Review article

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THE ROLE OF VITAMIN D IN TREATING PATIENTS WITH TYPE 2 DIABETES MELLITUS

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Vitamin D is a steroid hormone the primary role of which is to maintain adequate blood levels of calcium and phosphorus needed for the normal bone mineralization process. Receptors for vitamin D active form and enzymes involved in its activation have been found in many other body tissues, leading to a conclusion that vitamin D deficiency is connected with the development of many chronic diseases such as hypertension, multiple sclerosis, certain malignant tumors and type 2 diabetes mellitus (T2 DM). Numerous observational studies have shown that patients with T2 DM have lower blood levels of vitamin D compared to healthy subjects. This indicates that vitamin D could play an important role in the pathogenesis of this chronic non-communicable disease. By monitoring parameters related to glycemic status, insulin secretion and insulin resistance, many researchers tried to answer the question whether vitamin D supplementation could help patients with diabetes better control their disease and prevent the complications. The results were contradictory and failed to provide enough solid evidence for recommending vitamin D supplementation as a therapeutic measure for these patients. However, patients who might benefit from supplementation are those with the increased T2 DM risk or those at the beginning of the disease. In order to assess which group of patients could benefit from such a supplementation, it is necessary to provide well-designed, long-term experimental studies with precisely defined groups of patients (e.g. prediabetes, early T2 DM, etc.), supplemented with sufficiently high vitamin D doses in relevant monitoring periods.

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Introduction

Vitamin D is a steroid hormone the primary role of which in bone metabolism is widely acknowledged. Owing to this hormone, optimal concentration of calcium and phosphate necessary for bone mineralization process is maintained in blood. In addition to its "classical" role, more attention is being paid to its possible "non-classical" effects in prevention and treatment of numerous chronic non-communicable diseases (1, 2). The reason is in the fact that the receptors for active D vitamin metabolite (1,25-dihydroxy vitamin D), as well as the enzyme involved in its activation, are found not only in tissues related to bone metabolism, but also in 38 other tissues (brain, prostate, breasts, etc.) in which the hormone regulates the processes of cell proliferation, differentiation, apoptosis and angiogenesis (3, 4). Vitamin D deficiency is therefore connected with the increased risk of hypertension, multiple sclerosis, significant number of malignant tumors, type 2 diabetes mellitus (T2 DM) (4-6). Essential role of vitamin D in the emergence of T2 DM is proven by results of numerous prospective studies which have shown that low vitamin D blood level is linked to the increased risk of this disease and a disturbed glucose metabolism. However, the nature of this link is still not completely clear (6-9). If vitamin D was one of the causal factors, instead of being a consequence of specific pathophysiologic processes responsible for the disease, we would have a natural, cheap and easily available means, which could be compensated for taking an important step towards prevention and treatment of this chronic non-communicable diseases and its complications (10).

The goal of this paper is to summarize the existing knowledge on the possible role and effects of vitamin D supplementation in treating patients with T2 DM.

Vitamin D

Vitamin D implies two forms: vitamin D2 (ergosterol) and vitamin D3 (cholecalciferol) (11, 12). Vitamin D2 is converted from sterols by ultraviolet (UV) radiation in mushrooms exposed to sunlight and enters the body solely through food. Although it can be found in food, the greatest source of vitamin D for people is its endogenous production during skin exposure to sunlight. Namely, the cells of epidermis and dermis contain 7-dehydrocholesterol, a cholesterol derivative which absorbs UVB rays during sun exposure (at wavelengths between 290-320 nm) and transforms into provitamin D3, which then isomerizes into a thermally more stable form of vitamin D3 (cholecalciferol) (13, 14). Upon synthesis in the skin, or absorption from the digestive system if taken through food, vitamin D (D2, D3 or both) is biologically inactive. Two enzyme-mediated reactions of hydroxylation have to take place to activate inactive cholecalciferol. The first hydroxylation occurs in the liver catalyzed by the enzyme 25-hydroxyvitamin D hydroxylase and produces 25-hydroxyvitamin D3 (calcidiol). The second reaction of hydroxylation takes place in the kidneys, catalyzed by enzyme 25-hydroxyvitamin D-1α-hydroxylase, producing the active form of vitamin D, i.e. 1,25-dihydroxyvitamin D3 (calcitriol). This active form goes to target tissues where it binds to vitamin D-specific receptor. In the intestinal tissue it is responsible for the increased intestinal absorption of calcium and phosphorus and increased reabsorption of calcium in the kidneys respectively. As soon as blood calcium level becomes low, parathyroid glands secrete parathyroid hormone (PTH) which stimulates the production of vitamin D's active form in the kidneys, which further increases the calcium level presumably via increased intestinal resorbtion. If this is insufficient, vitamin D stimulates the osteoclasts function and consequent bone resorption process in coordination with PTH (15-17). Lowered calcium intake may lead to bone damaging, but this is rarely the case. A considerably more frequent reason for inadequate bone metabolism is the vitamin D deficiency. The metabolite generated after the first hydroxylation in the liver, 25-hydroxyvitamin D3 (25(OH)D3), is used for estimating blood vitamin D concentration, since its half-life in circulation is longer (around 2-3 weeks) in comparison to the active metabolite 1,25(OH)2 D3 generated in the kidneys, with the half-life of around 4 hours. Additionally, circulating concentrations of vitamin D's active form are 1000 times lower than 25(OH)D3 and are mostly normal or moderately elevated, even in vitamin D deficiency due to secondary hyperparathyroidism (3, 4).

Recommendations regarding the optimal blood level of vitamin D metabolite are still not completely harmonized. This is due to a great number of factors influencing the vitamin D production in skin and its food intake, as well as due to a great number of clinical tests for determining 25(OH)D3 levels, whose values are very variable. Moreover, optimal levels for maintaining an adequate bone metabolism and health in general could be different (18, 19).

According to the guidelines for treatment and prevention of vitamin D deficiency published by The Endocrine Society, the optimal level of circulating vitamin D should be above 30 ng/ml (75 nmol/L), because PTH values in blood are minimal above that level (4, 5). Level of 20-30 ng/ml (50-75 nmol/L) implies vitamin D insufficiency, since PTH levels are elevated; however, vitamin D level is sufficient for an increased intestinal absorption of calcium and phosphorus. Vitamin D deficiency occurs when its blood level is below 20 ng/ml (50 nmol/L) and this condition is connected with malabsorption of Ca and phosphorus, as well as with a disturbed mineralization, i.e. bone resorption, in order to provide sufficient quantity of Ca and P in blood. This leads to rickets in children and osteomalacia in adults (3, 4). Therefore, many experts suggest that normal bone metabolism requires maintaining the blood level of 25(OH)D3 above 20 ng/ml (50 nmol/L), whereas its optimal value should be above 75 nmol/L so that it could contribute to general health improvement. On the other hand, lower values may lead to immunity impairment, myopathy, DM and increased risk of some types of carcinoma (20).

These recommendations are not fulfilled with most people. It is estimated that around 1 billion of world population has vitamin D insufficiency or deficiency (21). The primary reasons are seldom and inadequate sun exposure, as well as a diet lacking in vitamin D (5, 13, 22). Its quantity in the body is influenced by other factors as well, e.g. birth year, race, season, latitude, use of sun protection creams and use of some medications (anticonvulsants, corticosteroids etc.) (4, 13, 22, 23).

Vitamin D and type 2 diabetes mellitus

Numerous observation studies have shown that decreased levels of 25(OH)D3 in blood may have a role in pathogenesis of this disease (24-27).

Meta-analysis, which included 21 prospective studies with 4996 patients suffering from T2 DM and 76 220 subjects without this diagnosis, has shown inverse correlation between vitamin D blood level and the risk of developing T2 DM (RR 0,62 [95% CI 0.54–0.70]) (7). However, the mechanisms and the causes of this relationship are still incompletely clarified. It is not yet established whether these low levels are the cause of diabetes, or they are only a reflection of impaired health (28-30). The three processes which play an important role in T2 DM pathogenesis and could be influenced by vitamin D are the following: insulin secretion (IS), insulin resistance (IR) and inflammation (31).

Vitamin D and insulin secretion

Pancreatic beta-cells responsible for insulin secretion, contain not only receptors for vitamin D active form, but also the 25-hydroxyvitamin D-1α-hydroxylase enzyme, which is responsible for its activation. In addition to the direct influence, vitamin D could also have an indirect influence on IS by increasing the concentration of intracellular calcium in beta-cells, bearing in mind that insulin secretion is a process dependant on calcium. This means that sufficient quantity of vitamin D in blood would facilitate an adequate response of beta-cells to glucose stimu-

lation, whereas its deficiency would decrease IS. Vitamin D has no impact on other pancreatic hormones, or on basal insulinemia (32, 33).

Vitamin D and insulin resistance

Modified cell response to insulin action is an important factor which contributes to T2 DM pathogenesis and which can also be under the direct or indirect influence of vitamin D. Directly, vitamin D influences the expression of insulin receptors on target organs' cells, which improves the cell response to insulin, whereas indirectly it can contribute to the increased concentration of intracellular calcium, which can raise the glucose transport in insulin-dependent tissues. Taking these facts into account, it is clear that the lack of vitamin D could lead to an increased cell resistance to insulin (34, 35).

Vitamin D and inflammation

Inflammation per se, through the activation of inflammatory network factors (fibrinogen, interleukin-6, C-reactive protein) can raise the risk for developing T2 DM (36). These factors can also have an impact on IR and can contribute to damage to beta-cells, causing their apoptosis. Vitamin D could manifest its favorable effect by reducing the production of these cytokines and by modulating their effects (37).

On that account, by examining the effect of vitamin D supplementation with or without calcium, some trials have shown that the intake of this vitamin could be useful in prevention and even delay the onset of T2 DM (38-40). However, the question remains what happens to patients who are already suffering from this disease.

Effects of vitamin D supplementation in patients with T2 DM

Studies conducted in order to explore the role of vitamin D in treating patients with diabetes have shown opposing results (41). Most of them monitored the glycemic status, IS and IR as the final outcome of disease control.

One of the meta-analyses conducted by Pittas et al. tried to provide an answer to that question by summing up the results of intervention studies which had investigated supplementation effects on glucose metabolism. Among the the analyzed studies four of them were short-term and included a small number of patients, whereas the two other were long-term, primarily designed to explore the effect of supplementation on bones. Some studies incorporated only patients with T2 DM, while others included patients with prediabetes, as well as healthy patients. Considering that these studies were distinctively designed and that various forms and doses of vitamin D were used with different patient groups, this meta-analysis could not provide concrete answers on the effect of vitamin D supplementation in patients with T2 DM, but in conclusion, it indicated that a combination of vitamin D and Ca supplements could provide favorable results in regulating glucose metabolism, especially in patients at risk. Conclusion presented by Pittas et al. is mostly based on results of a randomized, double-blind, placebo-controlled study which included a group of 314 patients older than 65, who had been administered with a combination of 700 international units (IU) of vitamin D3 and 500 mg of calcium or a placebo over the period of 3 years. The study was primarily designed to investigate the effects of supplementation on bones. However, *post hoc* analysis of morning glycemia and HOMA-IR index (*Homeostasis model assessment of insulin resistance index*) revealed that patients with primarily irregular values of fasting glycemia had a significant improvement in controlling glucose metabolism after 3 years of vitamin D supplementation (0,4 vs. 6,1 p = 0,04). In patients with normal values of fasting glycemia no effect was documented (37).

Several years later, a systematic review and meta-analysis encompassing a much larger number of studies were conducted for the purpose of providing an answer whether vitamin D supplementation with or without Ca could favorably affect the IR, C-peptide level, morning glycemia and glycosylated hemoglobin (HbA1c), as well as the development of microvascular (retinopathy, nephropathy, neuropathy) and macrovascular (heart attack, stroke, peripheral vascular disease) complications. Inclusion criteria were fulfilled by 15 studies of different quality; some of them included patients with T2 DM, or patients with impaired glucose tolerance, or even healthy subjects. Various forms of vitamin D in doses less than 2000 IU per day were used for supplementation. Some studies combined calcium with vitamin D, but also with placebo. Majority of studies were conducted on a small sample with an average duration of several months.

Out of 15 analyzed studies, 8 explored the influence of vitamin on fasting glycemia level, whereas 4 out of those 8 included subjects with normal fasting blood glucose levels. The analysis revealed a small, but significant decline of fasting glycemia in patients with T2 DM or with impaired glucose tolerance who were administered with some form of vitamin D in comparison to those who were administered with placebo (mean value of difference -0.32 mmol/l, 95% confidence interval, -0.57 to -0.07, p = 0,01).

Vitamin D supplementation also led to IR improvement (measured by using HOMA-IR model or the relation between morning insulinemia and C-peptide values) in patients with impaired glucose tolerance (mean value of difference -0.25, 95% confidence interval, -0.48 to -0.03, p = 0,03).

The impact of vitamin D on the level of HbA1c was explored in 4 studies in which vitamin D supplementation in patients with diabetes or impaired glucose tolerance did not cause decrease in the level of HbA1c compared to placebo (0,03%, 95% confidence interval, -0,18% to 0,23%). In patients with normal glycemic values there was no significant difference in values of these parameters. Moreover, there was no sufficient data to make a conclusion on the effect of supplementation on micro- and macrovascular complications (42).

Nigil Haroon et al. conducted a systematic review encompassing 17 randomized and controlled studies and 7 longitudinal surveys. Tracking period

for all studies was longer than a month; therefore, studies with tracking period of up to 3 months were considered short-term (total of 16 studies), while other studies were long-term ones with tracking period between 4-18 months. As opposed to previous studies, this systematic review comprised studies in which more than 70% of subjects were T2 DM patients. In most cases, cholecalciferol was administered as supplement in the dose of 400 IU to 5700 IU per day. A single-dose intramuscular injection of vitamin D3 was given in 5 studies. The number of patients varied from 10 to 204. Parameters investigated were the following: HbA1c, HOMA-IR, HOMA-B for glycemia control estimate, IR and IS (function of pancreatic beta-cells).

Majority of short-term studies (total of 10) revealed improvement in HbA1c, HOMA-IR and HOMA-B, whereas most of long-term studies did not document any significant effects (43).

Despite great expectations, numerous studies provided different results; hence, the role of vitamin D in treating this chronic non-communicable disease cannot be precisely determined (Table 1). Before proceeding with further research of the matter, one should bear in mind the reasons why surveys conducted so far produced different and inconsistent results. First of all, some studies included heterogeneous patient groups with regard to gender, age, BMI, ethnic affiliation and the existence of an impaired glucose metabolism, considering that some of them were conducted simultaneously among healthy subjects, those at risk, as well as among those who are already T2 DM patients (37). There are also great discrepancies in the form and method of supplement dosage. Different vitamin D forms were used (inactive and active), different doses and routes of administration (oral, intramuscular). Additionally, various effects in elevating the blood level of 25OHD occurred. Most patients in many studies reported 25OHD3 levels lower than 75 nmol/L, which was probably insufficient to demonstrate favorable effects on glucose metabolism, since some studies showed favorable effects on IR only after the 25 OHD3 blood levels had reached values between 80 and 119 nmol/l (34,58), or even between 100 and 150 nmol/L (59). Therefore, overall effect might have failed to produce results with regard to IR, but the patients who corrected the vitamin D deficiency the most were the only ones who demonstrated a decrease in IR, despite the fact that there was no significant improvement of this parameter in the entire group (45). All of the above mentioned implies the need to define the optimal 25 OH vitamin D blood level, which would have a favorable influence on health in general, and not solely on the bones, as well as to define the necessary dosage and length of supplementation period which would suffice to achieve and maintain the optimal level reached.

Table 1 Randomized clinical research (N > 30) during which vitamin D supplementation effect was tested with or without calcium on glucose metabolism in patients with T2 DM

Study lead author, year	Patients and sample size (N)	Sex M/F	Age, years [a]	Type, dose of used supplement	Time period	Vitamin D level[a]		Result and comment (↔, ↑, ↓) [b]
						Before intervent.	After intervention	
Ljunghall et al. 1987 (44)	Prediabetes and T2 DM [c] (N=65)	M	61-65	1(OH)D3 0,75 mcg/day (N=33); Control group: placebo (N=32)	12 weeks	25(OH)D3 38 ng/ml	NF [d]	↔ HbA1c [e] (values before and after intervention (%):6,46-5,90 vs 6,28-5,70, P<0,01) ↔ IR [*] after IVGTT [**] (I/G [***] values before and after intervention: 0 min. 1,84-1,98 vs. 2,35-1,98, p<0,05; 60. min. 3,56-2,58 vs. 3,90-3,56, p<0,01)
Sugden et al. 2008 (45)	T2 DM (N=34)	M and F	64	Ergocalciferol 100 000 IU [#] in a single dose (N=17); Control group: placebo (N=17)	8 weeks	25(OH)D3 38 nmol/l	25(OH)D3 61 nmol/l in group admin. with ergocalciferol	↔ HbA1c (change compared to basal value (%): 0,01 vs. -0,05 p=0,74) ↑ IS_{HOMA} [##] with patients with 25(OH)D3 level increased by value which is ≥ 11 nmol/l, HOMA +15 vs. -98 p=0,003
Jorde, Figenschau 2009 (46)	T2 DM (N=32)	M and F	56	D3 40 000 IU/week (N=16); Control group: placebo (N=16)	6 months	25(OH)D3 59 nmol/L	25(OH)D3 57 nmol/L	↔ HbA1c (change compared to basal value (%):-0,2 vs.-0,2, p=0,90) ↔ IR_{HOMA} [###] (change compared to basal value: 0,3 vs.-0,2, p=0,58) ↔ IS_{HOMA} (change compared to basal value: 10 vs.63, p=0,99)
Witham et al. 2010 (47)	T2 DM (N=61)	M and F	66	D3 100 000 IU in a single dose (N=19); D3 200 000 IU in a single dose (N=17); Control group: placebo (N=22)	16 weeks	25(OH)D3 45 nmol/L	25(OH)D3 65 nmol/L	↔ HbA1c (change compared to basal value (%):$0,1_{(100\ 000\ IU)}$ vs. $0,3_{(200\ 000IU)}$ vs. $-0,1_{(placebo)}$, $p=0,65_{(placebo\ vs.\ 100\ 000\ IU)}$; $p=0,87_{(placebo\ vs.\ 200\ 000\ IU)}$) ↔ IR_{HOMA} (change compared to basal value: $2,4_{(100\ 000\ IU)}$ vs. $-1,4_{(200\ 000IU)}$) vs. $-8,1_{(placebo)}$, $p=0,95_{(placebo\ vs.\ 100\ 000\ IU)}$; $p=0,11_{(placebo\ vs.\ 200\ 000\ IU)}$)

Nikooyeh et al. 2011 (48)	T2 DM (N=90)	M and F	51	D3 1000 IU/day+Ca 300 mg/day (N=30); D3 1000IU/day+ Ca 500 mg/day (N=30); Control group: Ca 300 mg/day (N=30)	12 weeks	25(OH)D3 43,5 nmol/L	25(OH)D3 63 nmol/L	↓HbA1c (%):−0.4 % (p < 0.001) ↓ IR_{HOMA} 3.3 vs. 2.7 (p=0,001)
Shab-Bidar et al. 2011 (49)	T2 DM (N=100)	M and F	52,5	D3 1000 IU/day+ Ca 240 mg/day (N=50); Control group: Ca 240 mg/day (N=50)	12 weeks	25(OH)D3 38 nmol/L	25(OH)D3 53 nmol/L	↓ HbA1c (change compared to basal value in vitamin D group (%):-0,9, p=0,001) ↑ QUICKI † (change compared to basal value in vitamin D group:0,01, p=0,001)
Eftekhari et al. 2011 (50)	T2 DM (N=70)	M and F	54	Calcitriol 0,25 μg/day (N=35); Control group: placebo (N=35)	12 weeks	25(OH)D3 40,5 ng/ml	25(OH)D3 32,5 ng/ml	↑ HbA1c (change compared to basal value (%):0,82 vs. 1,56, p<0,005) ↑ IS_{HOMA} (values before and after intervention in vitamin D group:3.4 vs. 4.8, p<0,005) ↑ IR_{HOMA} (values before and after intervention in vitamin D group: 3.6 vs. 4.8, p=0,02)
Heshmat et al. 2012 (51)	T2 DM (N=42)	M and F	56	D3 300 000 IU in a single dose (N=21); Control group: placebo (N=21)	3 months	NF	25(OH)D3 78 ng/ml	↔ HbA1c (change compared to basal value (%):-0,01 vs. -0,2, p=0,495 ↔ IR_{HOMA} (change compared to basal value:0,2 vs. -0,9, p=0,017)
Soric et al. 2012 (52)	T2 DM (N=31)	M and F	54	D3 2000 IU/day (N=16); Control group: vitamin C (N=15)	12 weeks	NF	NF	↓ HbA1c (change compared to basal value (%):-1,4 vs. 0,2, p=0,013), statistically significantly decreased value in patients with HbA1c>9,0 %
Yiu et al. 2013 (53)	T2 DM (N=100)	M and F	65	D3 5000 IU/day (N=50); Control group: placebo (N=50)	12 weeks	NF	25(OH)D3 87 nmol/L	↔ HbA1c (change compared to basal value (%):7,35 vs. 7,20, p=0,008)
Breslavsky et al. 2013 (54)	T2 DM (N=47)	M and F	67	D3 1000 IU/day (N=24); Control group: placebo (N=23)	12 months	NF	NF	↔ HbA1c (values before&after intervention in vit. D group (%): 7,0 vs. 7,3, p=0,212 ↔ IR_{HOMA} (values before&after intervention in vit. D group: 4,2 vs. 6,1, p=0,243) ↔ IS_{HOMA} (values before&after intervention in vit. D group: 84,7 vs. 42,5, p=0,184)
Tabesh et al. 2014 (55)	T2 DM (N=118)	M and F	50	D3 50 000 IU/week (N=29); D3 50 000 IU/week + Ca carbonate 1000mg/day (N=30); Control groups: Ca carbonate 1000 mg/day (N=29); Placebo (N=30)	8 weeks	25(OH)D3 16 ng/ml	25(OH)D3 35,1 ng/ml in vitamin D group	↓ HbA1c (change compared to basal value in vitamin D + Ca group (%):−0,70 ± 0,19, p = 0,02) ↓ IR_{HOMA} (change compared to basal value in vitamin D + Ca group:−0,46 ± 0,20, p = 0,001)
Jehle et al. 2014 (56)	T2 DM (N=55)	M and F	67	D3 300 000 IU in a single dose (N=29); Control group: placebo (N=26)	6 months	25(OH)D3 32 nmol/L	25(OH)D3 84,9 nmol/L in vitamin D group	↓ HbA1c (change compared to basal value (%): 2,9 vs. 6,9, p=0,041) ↓ IR_{HOMA} (change compared to basal value:-12,8 vs. 10, p=0,032
Strobel et al. 2014 (57)	T2 DM (N=86, 14 given up)	M and F	30-78	D3 1902 IU/day N=39; Control group: placebo (N=33)	6 months	25(OH)D3 11,9 ng/ml	25(OH)D3 35 ng/ml in vitamin D group	No effect on the values of metabolic parameters. Patients with the level of 25(OH)D3>20 ng/ml had significantly lower value of HbA1c at the beginning and at the end of the survey compared to group with the level of 25(OH)D3≤20 ng/ml. (HbA1c (mmol/mol Hb):48 vs. 52, p=0,008; 54 vs. 50, p=0,009)

[a] data presented as a mean value or a range; [b] ↔ no statistically significant difference; [c] T2 DM – type 2 diabetes mellitus;
[d] NF – not familiar; [e] HbA1c – glycolized hemoglobin;
↑ statistically significantly increased values;
↓ statistically significantly decreased values;
* IR – insulin resistance;
** IVGTT - intravenous glucose tolerance test;
*** I/G – relation between values of basal insulinemia and glycemia;
# IU-international unit;
ISHOMA- homeostasis model assessment of basal insulin secretion;
IRHOMA- homeostasis model assessment of insulin resistance index;
† QUICKI-quantitative insuline sensitivity check index

Many studies failed to take into account various therapeutic regimes, physical activity, diet, season and other relevant factors which may influence the rise of vitamin D blood level (60). For example, obese patients require larger doses, due to vitamin D's ability to store in adipose tissue (61). Diet and physical activity can influence both the glycemia control and the level of 25(OH)D3 (35). During physical activity, the time spent outdoors and UV rays can cause the increase in vitamin D level, both in patient group and in control group (40). It is, therefore, essential to consider all relevant factors which might have an impact on the lack of manifestation of differences in supplementation effects in various groups of patients. Additionally, it should be noted that not all studies in which the subjects demonstrated high levels of 25(OH)D3 showed benefits in the case of glycemia control, IS and inflammation (62). The question is to what extent vitamin D can help patients with advanced disease when beta-cells have already been exhausted (35). Some studies reported that the major benefit from vitamin D supplementation would be for patients with an increased risk for T2 DM, and for those patients in early stages of the disease (35, 37, 40). Finally, all studies comprised a small sample and mostly had a short tracking period (shorter than a year).

Conclusion

At the present moment, there is no sufficient evidence to recommend vitamin D to patients with T2 DM as a therapeutic tool for better metabolic control. Therefore, it is necessary to conduct well-designed research which would include a sufficient number of precisely defined patient target groups (who are at risk or already affected in the same disease period), with clearly determined doses of the relevant vitamin D form and a sufficiently long follow-up period, in order to clarify to what extent and at which stage of the disease the patients may have benefit from vitamin D supplementation.

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ULOGA VITAMINA D U LEČENJU BOLESNIKA OBOLELIH OD DIJABETESA MELITUSA TIPA 2

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Vitamin D je steroidni hormon čija je osnovna uloga da održava adekvatnu koncentraciju kalcijuma i fosfora u serumu potrebnu za proces mineralizacije kostiju. Otkriće receptora za aktivni oblik ovog vitamina, kao i enzima koji učestvuje u njegovoj aktivaciji u mnogim drugim tkivima u organizmu, dovelo je do toga da se njegov nedostatak povezuje sa nastankom mnogih hroničnih bolesti kao što su hipertenzija, multipla skleroza, neke vrste malignih tumora i dijabetes melitus tip 2. Mnogobrojne opservacione studije su pokazale da oboleli od dijabetesa melitusa tipa 2 imaju niže vrednosti vitamina D u krvi u odnosu na zdrave ispitanike. To je navelo na pomisao da bi vitamin D mogao igrati bitnu ulogu u patogenezi ove hronične nezarazne bolesti. Istraživanja koja su pokušala da odgovore na pitanje da li bi suplementacija vitaminom D mogla pomoći ovim bolesnicima da bolje kontrolišu svoju bolest i spreče nastanak komplikacija, kao krajnji ishod pratila je parametre vezane za glikemijski status, sekreciju insulina i insulinsku rezistenciju. Dobijeni rezultati su oprečni i nisu dali dovoljno čvrstih dokaza na osnovu kojih bi mogli preporučiti vitamin D kao terapijsko sredstvo. Međutim, benefit od suplementacije bi mogli imati bolesnici koji su u riziku ili oni na početku bolesti. Da bi procenili koja grupa bolesnika može imati dobiti od suplementacije ovim vitaminom, potrebne su dobro dizajnirane eksperimentalne studije sa precizno definisanim grupama ispitanika (onih koji su u riziku ili već oboleli sa jednakim stažom bolesti), dovoljno visokim dozama vitamina D i dovoljno dugim periodom praćenja.

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Ključne reči: *vitamin D, suplementacija, efekat, dijabetes melitus tip 2*