In another study, the administration of vitamin D to children and adolescents caused a decrease in fasting glucose and glycosylated hemoglobin [44]. In [45] it was shown that in patients with adequately controlled DM1 in the absence of albuminuria and the corresponding progressive loss of vitamin D metabolites, the total level of 25 (OH) D and the therapeutic response to cholecalciferol were the same as in healthy people, however, diabetics have a disturbed relationship between free and bound forms of vitamin D. The authors believe that the lack of increased levels of VDBP in patients with diabetes may indicate a violation of the regulation of the mechanism of prevention of vitamin D toxicity, so high doses should be used with caution. The authors of the study [46] also did not establish significant effects of additional vitamin D on the course of DM1.

Contradictory results of vitamin D preparations are probably related to different doses (from 2 to 10 thousand IU) and the term of vitamin administration (from 3 to 12 months), different forms and individual response to calciferol due to polymorphism of genes of this vitamin metabolism [47].

5. Conclusions

Thus, clinical observations and experimental studies indicate that:

1. Vitamin D deficiency can be a predictor of DM1 development.

2. Vitamin D deficiency accompanies already manifested diabetes.

3. The use of vitamin D drugs can be effective for both prevention and correction of diabetes.

However, the literature data are contradictory in certain respects, so they obviously need further research. The question of the optimal state of vitamin D and the most important marker for its evaluation remains unresolved. Additional studies are also needed to determine the appropriate dose and form of vitamin D, taking into account the individual needs of patients with DM and the polymorphism of genes involved in vitamin metabolism.

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