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ORIGINAL ARTICLE

DIABETES MELLITUS TYPE 1 IN ADOLESCENTS: IMPACT OF VITAMIN D STATUS

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ABSTRACT

The aim: To evaluate the effect of vitamin D deficiency or insufficiency on the compensation of the disease in adolescents with diabetes mellitus type 1.

Materials and methods: 124 patients were examined, among them: 33 from the control group, 91 adolescents with type 1 diabetes mellitus. All patients were between 10-18 years old and were residents of the Podillya region of Ukraine.

Results: According to the results of the study Vitamin D levels in adolescents with type 1 diabetes mellitus are significantly lower, comparing with healthy adolescents of the same age group. Vitamin D levels among boys with type 1 diabetes mellitus were significantly lower comparing to girls of the same group. The boys of the control group had significantly higher levels of vitamin D in the blood comparing to boys with type 1 diabetes mellitus, $p < 0.001$.

Conclusions: The majority of adolescents aged 13-18 years with type 1 diabetes mellitus have vitamin D deficiency or insufficiency regardless of the state of glycemic control of the disease.

KEY WORDS: diabetes mellitus, adolescents, vitamin D, glycated hemoglobin, carbohydrate metabolism

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INTRODUCTION

Diabetes mellitus (DM) is one of the most common non-infectious diseases with the tendency to increase.

According to the International Diabetes Federation (IDF) data more than 1.1 million of children and adolescents suffer from the DM type 1. More than 128 900 new cases of diabetes in children and adolescents are diagnosed annually in the world.

In 2019 almost 300 000 children were known to have type 1 diabetes mellitus in Europe [1]. The main problem of treatment of DM remains optimization of the glycemic control especially in childhood.

Thus, the DCCT (Diabetes Control and Complication Trial) study found that normalization of blood glucose levels and disease compensation in adolescents is more difficult than in adult patients [2]. It is also known that in pubertal age there are factors that directly or indirectly can influence the achievement of optimal glycemic control. Such factors include the rapid linear growth of the child that is influenced by the action of sex hormones during puberty , intensive hormonal changes in the body, which leads to increased daily insulin needs.

DM type 1 is a result of cell-mediated autoimmune destruction of β - cells of the pancreas. According to the newest data about the effect of vitamin D, as a part of the body's hormonal system, the authors are interested in the effect of vitamin D on homeostasis not only on calcium- phosphorus metabolism, but also on carbohydrate metabolism [3].

Vitamin D deficiency is common global problem that constantly increases with the level of urbanization. Low vitamin D status effects the skeletal system, plays a significant role in the pathogenesis of diabetes, taking part in the insulin secretion [4,5]. The active metabolites of vitamin D regulate the proliferation and differentiation of cells, synthesis of lipids, proteins, enzymes and the work of organs and systems [6,7].

Patients with type 1 and type 2 diabetes mellitus have low levels of vitamin D and low values of 25(OH)D in the blood serum are associated with increased levels of glycated hemoglobin (HbA1C) [8].

The connection between vitamin D intake and a reduced risk of type 1 DM has been demonstrated in a large cohort study in Finland. It was found that the children who received 2,000 IU of cholecalciferol daily had 88% lower risk of the development of DM type 1 compared to children, who did not receive vitamin D [9]. The dose-dependent effect was found: children, who received higher doses of cholecalciferol had a lower risk of developing DM type 1 [10].

According to the published data of cross sectional study in Poland, the lowest levels of 25(OH)D (13,1 ± 4,7 ng/ml) were observed in children aged from 15 to 20 years [11].

THE AIM

To evaluate the effect of vitamin D deficiency or insufficiency on the compensation of the disease in adolescents with diabetes mellitus type 1.

Table I. Vitamin D levels among adolescents of different age groups

Vitamin D status	Adolescents with DM type 1 (n = 91)		Control group (n = 33)	
	Early puberty (10-12 years)	Intensive puberty (13-18 years)	Early puberty (10-12 years)	Intensive puberty (13-18 years)
Deficiency (ng/ml)	13.14 ± 2.06 **,*** n=10	13.42±2.31 n=54	18.12±2.48 n=2	17.96 ± 2.13 n=8
Insufficiency (ng/ml)	20.81 ± 2.12 *,** n=5	25.45 ± 2.07 n=16	25.73± 2.23 n=5	25.68 ± 2.56 n=13
Optimal level (ng/ml)	32.54 ± 3.24 n=2	32.16 ± 4.27 n=4	32.61 ± 4.32 n=1	34.32 ± 3.89 n=4

Note: The difference is significant when compared to:
* – adolescents with type 1 diabetes in early puberty and intensive puberty (p <0,05);
** – adolescents of the main and control group aged 10-12 years (p <0.05);
*** - adolescents of the main group aged 13-18 years old and adolescents of the control group of the same age.

Table II. Average vitamin D levels among different stages of compensation of diabetes mellitus type 1 in adolescents

HbA1C	Deficiency of vitamin D, ng / ml, n = 64	Insufficiency of vitamin D, ng / ml, n = 21	The rate of vitamin D, ng / ml, n = 6
Compensation of diabetes, n = 20	15.59 ± 3.82	24.83 ± 1.92	30.22
Subcompensation of diabetes, n = 21	12.45 ± 3.88	22.16 ± 1.55 *	-
Decompensation of diabetes, n = 50	13.87 ± 3.42	25.27 ± 2.67 *	39.66 ± 14.42

Note: * – reliability in the group of vitamin D deficiency between adolescents in a state of sub – and decompensation of the disease, p = 0.02.

MATERIALS AND METHODS

The study was conducted in Vinnytsia Regional Clinical Highly Specialized Endocrinology Center. The study involved 124 children aged 10-18 years (average age 14,38±2,15), among them 61 girls, 63 boys. All participants were divided in 2 groups: 91 children with type 1 DM (group 1), average age 14,43±2,18 and 33 healthy children of the same age (group 2) whose average age was 14,21±2,07.

Clinical evaluation of the patients, medical history, laboratory and statistical methods of research were used during the study. The mathematical processing was performed on a personal computer using a standard statistical package STATISTICA 6,0.

Exclusion criteria for the group 1 was: chronic concomitant diseases, as well as the presence of skeletal system disorders, which could have impact on the calcium and phosphorus metabolism. Exclusion criteria for the group 2 contained skeletal diseases, acute and chronic diseases, as well as autoimmune diseases, which could influence the metabolism of vitamin D.

The study was approved by the Ethics Committee of National Pirogov Memorial Medical University (Vinnytsya, Ukraine). All study staff prior to specimen collection voluntarily agreed to participate in the study and signed an informed consent form. All study personnel data were anonymized prior to the analysis. Ethical considerations including privacy of personal data were considered during all steps of the research.

Clinical examination of the adolescents included evaluation of physical (weight, height, body mass index) and sexual development (Tanner stage). The children were divided into periods of puberty (Tanner stage 1-2 - early puberty, Tanner stage 3-4 - late puberty). Measurements of glycated hemoglobin (HbA1C) were provided for group 1 in order to determine the state of compensation of DM (HbA1C <7.5% was considered as good compensation of the disease, 7.5-9% sufficient compensation, HbA1C > 9% - insufficient compensation of DM). The level of HbA1C was determined using the method of high performance liquid chromatography (analyzer D -10 Bio - Rad).

The concentration of 25(OH)D hydroxycholecalciferol in the blood serum was conducted using electrochemiluminescence method (Cobas analyzer). Measurements of 25(OH)D level was done during the year. Further analysis regarding the influence of the season of sample collection (autumn-winter, spring-summer) and place of living of the participant (urban/rural) on the vitamin D status in adolescents was provided [12].

The levels of total and ionized calcium were conducted using colorimetric and photometric method with Arsenazo III (analyzer AU 480 Beckman Coulter). Blood sampling was performed between 8 and 10 am.

The diagnosis of vitamin D deficiency was established according to the Endocrine Practice Guidelines Committee and Institute of Medicine. The level of vitamin D: <20 ng/ml (50 mmol/l) was marked as deficiency of vitamin D,

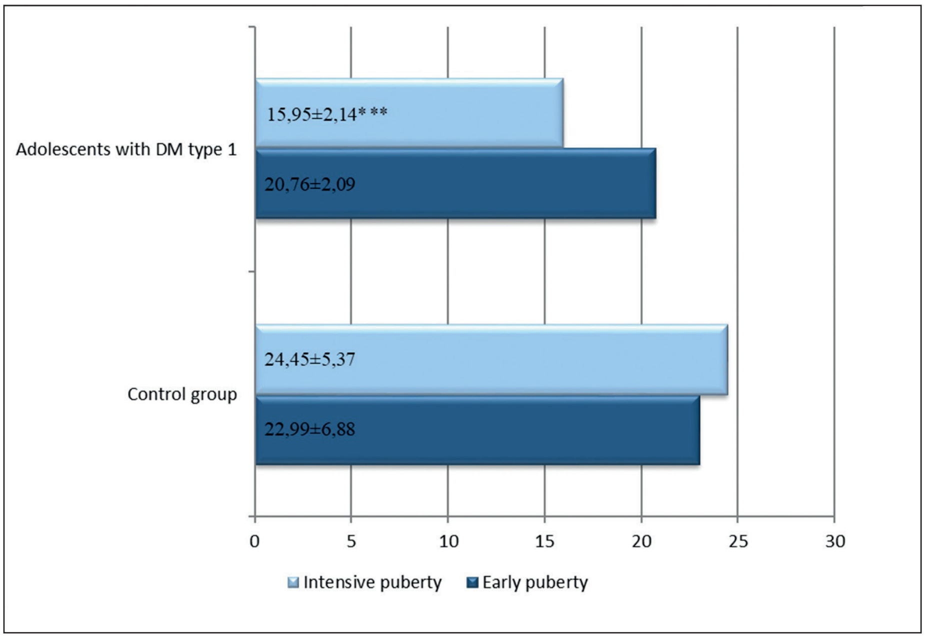

Fig. 1. Average levels of 25 (OH) D in serum (ng/ml) among age groups
Note: The difference is significant when compared to: * - adolescents with type 1 diabetes of different age groups (10-12 years and 13-18 years), p <0,05; ** - adolescents of the main and control groups aged 13-18 years, p <0,01.

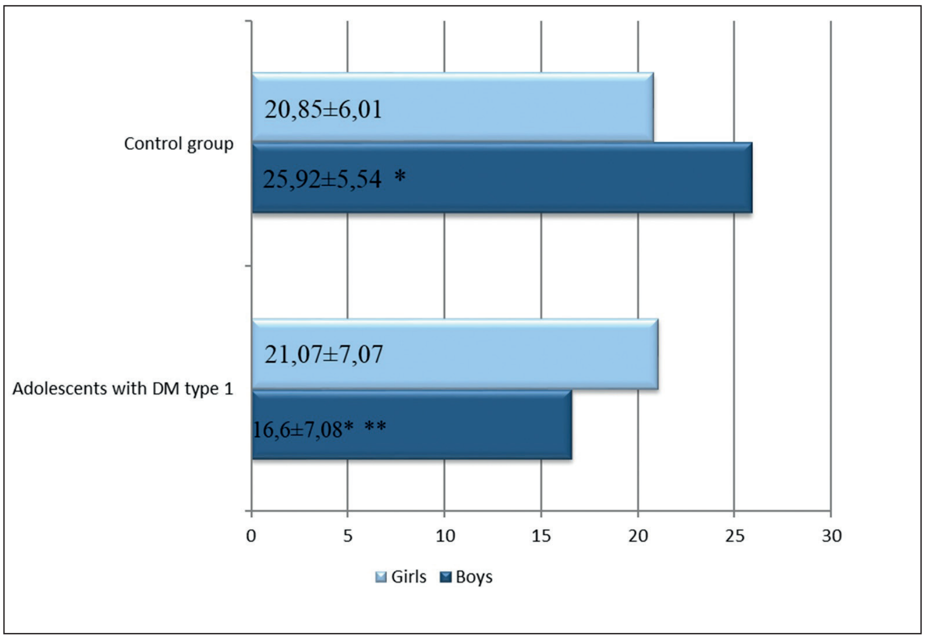

Fig. 2. Average 25 (OH) D levels (ng / ml) among girls and boys
Note: The difference is significant when compared to: * - girls with type 1 diabetes, p <0,05; ** - boys of the control group, p <0,01.

21-29 ng/ml (50.1-74.9 nmol /l) - insufficiency, above 30 ng/ml (75.0 nmol /l and more) was considered to be optimal [13, 14].

RESULTS

According to the results of the study the decreased level of 25 (OH) D in the blood serum was observed with almost the same frequency in adolescents of the main group (93.41% of the participants), as well as in the control group (84.85%).

All participants were divided according place of residence (rural /urban) and season of blood collection. Thus, we found that among adolescents with type 1 DM there was no significant difference in the average levels of vitamin D depending on the season of blood sample collection. During analysis according to the place of living of the adolescents, vitamin D deficiency was significantly more common in adolescents who live in the urban areas than in adolescents who live in the rural areas, regardless of the study group (p <0.05).

Taking into account the peculiarities of hormonal balance during puberty, after the assessment of Tanner stage, adolescents were divided into 2 groups: 10-12 years (beginning of puberty) and 13-18 years (intensive puberty with a growth spurt).

According to the vitamin D levels and for the purpose of more detailed analysis of indicators, all adolescents with type 1 DM additionally were divided: adolescents with vitamin D deficiency (n = 64), vitamin D insufficiency (n = 21), adolescents with normal levels of vitamin D in the blood (n = 6). The average levels of vitamin D in different groups are shown in table I.

The majority of adolescents with type 1 DM showed generalized vitamin D deficiency in the age of intensive puberty (54 patients, 59.34 %) which in 4.7 times dominate the participants of the same group who had early puberty (10.98 % $p < 0.05$). Among children of the control group, the majority of adolescents was characterized by vitamin D insufficiency at the age of intensive puberty (13 participants, 39.4%), $p<0,05$.

According to the results vitamin D deficiency in the group of adolescents with type 1 diabetes, as well as among adolescents of the control group at the age of 13-18 years was more common compared to adolescents of the earlier puberty (10-12 years).

In general, the data clearly reflect the absolute prevalence of low vitamin D status in adolescents: 70.33% of participants with type 1 diabetes have vitamin D deficiency, 23.08% - insufficiency. According to our study results, only 3.29% of adolescents with type 1 diabetes in early pubertal age and 4.39% of the children who were in intensive puberty had optimal vitamin D levels.

Significant difference between the average levels of vitamin D (deficiency and insufficiency) was found in adolescents of the main and control group in early pubertal age, $p<0.05$. Thus, in adolescents of the main group at the age of early puberty, with vitamin D deficiency (average level 13.14 ± 2.06 ng/ml) was significantly lower than in children of the control group (average level 18.12 ± 2.48 ng/ml), $p<0.05$. Similar results were observed in the group of vitamin D insufficiency of the main group of adolescents at the age of early puberty, $p <0.05$. Thus, the level of serum hydroxyvitamin D was significantly lower in adolescents with type 1 diabetes at the age of intensive puberty (13.42 ± 2.31 ng / ml) than in adolescents of the control group of the same age(17.96 ± 2.13 ng / ml) , $p <0.05$.

Analysis of the average vitamin D levels in blood serum depending on the period of puberty was provided (fig.1). The average level of 25 (OH) D (group 1) was found to be significantly lower among children in the intensive puberty (15,95 ± 2.14 ng/ml), and participants at the age of early puberty (20.76 ± 2.09) ng/ml, $p <0.05$. Among children of the control group, significant difference in vitamin D levels depending on age (in the group of intensive puberty the average level was 24.45 ng/ml, early puberty - 22.99 ng /ml) was not found. Thus, the lowest vitamin D status was present among the adolescents with carbohydrate metabolism disorders and had intensive puberty (13-18 years). The results are reflected in figure 1.

Taking into account the possibility of influence of the gender on vitamin D status among adolescents, the vitamin D levels among different gender groups were analyzed. The distribution by gender among adolescents of the main group was 50.55% - boys, 49.45% - girls. Among adolescents of the control group, the distribution by gender was similar. The results of average of 25 (OH) D levels are shown in figure 2.

The average levels of 25 (OH) D in the serum of adolescents of the main group had significant difference: 21.07 ± 7.07 ng/ml among girls and 16.60 ± 7.08 ng/ml among boys, $p <0.05$.

Also it was found that the boys of the control group had significantly higher levels of vitamin D (25.92 ng/ml) compared to boys with type 1 DM (16.6 ng/ml) , $p <0.001$. A similar significance of the average vitamin D level among girls of the main and control groups was not found, $p>0.05$.

Among somatically healthy adolescents (n=33) the vitamin D levels were analyzed: the average level among boys was 25,92 ng/ml. It was significantly higher compared to girls of the same group (20.85 ng/ml), p= 0,01.

Analyzing the state of calcium metabolism among the surveyed adolescents, we have found that there are no deviations of total calcium levels of adolescents. Thus, the average levels of total calcium among boys with type 1 diabetes was 2.41 ± 0.10 mmol/l, among girls it was slightly lower and was 2.38 ± 0.13 mmol/l. Among adolescents of the control group the average level of total calcium was 2.37 ± 0.09 mmol/l (boys) and 2.36 ± 0.08 (girls).

Considering the aim of detecting the effect of vitamin D status on glycemic control of the adolescents with type 1 DM, adolescents were also divided by the stage of compensation of carbohydrate metabolism (HbA1C <7.5% was considered to be compensated stage, 7.5-9% - subcompensated and HbA1C>9% - decompensation of DM). The obtained data are shown in table II.

In the group of vitamin D deficiency (n = 64) decompensation of DM was common: only 23.80% of adolescents had the level of HbA1C <7.5%; 25.39% of the examined had subcompensation of the disease (HbA1C - 7.6 -9.0%) and 50.81% of adolescents had decompensation of carbohydrate metabolism (HbA1C > 9%). In the group of insufficiency of vitamin D compensation of the disease had only 20.83% of children, while 79.17% of surveyed were sub - or decompensated.

The average level of vitamin D was significantly lower in the group of vitamin D deficiency among adolescents with HbA1C 7.5-9%, compared to adolescents whose HbA1C was> 9% (25.27 and 22.16 ng / ml, respectively) (p = 0.02).

DISCUSSION

The results of our study are close to the data of numerous scientific studies according the prevalence of vitamin D deficiency and insufficiency in children with type 1 DM. Thus, according to an American study concerning vitamin D status among children and adolescents with type 1 DM (n = 395) 64% of the patients had a serum 25(OH) vitamin D level below 30 ng/ml [15].

Also the attention of scientists is drawn to the levels of vitamin D in healthy adolescents. Thus, a cross-sectional study conducted in Tehran, which enrolled 444 adolescents (mean age 14.34 years), have showed that only 22.41% of participants had normal vitamin D levels (34.2% had vitamin D insufficiency, 43,3% - vitamin D deficiency). Levels of vitamin D, osteocalcin, alkaline phosphatase were significantly higher in boys compared to girls of the same age [16].The prevalence of vitamin D deficiency among healthy girls compared to boys was also confirmed in our study. Another cross-sectional study which was conducted in Kuwait have found that 81.21% of somatically healthy adolescents had vitamin D deficiency, including 39.48% children with severe deficiency of vitamin D. Only 3.6% had a sufficient supply of vitamin D despite the fact of sufficient UV radiation of the participants [17]. In our study 84.85% of the healthy adolescents showed unsatisfactory vitamin D status.

In our study the possible impact of vitamin D deficiency on glycemic control was investigated. Literature data also indicate the dependence of vitamin D levels on the glycemic control of the disease. The results of Italian study, which compared the level of HbA1C with the level of vitamin D in adolescents with type 1 diabetes (n = 141), found that 25(OH)D levels can negatively correlate with the level of HBA1C ($p < 0.001$), as well as with the daily insulin dose ($p < 0.05$). The authors found reliable differences in the levels of vitamin D ($p<0.01$) between the teenagers with different states of metabolic control (HbA1C <7.5%, 7.5-8%,> 8%) [18].

A study conducted by Spanish researchers, which involved 64 children aged 0 to 14 years, with newly diagnosed type 1 diabetes, found a positive correlation between vitamin D levels and blood pH ($r = 0.279$), as well as blood bicarbonate ($r = 0.338$) also. In the analysis of glycemic control in this group of patients, it was found that children with vitamin D levels higher than 30 ng/ml had better glycemic control and glycated hemoglobin levels [19].

As the part of the study we would like to check glycemic changes after vitamin D supplementation of the adolescents with type 1 DM. Recently it was shown that treatment of vitamin D deficiency in patients with DM type 1 can potentially improve the glycemic control [20]. According to a German study it was found that high doses of vitamin D can reduce insulin requirements ($p = 0.003 – 0.039$) and improve the level of glycated hemoglobin in patients with type 1 DM ($p <.001$) [21].

As a summary, we concluded that the results of our study were similar to the data of previous scientific publications regarding the prevalence of vitamin D deficiency and it's possible impact on the glycemic control. Further studies are needed to understand the mechanisms of influence and additional cholecalciferol supplementation in adolescents with type 1 DM.

CONCLUSIONS

1. Vitamin D levels in adolescents with type 1 diabetes mellitus are significantly lower, comparing with healthy adolescents of the same age group.
2. Vitamin D levels among boys with type 1 diabetes mellitus were significantly lower comparing with girls of the same group. The boys of the control group had significantly higher levels of vitamin D in the blood comparing to boys with type 1 diabetes mellitus, $p <0.001$.
3. The majority of adolescents aged 13-18 years with type 1 diabetes mellitus have vitamin D deficiency or insufficiency regardless of the state of glycemic control of the disease. The correlations between vitamin D levels and carbohydrate metabolism in adolescents with type 1 diabetes, as well as the issue of additional supplementation with cholecalciferol should be investigated in the future studies.

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The Authors declare no conflict of interest

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