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Potential role of vitamin D in the prevention and treatment of type 1 diabetes mellitus

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The incidence of type 1 diabetes mellitus is increasing worldwide, and the number of people with vitamin D deficiency in all age groups, including children and adolescents, is simultaneously growing in the world. Over the past decades, it has been found that vitamin D, in addition to participating in the regulation of calcium homeostasis and bone metabolism, has an anti-inflammatory and immunomodulatory effect. Epidemiological evidence suggests the involvement of vitamin D deficiency in the pathogenesis of type 1 diabetes mellitus. Polymorphisms in genes important for vitamin D metabolism also modulate the risk of type 1 diabetes mellitus. Several studies have evaluated the role of vitamin D as adjuvant immunomodulating therapy in patients with newly diagnosed type 1 diabetes mellitus. The purpose of this review is to present current data on the involvement of vitamin D in the pathogenesis of type 1 diabetes mellitus and to evaluate its role as a drug for the prevention of the disease and its use in treatment in addition to insulin therapy.

Keywords: type 1 diabetes mellitus; vitamin D; cholecalciferol.

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Потенциальная роль витамина D в профилактике и лечении сахарного диабета первого типа

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Заболеваемость сахарным диабетом 1-го типа в мире увеличивается, также растет количество людей с недостатком витамина D во всех возрастных группах, включая детей и подростков. В последние десятилетия выявлено, что витамин D кроме регуляции гомеостаза кальция и метаболизма костей оказывает противовоспалительное и иммуномодулирующее действие. Эпидемиологические данные свидетельствуют о вовлечении дефицита витамина D в патогенез сахарного диабета 1-го типа. Полиморфизмы в генах, важных для метаболизма витамина D, также модулируют риск возникновения сахарного диабета 1-го типа. В ряде исследований была оценена роль витамина D в качестве адъювантной иммуномодулирующей терапии у пациентов с недавно выявленным сахарным диабетом 1-го типа. Цель данного обзора — представить современные данные об участии витамина D в патогенезе сахарного диабета 1-го типа и оценить его роль в качестве препарата для профилактики заболевания и дополнительного применения при инсулинотерапии.

Ключевые слова: сахарный диабет 1-го типа; витамин D; холекальциферол.

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In recent decades, the incidence of type 1 diabetes mellitus (T1DM) has been increasing by 3% annually, with a significant rise noted among young children [1–4]. Currently, there are 542,000 children and adolescents under the age of 14 years with T1DM worldwide, and most of them live in the United States, India, Brazil, and China [5]. The highest prevalence of T1DM is registered in Finland (more than 60 cases of newly diagnosed DM per 100,000 population per year) and Sardinia (more than 40 cases per 200,000 per year) [3, 6]. It should be noted that the number of people with vitamin D deficiency in all age groups, including children and adolescents, is growing in the world at the same time, which suggests the involvement of vitamin D deficiency in T1DM pathophysiology [7, 8]. The incidence of vitamin D deficiency in the population varies from 20% to 90% [9–11]. Deficiency and lack of vitamin D are widespread regardless of a country's geographic location, as vitamin D deficiency was revealed in 81.1% and 84.1%–86.9% of women of reproductive age in Brazil [10] and the North-West region of the Russian Federation, respectively [11].

There are no data on optimal serum vitamin D levels. According to the Russian Association of Endocrinologists, the sufficient vitamin D level in the blood serum is 30–60 ng/mL (75–150 nmol/L). A vitamin D level of 20–30 ng/mL (50–75 nmol/L) indicates insufficiency, less than 20 ng/mL (50 nmol/L) indicates deficit, and above 60 ng/mL (150 nmol/L) indicates a high serum concentration [12].

Vitamin D synthesis and metabolism

Vitamin D includes a group of secosteroids that are similar in chemical structure, namely, vitamin D_1 is a compound of ergocalciferol and lumisterol, vitamin D_2 is ergocalciferol, vitamin D_3 is cholecalciferol, vitamin D_4 is dihydrotachysterol, vitamin D_5 is sitocalciferol, and vitamin D_6 is sigma-calciferol [13]. In humans, vitamin D is mainly produced in the skin under the influence of ultraviolet (UV) radiation (80%), and a small amount (20%) enters the body with food [14]. Exposure to sunlight promotes the formation of vitamin D only in the form of vitamin D_3, which is produced in the skin from 7-dehydrocholesterol. Then, vitamin D_3 is transported to the liver using the vitamin D-binding protein (VDBR), where it undergoes 25-hydroxylation with the involvement of the CYP2R1 enzyme and is metabolized to 25-hydroxycalciferol 25(OH)D-calcidiol [15]. Then, 25(OH)D is transported to the kidneys, and as a result of 1α-hydroxylation (CYP27B1 enzyme), it is transformed into 1,25-dihydrooxycholecalciferol [$1,25(OH)_2D_3$], known as calcitriol, which is the most biologically active metabolite of vitamin D. To assess the vitamin D status in clinical practice, it is recommended to determine serum 25(OH)D instead of $1.25(OH)_2D$ because the latter has a short half-life of 6–8 h, which leads to significant daily fluctuations in serum concentration. The half-life of 25(OH)D is 3 weeks. In addition, in various diseases, as well as during pregnancy, the $1.25(OH)_2D$ level can be increased, despite an actual vitamin D deficiency [16]. A recent clinical report [17] showed that serum-free and serum bioavailable 25(OH)D, but not total 25(OH)D, are the most reliable markers for assessing vitamin D status.

Calcitriol initiates a signaling cascade by binding to the nuclear vitamin D receptor (VDR), which forms a heterodimer with the retinoic acid X receptor (RXR) and then binds to specific DNA sequences (vitamin D response elements), regulating the transcription of several genes [15]. VDR is encoded by a large gene located on chromosome 12q12q–q14 and includes two promoter regions, eight protein-coding exons, and six untranslated exons (1a–1f) [18]. VDR is found in almost all human cells (including immune cells) [19]. Vitamin D, in addition to calcium hemostasis and bone metabolism, is involved in cell growth modulation, as well as antiproliferative, anti-inflammatory, and immunomodulatory processes [20, 21].

Immunomodulatory effects of vitamin D

Vitamin D affects both the innate and adaptive immune systems through the VDR. Functional VDR has been identified in almost all immune cells, including antigen-presenting cells and T-lymphocytes, which is indirect evidence of vitamin D's effect on the immune system [22, 23]. Immune cells, especially antigen-presenting cells (activated macrophages and dendritic cells), express the enzyme 1α-hydroxylase and, thus, can synthesize and secrete calcitriol under the action of interferon-gamma (IFN-γ) [24, 25]. The immunomodulatory effects of vitamin D depend on the ability of its biologically active form, calcitriol, to regulate the expression of genes involved in cell proliferation, differentiation, and functioning [19, 26, 27].

Calcitriol suppresses adaptive immune responses, contributing to the induction of immunological tolerance, and has an anti-inflammatory effect through the following mechanisms:

- It inhibits the differentiation, maturation, and function of dendritic cells, preventing their action as mature antigen-presenting cells [28, 29].
- It stimulates the generation of defensins and promotes the differentiation and activation of macrophages, increasing their antimicrobial activity and enhancing chemotaxis and phagocytosis [30].
- It stimulates T cells by reducing the surface expression of major histocompatibility complex (MHC) class II molecules (molecules of the main class of histocompatibility) and promotes a shift in the polarization of macrophages from the proinflammatory phenotype (M1 or "classi-

cally activated" macrophages) toward anti-inflammatory (M2 or "associated macrophages").
- It inhibits the expression of proinflammatory cytokines by monocytes and macrophages [31–34].
- It has a direct inhibitory effect on the differentiation of B cells and production of immunoglobulins [35, 36].
- It normalizes the production of regulatory T cells and polarization of Th-cells, increases the number of Th_2 cells, and inhibits the production of Th_1 and Th_{17} cells, thereby stimulating the shift of T cells from the "effector" to the "regulatory" phenotype [37, 38].
- It prevents the hyperactivation of $CD8^+$ T cells and reduces the secretion of IFN-γ and tumor necrosis factor (TNF-α) [39].
- It regulates the production of cytokines by immune cells, increasing the production of anti-inflammatory cytokines (interleukin [IL]-4 and IL-10) and decreasing the synthesis of proinflammatory cytokines (IL-1β, IL-2, IL6, IL-17, IL-22, TNF-α, and IFN-γ) [40, 41].

The immunomodulatory effects of calcitriol, namely, the stimulation of induction of immune tolerance and T-cell anergy, impairment of B-cell activity and antibody production, and reduction of inflammatory responses, suggest the therapeutic potential of vitamin D in autoimmune diseases, including T1DM. Vitamin D probably plays an important role in reducing the risk of autoimmune diseases and improving their course.

Vitamin D deficiency in young NOD mice has been revealed to lead to higher morbidity and early T1DM development [42]. Calcitriol and its analogs prevent the development of DM in NOD mice, especially when administered at an early age, before an immune-mediated attack on beta cells [43, 44]. The disease progression can be stopped through administrating calcitriol at an older age and in a later phase of the disease [45]. Mathieu et al. showed that long-term treatment with high calcitriol doses (5 μg/kg), which was administered daily or every other day, led to a decrease in the incidence of DM in NOD mice without causing serious side effects [44]. Gregori et al. [45] revealed that short-term administration of a calcitriol analog to NOD mice suppresses the production of IL-12 and IFN-γ, terminates the infiltration of pancreatic islets by Th_1 cells, and increases the number of regulatory $CD4^+$ and $CD25^+$ T cells in the lymph nodes of the pancreas, thereby inhibiting DM development. NOD mice treated with calcitriol showed a significant change in the cytokine secretion profile from Th_1 (IFN-γ) to Th_2 (IL-4) [37]. In addition, dendritic cells exposed to calcitriol or its analog TX527 change the response pattern of GAD65, which are specific clones of T cells, inhibiting proliferation and promoting apoptosis [46]. Takiishi et al. [47] demonstrated that in NOD mice fed a diet enriched with vitamin D_3 (800 IU/day) throughout their life (3–35 weeks), the incidence of DM was significantly lower, and the insulin content in the pancreas was higher than in animals of the control group.

Inflammation plays an important role in the pathogenesis of T1DM, contributing to beta-cell dysfunction and apoptosis through cytokines and chemokines produced by both beta cells and immune cells [48]. Calcitriol increases the level of the antiapoptotic protein A20 and reduces IL-6 production, nitrogen synthesis, and MHC class I molecule expression in isolated human pancreatic islets exposed to anti-inflammatory cytokines such as IL-1β, TNF-α, and IFN-γ [48]. Wei et al. [49] revealed that the association of VDR with the chromatin remodeling complex (PBAF) enhances the VDR-dependent transcriptional program and leads to a decrease in the cytokine-induced proinflammatory response in beta cells and preservation of their function in both humans and NOD mice.

Role of vitamin D deficiency in the pathogenesis of type 1 diabetes mellitus

A large array of works indicated the role of vitamin D in beta-cell function and insulin secretion. Norman et al. [50] demonstrated for the first time that vitamin D deficiency suppresses insulin secretion in a rat's pancreas. It was established that beta cells of the human pancreas are capable of expressing both 1α-hydroxylase and VDR [51, 52]. VDRs have been identified in the human insulin gene promoter [53]. According to Bourlon et al. [54], calcitriol promotes *de novo* insulin biosynthesis and accelerates the transformation of proinsulin into insulin in rat pancreatic islets. The administration of vitamin D to mice and rabbits in deficiency cases leads to the elimination of disorders in insulin secretion [50–56]. This suggests that vitamin D and its analogs can protect beta cells from immune-mediated attack, facilitating the transition of Th_1 cells to Th_2 cells, reducing the infiltration of pancreatic islets by Th_1 cells, and minimizing cytokine-induced damage to beta cells.

Various gene polymorphisms involved in vitamin D metabolism, especially those encoding vitamin D hydroxylases, *VDBR* and *VDR*, may influence the risk of T1DM. In 2007, Ramos-Lopez et al. [57] identified an association of single nucleotide polymorphisms (SNPs) in the *CYP2R1* gene encoding vitamin D 25-hydroxylase in patients with T1DM and serum 25(OH)D levels; therefore, they suggested that the G allele of SNP rs10741657 predisposes the development of T1DM, whereas the A allele of the same SNP protects against disease development. Another study revealed a significant relationship between SNP rs10741657 and rs12794714 in the *CYP2R1* gene and the risk of T1DM [58]. In a large case-control study conducted in the UK, involving 7854 patients with T1DM and 8758 healthy people, an association was established between two SNPs (rs10877012 and rs4646536) in the *CYPB1* gene encoding vitamin D 1α-hydroxylase with T1DM [59]. The authors also reported that the GG genotype

CYP2R1 (SNP rs10741657) or the CC genotype *CYP27B1* (SNP rs10877012) increases the risk of T1DM [60]. People with both genotypes had a significantly higher risk of T1DM than those with only one genotype, indicating a potential synergy between the GG genotype *CYP2R1* and the CC genotype *CYP27B1* in determining the risk of T1DM development. In addition, the serum 25(OH)D level was significantly lower in people with the GG genotype *CYP2R1* and the CC genotype *CYP27B1* than in those with the AA *CYP2R1* and AA *CYP27B1* genotypes, respectively. However, Danish researchers did not find an association between SNP *CYP2R1* and *CYP27B1* (rs10741657 and rs4646536, respectively) and the risk of T1DM in children [61].

The potential role of *VDR* gene polymorphisms in the pathogenesis of T1DM has been suggested. A major study TEDDY by Norris et al. [62] examined 424,788 newborns (in six US states and five European countries) between 2004 and 2010. The results of the primary screening revealed that 8676 children had an increased risk of developing T1DM (the presence of GADA, IAA, and IA-2A antibodies in children) with and without first-line relatives with T1DM. The study was conducted in children aged 4 months and lasted for 6 years. The polymorphism in genes *VDR*, *CYP24A*, *CYP27B1*, *GC*, and *RXR* was analyzed. Vitamin D 25(OH) deficiency was found in 42% of children in the TEDDY study and 22%–67% of children with developed T1DM. The highest plasma concentrations of vitamin D 25(OH) and a low risk of T1DM were recorded in children with the minor allele of the vitamin D receptor, *VDR rs7975232*. Norris et al. showed that higher 25(OH)D levels contribute to a decrease in possible autoimmune damage to the islet apparatus of the pancreas in children with a genetic predisposition to T1DM. A recent study revealed that higher 25(OH)D levels in umbilical cord blood were a favorable predictor of a reduced risk of developing T1DM in children homozygous for the *VDR* rs11568820 G/G genotype [63]. Habibian et al. [64] demonstrated an association between an increased risk of T1DM and some polymorphisms in the *VDR* gene (especially Bsm-I and Fok-I), although the alleles most predisposing to T1DM development are still not definitively identified. A sufficient 25(OH)D level in serum (≥30 ng/mL) and some SNP genotypes (TaqI and BsmI) in the *VDR* gene were interrelated with an increased C-peptide level in patients with newly diagnosed T1DM, which probably contributes to the preservation of function of pancreatic residual beta cells [64]. Research results indicate that SNPs in genes that are important for vitamin D synthesis, transport, and action may influence the risk of T1DM.

Vitamin D levels in patients with T1DM

In recent decades, there has been an increase in the prevalence and incidence of vitamin D deficiency and T1DM [3, 7, 65–67]. The DIAMOND research team found a higher incidence of T1DM (data collected from 1990 to 1994) in countries located at higher latitudes (with low UV radiation). The number of newly diagnosed T1DM cases per 100,000 population per year is 36.5 in Finland, 27.5 in Sweden, and 21.2 in Norway [68]. Some studies have demonstrated a seasonal pattern of T1DM onset, namely, increased incidence in winter, early spring, and late autumn with a pause in summer [69–71]. Mohr et al. [71] revealed that low intensity of UV radiation contributed to the higher incidence of T1DM in childhood. In addition, the authors reported a gradual increase in the incidence of T1DM in Finland (from 18 per 100,000 population in 1965 to 64 per 100,000 in 2005), which, in their opinion, was associated with the introduction of official state recommendations on gradually reducing the daily intake of vitamin D into medical practice [71]. In patients with newly diagnosed T1DM, the 25(OH)D levels were significantly lower than in healthy people [72–75]. According to a study conducted in Sweden, which involved 459 patients with T1DM aged 15–34 years, the 25(OH)D levels in their blood was significantly lower than in patients of the control group [92]. Similar results were obtained by researchers in India, Italy, Qatar, and Kuwait [73–76]. In Switzerland, 129 children and adolescents with T1DM were vitamin D deficient in 60.5% of cases, and vitamin D deficiency was registered in 26.4% of cases [77].

Effect of vitamin D on the course of T1DM: epidemiological evidence

The problem of vitamin D deficiency in T1DM patients is well known, but it is not entirely clear whether an insufficient concentration of vitamin D is a trigger of T1DM or a consequence of the disease. According to the literature, the effect of vitamin D on the risk of developing T1DM depends probably on the patient's age [78]. A cohort study in Norway, which included 29,072 female patients, showed that 25(OH)D levels during pregnancy were significantly lower in women whose children developed T1DM during the first 15 years of life [79]. In addition, in pregnant women with a 25(OH)D level of 21.6 ng/mL or lower in trimester I, the risk of developing T1DM in children was twice as high. Jacobsen et al. [80] noted a significant risk of developing T1DM (1.5–2 times higher) in children under 14 years of age whose mothers did not consume vitamin D-fortified margarine during pregnancy than in those whose mothers used it. However, Miettinen et al. [81] did not reveal significant differences in 25(OH)D levels during pregnancy in mothers whose children subsequently (by the age of 7 years) developed T1DM than in women in the control group. Dong et al. [82] did not report a significant association between the intake of vitamin D by women during pregnancy and the risk of T1DM in their children. Silvis et al. [83] found that vitamin D intake during pregnancy does not affect the risk of developing T1DM in

children with an increased genetic predisposition to the disease.

At the same time, according to various studies, the intake of vitamin D in early childhood has a more pronounced effect on reducing the risk of developing T1DM than intrauterine exposure to this vitamin. A study in Finland showed that vitamin D supplementation during the first year of life in infants reduced the incidence of T1DM. Moreover, vitamin D intake at a dose of 2000 IU per day reduced the risk of T1DM more significantly (4–5 times) than at a dose of less than 2000 IU per day [84]. According to the multicenter study EURODIAB 2, vitamin D intake from early childhood (data collected using standardized questionnaires and surveys) contributed to a decrease in the risk of developing T1DM in later life [85]. Stene et al. [86] showed the importance of timing of vitamin D intake in childhood. Children who received cod liver oil supplements at the age of 7 years to 12 months had a lower risk of T1DM than those who received these food additives before the age of 6 months. This is probably because the adaptive immune system does not fully mature during the first months of life, and the beneficial immunomodulatory effect of vitamin D is absent. Thus, in young children, vitamin D protects against T1DM. The effect of vitamin D and its supplementation during pregnancy on the risk of developing T1DM is currently being discussed and requires clarification.

At a young age, vitamin D has a clear effect on T1DM development. Gorham et al. [87], among US military personnel, demonstrated that in T1DM patients, the 25(OH)D level was significantly lower 1 year before the disease was diagnosed. In another study, individuals with a normal 25(OH)D level (≥100 nmol/L) were less likely to develop T1DM than those with a 25(OH)D level lower than 75 nmol/L [88]. There was also a trend toward a higher T1DM risk in those with the lowest 25(OH)D levels.

Vitamin D deficiency is associated with various vascular DM complications. In Canada, 14 studies were analyzed, including 10,007 T1DM patients with diabetic retinopathy. A statistically significant relationship was established between the severity of vitamin D deficiency and diabetic retinopathy [89]. The prospective study EURODIAB, which included 532 patients with T1DM at the age of 40 ± 10 years, showed that the higher the 25(OH)D level is, the lower is the incidence of macroalbuminuria. There was no relationship between vitamin D levels and other vascular complications such as microalbuminuria and nonproliferative and proliferative retinopathy [90]. A Japanese study of 75 patients with T1DM and diabetic retinopathy revealed no relationship between vitamin D levels and T1DM complications [91].

Vitamin D as an adjuvant therapy for T1DM

According to numerous studies, vitamin D in T1DM patients has a positive effect on the maintenance of residual pancreatic beta-cell function and glycemic control [92, 93]. The patients under follow-up showed a higher stimulated C-peptide level on an empty stomach and/or a lower daily insulin dose. Mishra et al. [94] revealed a tendency for a slower decrease in the residual function of pancreatic beta cells in T1DM patients who received vitamin D in addition to insulin therapy. In addition, the intake of calcidiol contributed to significant suppression of autoaggression and had a protective effect on the function of beta cells [95]. Gabbay et al. [96] demonstrated that daily supplementation of cholecalciferol to insulin at a dose of 2000 IU for 12 months contributed to a significant increase in the number of regulatory T cells in patients with recently diagnosed T1DM (disease duration less than 6 months). Glycated hemoglobin (HbA1c) level after 6 months, as well as anti-GAD65 antibody titers after 18 months, decreased significantly in the group of patients who took calciferol than in those who received placebo. Two retrospective studies conducted among T1DM patients showed that 3-month adjuvant therapy with cholecalciferol at various doses (400–6000 IU/day) resulted in an improvement in glycemic parameters and a decrease in HbA1c levels after treatment [93, 95]. In a prospective study, Panjiyar et al. [97] revealed that cholecalciferol supplementation at a dose of 3000 IU per day as adjuvant therapy for 12 months improved glycemic parameters and slowed down the residual function of beta cells in T1DM pediatric patients. At the end of the study, the children had lower mean fasting glucose values, as well as decreased HbA1c and total daily insulin levels, and higher mean stimulated C-peptide levels than the control patients receiving insulin therapy alone. It is noteworthy that the mean serum 25(OH)D levels in T1DM patients remained in a sufficient range (>30 ng/mL) at all subsequent visits.

However, other studies have not found significant changes in the course of T1DM with the addition of vitamin D to insulin therapy. So, Shih et al. [98] reported that the use of cholecalciferol at a dose of 20,000 IU per week for 6 months did not affect the HbA1c level and daily insulin demand. In 2017, Perchard et al. [99] demonstrated that a single oral dose of 100,000 or 160,000 IU of cholecalciferol did not lead to any significant differences in HbA1c levels in children with vitamin D deficiency and T1DM. The authors hypothesized that a single high dose of oral cholecalciferol could not maintain residual serum 25(OH)D levels over an extended follow-up period.

In other studies, it was revealed that in T1DM patients, when using cholecalciferol in combination with omega-3 polyunsaturated fatty acids, protective effects were noted on the pancreatic beta-cell function. The study by Niinisto et al. [100], which focused on the prognosis and prevention of DM in Finland, included 7782 children with a human leukocyte antigen predisposition to T1DM. The authors showed that an increase in the ratio in blood serum of arachidonic acid and docosahexaenoic acid at 3 months old and a higher

omega-6/omega-3 ratio at 6 months old are significantly associated with an increased risk of developing T1DM. In the experimental work, Bi et al. [101] demonstrated that supplementing the diet of NOD mice with omega-3 reduces the incidence of severe DM and the level of proinflammatory cytokines. According to a retrospective study, the intake of cod liver oil (high amounts of vitamin D and omega-3) during pregnancy and the first year of life reduces the risk of T1DM later in life, which suggests a synergistic effect of vitamin D and omega-3 polyunsaturated fatty acids [86, 102].

In the studies of the last decade, it has been established that the effect of vitamin D is associated not only with the regulation of calcium and phosphorus homeostasis but also with its anti-inflammatory and immunomodulatory effects.

There is growing evidence that vitamin D deficiency may be significant in T1DM pathogenesis. Adequate vitamin D intake, especially during early childhood, can reduce the risk of DM later in life. Thus, timely detection and elimination of vitamin D deficiency during the first years of life in children with a high genetic risk of T1DM may prevent the development of this disease in the future. Since 2019, the UK Scientific Advisory Committee has recommended dietary vitamin D intake of 400 IU per day for populations of 4 years of age and older given the global prevalence of vitamin D deficiency [103]. The American Society of Clinical Endocrinology recommends a minimum vitamin D intake of 400 IU per day for children (under 1 year old) and 600 IU per day for children, adolescents, and adults [104].

Thus, the potential ability of vitamin D to restore immunotolerance, counteract autoimmune responses, slow down or halt disease progression, maintain residual beta-cell mass and function, and improve glycemic control is the basis for research to investigate the drug as adjuvant therapy for T1DM. The individual response of the body to vitamin D intake depends on factors such as baseline vitamin D status, body fat percentage, gender, ethnicity, genetic factors, and medication intake [105, 106]. The beneficial immunological effect of vitamin D in autoimmune diseases can only be noted when serum 25(OH)D levels are higher than those required for normal bone health (≥30 ng/mL).

Gene polymorphisms in vitamin D hydroxylases, VDBP, and VDR require further studies to assess their effect on vitamin D. This enables us to identify the patient populations who may require higher vitamin D doses to achieve the desired target serum 25(OH)D levels for the prevention and treatment of T1DM.

ADDITIONAL INFORMATION

Author contributions. *E.V. Misharina*, *M.I. Yarmolinskaya*, and *E.I. Abashova* created the concept and design of the review and wrote the text of the manuscript. *E.V. Misharina* and *E.I. Abashova* collected and processed the material.

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