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VITAMIN D STATUS OF PEDIATRIC PATIENTS WITH TYPE 1 DIABETES MELLITUS

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Abstract

The aim of this study was to examine the serum levels of 25(OH)vitamin D in pediatric patients with type 1 diabetes and controls, and to determine whether patients had higher prevalence of vitamin D alterations and if they were correlated to disease duration/metabolic control.

A cross-sectional study of 123 patients (65 females) aged 11.84 ± 3.86 years and 46 non-diabetic controls (23 females), aged 10.2 ± 4.69 years was performed. 25(OH)vitamin D level was determined by electrochemiluminescence detection technology.

There was no statistically significant difference between 25(OH)vitamin D levels in diabetic patients and in controls ($p = 0.17$). The mean level of 25(OH)vitamin D in patients was lower – 71.61 ± 32.34 nmol/L than in controls – 78.32 ± 26.49 nmol/L. We used the Bulgarian Society of Endocrinology recommended ranges to define vitamin D deficiency and insufficiency as 25(OH)vitamin D level < 25 nmol/L and 25–49 nmol/L, respectively. None of the patients and 4.3% of controls ($n = 2$) had vitamin D deficiency. Vitamin D insufficiency was observed in 19% of patients ($n = 23$) and in 8.7% of controls ($n = 4$).

Mean level of HbA1c in all patients was 78 mmol/mol ($9.28\% \pm 1.85$) whereas the mean duration of the disease was 5.25 ± 4.03 years. No correlation

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between metabolic control and disease duration on the one hand, and vitamin D levels on the other, was found.

To our knowledge this is the first study to examine vitamin D levels in Bulgarian pediatric patients with type 1 diabetes. Presence of disease does not influence vitamin D levels – we found no correlation with metabolic control (HbA1c), nor with disease duration. Our results show no significant differences between 25(OH)vitamin D levels in diabetic patients and in controls. Vitamin D insufficiency is slightly but not significantly prevalent in diabetic patients.

Key words: pediatrics, type 1 diabetes, vitamin D

Introduction. Diabetes mellitus type 1 is one of the most common chronic diseases in childhood with constantly increasing incidence. In many Western countries, type 1 diabetes (T1D) accounts for over 90% of childhood and adolescent diabetes, while across the life span, T1D accounts for 5% to 10% of the individuals with diabetes [1].

Worldwide there is a parallel rise in incidence of both T1DM and vitamin D deficiency. This raises the possibility that vitamin D may play a role in the pathogenesis of T1DM [2].

There is an increasing awareness that the skeleton is also adversely affected by T1D with impaired bone quality, resulting in a lifelong increased risk for fractures. Recent study reveals that the increased fracture risk is already evident in childhood and extends across life span [3].

The contemporary hypothesis [4] of the pathogenesis and natural history of T1D incorporates genetic susceptibility, environmental triggers and immune dysregulation in the autoimmune destruction of pancreatic islet cells.

Vitamin D has a classic role in calcium-phosphate metabolism and bone formation. Its non-classic role includes regulation of the expression of over 500 genes, while over 150 of them are immune-related genes in human monocytes [5]. Thus vitamin D has pleiotropic extra-skeletal effects like regulation of immunity, protection against infection and inhibition of autoimmune disease, although the causal role of vitamin D deficiency with these extraskeletal systems remains to be established [6].

Vitamin D insufficiency and deficiency are common in youth, especially in youth with diabetes – both type 1 and type 2 [7]. Possible mechanisms [7] of an increased prevalence of vitamin D insufficiency and deficiency include genetic inheritance, increased body mass index (BMI), and concurrent albuminuria with enhanced excretion of vitamin D binding protein and less healthy diets in youth with diabetes.

In addition to bone health, youth with diabetes may have additional benefits from being vitamin D sufficient. Past research has demonstrated that vitamin D insufficiency/deficiency in pediatric diabetes may contribute to insulin resistance, poor glycemic control and the development of microvascular and macrovascular complications [7].

There is increasing evidence that maternal vitamin D status is an important risk factor for occurrence of T1D in offspring. Dietary supplementation with vitamin D during infancy reduces the risk of development of T1D in at risk subjects in later life [8]. A number of studies have shown that patients with T1D have low levels of vitamin D [9–11], although other studies have conflicting results.

Thus our aim was to examine the serum levels of 25(OH)vitamin D in children and adolescents with T1D and in controls and to determine if patients with diabetes had higher prevalence of vitamin D deficiency/insufficiency and whether it was correlated to the disease duration and/or metabolic control.

Materials and methods. Blood samples were drawn from 123 patients and 46 controls between 6 and 8 h a.m. after overnight fasting. Patients with T1D were hospitalized in Endocrinology and Diabetes Department of University Children's Hospital in Sofia, Bulgaria from March 2011 to November 2014. Their diagnosis was based on laboratory measurement of plasma blood glucose and presence of symptoms according to ISPAD Guidelines [12]. Controls were children and adolescents hospitalized during the same period. Those who had conditions altering their bone metabolism were excluded. The controls had mainly acute illnesses, e.g. laryngitis. All were enrolled in the study after their legal guardians signed an informed consent. Demographic information was retrieved from the medical records and included: age at onset, disease duration, longstanding metabolic control expressed as mean HbA1c level measured from diabetes onset until current hospitalization.

Levels of 25(OH)vitamin D were determined by electrochemiluminescence detection technology on Cobas 411 analyzer (Roche Diagnostics, Rotkreuz, Switzerland). The accuracy of the used method is up to 7.5 nmol/L with range of detection 7.50–175 nmol/L. Level of HbA1c was determined by immunoassay method on Cobas Integra Analyzer (Roche Diagnostics, Rotkreuz, Switzerland).

Blood samples in 43% ($n = 56$) of the patients were drawn during a period with abundant sunlight (May-September), compared to 37% ($n = 18$) of the samples of the controls.

Mann–Whitney U test was used for the analysis of the quantitative data. Correlations between 25(OH)vitamin D level and other variables were evaluated by Spearman's correlation.

Results. The mean age of all patients (65 females) was 11.84 ± 3.86 years and that of the healthy controls (23 females) was 10.2 ± 4.69 years.

Mean level of 25(OH)vitamin D in patients was 71.61 nmol/L and in healthy controls – 78.32 nmol/L, $p = 0.17$.

When analyzing the data we used the reference values for vitamin D evaluation proposed by the Bulgarian Society of Endocrinology [12]:

- Recommended normal level ≥ 20 ng/mL (≥ 50 nmol/L)
- Insufficiency 10–19 ng/mL (25–49 nmol/L)
- Deficiency < 10 ng/mL (< 25 nmol/L)

Table 1

25(OH)vitamin D levels among patients and controls

	25(OH)vitamin D nmol/L						
Group	n	Mean	Median	Lowest	Highest	SD (standard deviation)	p
Patients	123	71.61	68.27	29.22	175	26.49	0.17
Controls	46	78.32	70.76	14.47	175.75	32.34	

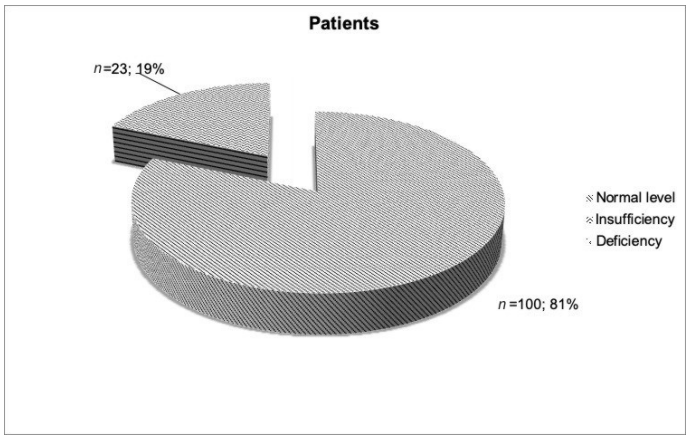


Fig. 1. Distribution of the examined patients according to their 25(OH)vitamin D level

In the patients' group 81% had normal level of 25(OH)vitamin D, whereas 19% were vitamin D insufficient. There were no patients with vitamin D deficiency.

In the controls group 87% showed normal level of vitamin D whereas 8.7% were insufficient and only 4.3% showed vitamin D deficiency.

Influence of T1D on 25(OH)vitamin D level. The patients had mean disease duration 5.25±4.03 years (from 0.00 to 15.65). The mean level of their metabolic control, expressed as HbA1c was 78 mmol/mol (9.28% ± 1.85).

When performing correlation analysis we did not find any significant correlations between the level of 25(OH)vitamin D and duration of disease ($r = 0.125$, $p > 0.05$), nor with HbA1c level ($r = 0.085$, $p > 0.05$).

Discussion. To the best of our knowledge this is the first study in Bulgaria to investigate 25(OH)vitamin D levels in pediatric patients with T1D.

The mean levels of 25(OH)vitamin D in both patients' and controls' groups are within the recommended range. Among the patients there is a tendency towards lower levels but the difference is insignificant. In the patients' group there is a bigger proportion of vitamin D insufficient patients but interestingly there are

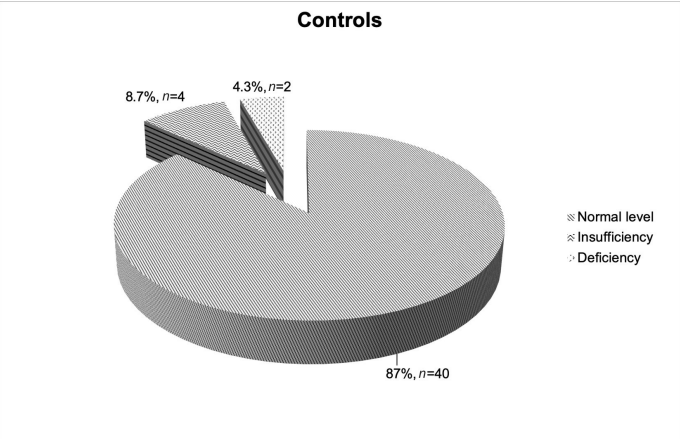


Fig. 2. Distribution of the examined controls according to their 25(OH)vitamin D level

no patients with vitamin D deficiency. At the same time, bigger proportion of healthy controls have normal vitamin D levels (87%) and only 8.7% of them are vitamin D insufficient. In the same group vitamin D deficiency is more prevalent (4.3% of all). The proportion of children and adolescents with alterations in vitamin D metabolism is quite similar between the two groups. This means that despite their chronic condition patients with T1D manage to achieve vitamin D levels not significantly different from these of non-diabetic children.

Most of the recent studies of vitamin D status among Bulgarian adults with or without diabetes found low levels of 25(OH)vitamin D [13–15]. Of interest is the study of Bakalov et al. [14] who used the same method for 25(OH) vitamin D determination in adults with type 2 diabetes. They found a mean level of 27.9 ± 15.8 nmol/L (7.5–85.1). Another large, Bulgarian population-based study [15] found a mean level of 25(OH) vitamin D of 38.75 nmol/L. Interestingly the highest level was observed among the youngest group (20–44 years old), though the differences were not significant. Since the method for 25(OH)vitamin D determination was different, we cannot directly compare our results. Nevertheless the proportions of vitamin D deficiency, insufficiency and sufficiency estimated in the study were 21.3%, 54.5% and 24.2%, respectively. Although there are many confounding factors, we may say that the vitamin D status of the examined children with T1D is not much different from that of the healthy controls on the one hand, and better than that of Bulgarian adults, both healthy and with type 2 diabetes, on the other. This is probably due to the more active lifestyle of the pediatric population, including more time spent outdoors and an effective prevention strategy as well.

There are many contradictions regarding levels of 25(OH)vitamin D among diabetic patients and non-diabetic controls on the one hand, and the influence

of disease, expressed as HbA1c and disease duration, on the other. Regarding the difference between diabetic and non-diabetic patients, our results are similar to those of other authors [14–16] who also did not find such. But our results are in contrast to others who found significantly lower 25(OH)vitamin D levels in T1D patients [7,17] However, the mean level of 25(OH) vitamin D in our patients tended to be lower than that of the controls. Besides, most of their blood samples were drawn during a period of abundant sunshine, compared to controls. One may speculate that this difference would become significant if the number of investigated patients and controls was bigger.

When comparing the mean level of 25(OH)vitamin D in our patients with other T1D patients, our results are lower than those found by some authors [8], but higher compared to others, conducted at similar latitude [5].

The same is with the prevalence of vitamin D alterations. Our results show lower prevalence of vitamin D insufficiency and deficiency compared to those found in a large multi-centre study [7].

Level of 25(OH)vitamin D was not influenced by the presence of T1D, expressed as HbA1c and diabetes duration, which is in agreement with other studies [8,17].

There are other authors who found inverse association between vitamin D level and HbA1c [21,22].

Lack of correlation between metabolic control and 25(OH)vitamin D, may be due to the fact that both parameters represent a temporal state of metabolism and are probably a subject to different regulating mechanisms. This and the lack of correlation with the disease duration could be explained, at least partly, by the heterogeneity of the examined patients in terms of diabetes duration and metabolic control as well.

Limitations. The results should be interpreted with caution because of the small number of controls. Another limitation is that our control group may not be representative of the whole population. It is likely that the mean serum 25(OH)vitamin D of the hospital control group would be lower, not higher, than the general population.

Conclusions. Presence of T1D does not influence 25(OH)vitamin D levels in the examined patients. We did not find correlation with diabetes' duration, nor with metabolic control (HbA1c). Our results show no significant differences between 25(OH)vitamin D levels in diabetic patients and in controls. Vitamin D insufficiency is slightly but not significantly prevalent in diabetic patients.

The evaluation of vitamin D status should be considered in pediatric patients, especially in those with diabetes. Additional research is needed to confirm whether youth with diabetes would have benefits, such as improved insulin resistance, glycemic control and prevention of diabetes-related complications from vitamin D supplementation.

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