THE IMPORTANCE OF DETERMINING THE VITAMIN D3 CONCENTRATION IN PATIENTS WITH TYPE 1 DIABETES

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ABSTRACT

Introduction: Many epidemiological studies have shown a connection between vitamin D deficiency and increased incidence of type 1 diabetes. Objective: The aim of this study is to determine the impact of vitamin D levels in children with newly diagnosed type 1 diabetes, taking into account the following parameters: gender, place of residence, positive/negative family history, comorbidities. Respondents and methods: The research was conducted through a retrospective analysis of the medical records of the Children's Disease Clinic of the University Clinical Hospital Mostar. The research included a sample of 30 children diagnosed with type 1 diabetes, treated at the Department of Endocrinology and Metabolic Diseases, Clinic for Children's Diseases, University Clinical Hospital Mostar. Results: The research consisted of 30 participants treated at the Department of Endocrinology and Metabolic Diseases, Clinic fo Children's Disease. The sample consists of 40% (n=12) male respondents and 60% (n=18) female respondents. Slightly more than half of the respondnents, 53.3% (n=16) lived in the city, while the remaining 46.7% (n=14) lived in the countryside. Statistical analysis of the patients with newly diagnosed type 1 diabetes, showed that there were significantly more patients (70%) with positive family history of diabetes mellitus than those with negative. In this study, 26.7% (n=8) patients with newly diagnosed type 1 diabetes had comorbidities, compared to 73.3% patients without comorbidities (n=22). Patients living in rural areas had significantly higher values of vitamin D3 concentration compared do those who lived in urban areas. Conclusion: 83.3% of subjects with newly diagnosed type 1 diabetes have a reduced level of vitamin D at the time of diagnosis. Numerous studies have shown a link between vitamin D deficiency and an increased risk of developing diabetes. Due to all of the above, supplementation and control of vitamin D is recommended, especially in children who have a risk in the form of positive family history and comorbidities such as Hashimoto's thyroiditis, and celiac disease from an early age for the purpose of prevention.

Keywords: Vitamin D, diabetes mellitus type 1, children

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INTRODUCTION

Numerous epidemiological studies have shown a connection between vitamin D deficiency and increased incidence of type 1 diabetes. According to some studies, the incidence of this disease is reduced by supplementing vitamin D in early childhood (1). Vitamin D is a prohormone with several active metabolites that act as hormones. It has two main forms: D2 (ergocalciferol) and D3 (cholecalciferol). Vitamin D3 is metabolized in the liver into 25(OH)D, which is then converted into 1,25(OH)2D (1,25-dihydroxycholecalciferol, calcitriol, or active vitamin D hormone) in the kidneys. The main circulating form, 25(OH)D, has some metabolic activity, but the most metabolically active is 1,25(OH)2D. The conversion to 1,25(OH)2D is controlled by its own concentration, parathyroid hormone (PTH) and serum Ca and phosphate concentrations (2,3). The effect of vitamin D on genes is mediated by the Vitamin D Receptor (VDR) (5). Vitamin D Receptor binds to DNA as VDR/VDR homodimers or VDR/RXR heterodimers in order to regulate gene expression. Dimers are subsequently recognized and bind to transcription factor IIB (TFIIB) (4,5). This complex then binds to the Vitamin D response element (VDRE), i.e. the promoter region of target genes on DNA and leads to transcriptional suppression or activation of genes regulated by vitamin D (6). Polymorphisms in the VDR gene are associated with health conditions that include diabetes mellitus (DM), low bone density, cardiovascular disease, cancer, autoimmune reactions, and infections (7). The indicator of vitamin D status in the body is the concentration of 25-OH D. The half-life of 25-OH D in the bloodstream is 2 weeks (14). Although recommended blood concentrations are not fully agreed upon, it is considered that a concentration lower than 75 nmol/L (30 ng/L) indicates a deficiency or insufficiency (hypovitaminosis D). Concentrations lower than 50 nmol/L (20 ng/mL) indicate vitamin D deficiency or insufficiency. In general, experts agree that 25-OH D concentrations of 75 to 100 nmol/L are desirable in the population, and those lower than 50 nmol /L are insufficient for the health of the musculoskeletal system. Excess vitamin D (hypervitaminosis D) is considered when the concentration of 25-OH D is higher than 250 nmol/L and with hypercalcemia. Toxic effects are observed at concentrations of 25-OH D > 375 nmol/L in the blood (11,12). Diabetes mellitus is the most common metabolic disease of multiple etiology, characterized by chronic hyperglycemia with a disturbance in the metabolism of carbohydrates, fats, and proteins, which occurs when the pancreas completely or partially stops producing insulin (15,16). Type 1 diabetes is suspected if the following symptoms are expressed: increased thirst and urination, itching and recurrent bacterial or fungal infections on the skin, buccal mucosa, gingiva, urinary system or external genitalia, increased hunger, weight loss, fatigue and drowsiness, and in more severe conditions, weakness, disturbance of consciousness or coma (17,18). The World Health Organization classifies diabetes into type 1

(formerly "insulin-dependent"), type 2 (formerly "insulin-independent"), other specific types, and gestational diabetes (18).

Diabetes mellitus type 1 is caused by the autoimmune destruction of pancreatic beta cells, which leads to a complete lack of insulin, and insulin replacement is necessary (16,19). Type 1 diabetes is usually more often detected in childhood or adolescence (15). Diabetes mellitus type 2 is caused by tissue insensitivity (resistance) to insulin (16). Gestational diabetes is diabetes that is diagnosed during pregnancy (16,17). According to some studies, vitamin D has an effect on the prevalence of type 1 diabetes. Supplementation of vitamin D in the diet is associated with a reduced risk of type 1 diabetes. Providing adequate vitamin D supplementation to infants could help reverse the trend of increasing incidence of type 1 diabetes (19, 20).

The main goal of this research is to determine the concentration of vitamin D in children with newly diagnosed type 1 diabetes. The specific goal of this study was to examine the influence of vitamin D taking into account the following parameters: gender, place of residence, positive/negative family history, and vitamin D concentration at the time of disease detection.

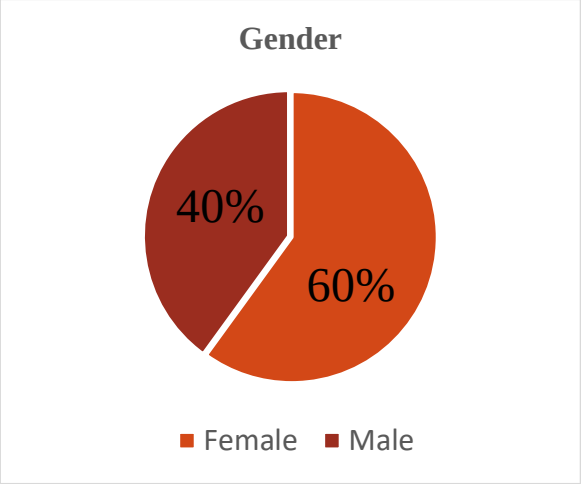
RESPONDENTS AND METHODS

This retrospective study was conducted at the Department of Endocrinology and Metabolic Diseases of the Children's Clinic in the University Clinical Hospital Mostar. The participants were children aged 0-18 living in three counties of Bosnia and Herzegovina (Herzegovina-Neretva County, West-Herzegovina County, and Herceg-Bosnia County) that were hospitalized at the Children's Clinic. Using medical history and other available medical documentation the following results were analyzed: gender, place of residence, family history, comorbidities, and vitamin D concentration at the time of diagnosis. The status of vitamin D in the body was determined by measuring the concentration of 25-hydroxy vitamin D (25-OH D) in the blood. Reference values are 75 nmol/L – 100 nmol/L. The serum levels lower than 50 nmol/L represents vitamin D deficiency, the levels between 50-75 nmol/L insufficiency, and levels greater than 100 nmol/L vitamin D sufficiency (11). Vitamin D values were determined by the electrochemiluminescence (ECLIA) method on the Roche's Cobas 601 analyzer in the University Clinical Hospital Mostar laboratory. Statistical processing of the collected data was done with the computer program SPSS 10.0 (SPSS for Windows, SPSS Inc. Chicago IL, USA). Data were processed using descriptive statistics methods, where categorical variables were presented as frequency and percentage and graphically, while continuous variables were presented through arithmetic mean and standard deviation. The comparison of frequencies for categorical variables was determined by the Chi-square test, while the differences in the values of continuous variables for independent samples were examined using the t-test. The Shapiro-Wilk test was used to test the normality of the distribution of a continuous variable. The level of

statistical significance in the paper is 5% with a confidence of 95%.

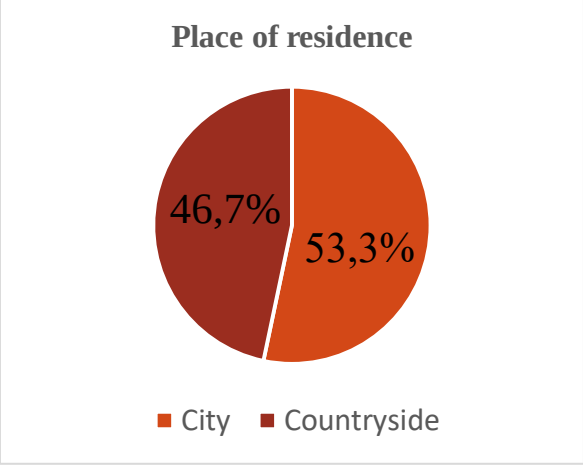
THE RESULTS

This study included 30 participants under the age of 18, of which 40% (n=12) were male and 60% (n=18) were female (Picture 1).



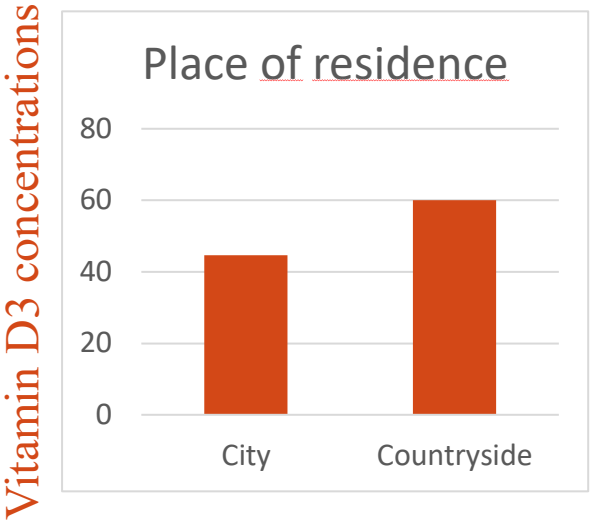
Picture 1. Graphic presentation of participants by gender (n=30).

Slightly more than half of participants, 53.3% (n=16) of them lived in the city, while the remaining 46.7% (n=14) lived in the countryside (Picture 2).



Picture 2. Graphic presentation of participants by the place of residence (n=30).

Using the Student t-test for independent samples, it was determined that there are statistically significant differences in vitamin D3 concentrations with regard to the place of residence, that is, whether the patient lives in the countryside or in the city. Patients living in rural areas had significantly higher values of vitamin D3 concentration (Picture 3).



Picture 3. Mean values of vitamin D3 concentration with regard to the patient's place of residence (n=30).

In this study there were statistically more patients without an associated disease compared to those with some comorbidity (Chi-square test, Table 1). 26.7% (n=8) patients with newly diagnosed type 1 diabetes had comorbidities, of which one had two and one had three comorbidities compared to 73,3% patients without comorbidities (n=22).

Table 1. Differences in the frequency of comorbidities in patients with newly diagnosed type 1 diabetes (n=30)

Comorbidities	N	X^2	df	p
Yes	8	6,533	1	<0,05
No	22			

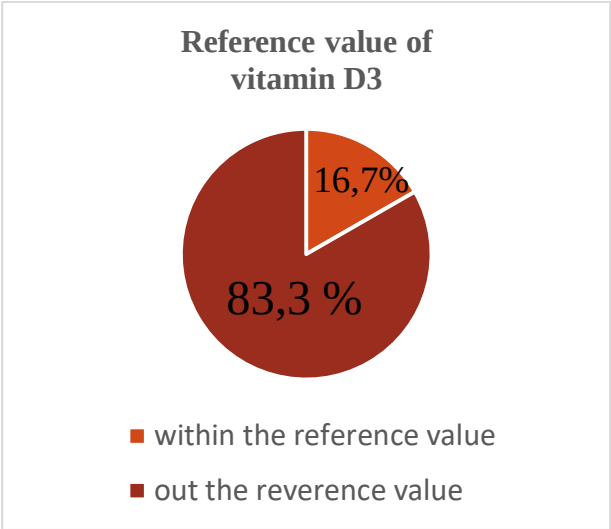
Table 2. Distribution of comorbidities in patients with newly diagnosed type 1 diabetes (n=8)

Comorbidities	f	%
Hashimoto's	5	45,4
Hypovitaminosis	2	18,2
Hypercholesterolemia	2	18,2
Hyperthyroidism	1	9,1
Hypothyroidism	1	9,1

The Shapiro-Wilk test determined that the distribution of vitamin D3 concentration results deviates statistically significantly from normal (S-W=0.922, df=12, p>0.05), which justifies the use of parametric methods of statistical data processing in further processing.

The minimum value of vitamin D3 concentration in patients from this study was 25.6 nmol/L. and the maximum was 94.6 nmol/L, while the average value was 51.84 (Sd=18.54).

The Picture 4 shows the distribution of patients with regard to whether their vitamin D3 concentration is within the reference values, and it was determined that the majority of patients, 83,3% (n=25) of them, have a vitamin D3 concentration value outside the reference values, while only 16,7% (n=5) of them have a normal vitamin D3 value, or from 75 to 100 nmol/L.



Picture 4. Distribution of patients with newly diagnosed type 1 diabetes with regard to the concentration of vitamin D3 (n=30).

DISCUSSION

Numerous previosus studies shows that vitamin D deficiency is associated with a higher incidence of diabetes. This study analyzed the influence of vitamin D concentration in patients with newly diagnosed type 1 diabetes, taking into account the following parameters: gender, place of residence, positive or negative family history, comorbidities, and the concentration of vitamin D measured at the time of diagnosis.

In this study, 26.7% patients with newly diagnosed type 1 diabetes had comorbidities, 5% of them had Hashimoto's thyroiditis, so we can confirm the close connection between these two diseases. This result is in corellation with recent meta-analysis of all available data in 10,920 patients with DM revealed a mean incidence of thyroid disease of 11%. A large pediatric diabetes center in Germany that recruited 495 patients with

T1DM described an additional rapid increase in the prevalence of thyroid antibodies with age, rising from 3.5% in patients younger than 5 years to 25.3% in those between 15 years of age. and 20 years (22). Radetti and al. showed a close connection between these two autoimmune diseases. Thyroid disorders remain the most common autoimmune disorders associated with type 1 diabetes. This was shown in a cross-sectional study involving 1419 children with type 1 diabetes, where 3.5% had Hashimoto's thyroiditis (23). When we talk about family anamnesis, among patients with newly diagnosed type 1 diabetes, there are significantly more patients with a positive family anamnesis than patients with a negative anamnesis, even 70% of them.

The question arises whether vitamin D participates in the etiology and pathogenesis of the disease. The results of our study showed that 83.3% of subjects had a lower concentration of vitamin D at the time of disease detection. The study, which was conducted in Olu and Lapland, northern Finland, collected data in the first year of life on the frequency and dose of vitamin D supplementation in children born in 1996. Of the 10,366 children included in the analyses, 81 were diagnosed with diabetes during the study. Vitamin D supplementation was associated with a reduced incidence of type 1 diabetes. This study confirmed that supplementing with dietary vitamin D reduces the risk of type 1 diabetes. Providing adequate vitamin D supplementation to infants could help reverse the trend toward increased incidence of type 1 diabetes. (24). Research carried out in Germany proved the association of vitamin D with diabetes mellitus type 1. The vitamin D system is associated with type 1 diabetes by epidemiological studies and studies of immune intervention as well as polymorphisms of the vitamin D binding gene (9). A study conducted by Tangjittipokin W et al, indicating the association between vitamin D and diabetes mellitus type 1, the study was conducted among 100 T1D children and 100 control groups. Relationships between T1D polymorphism and CYP2R1 and VDR haplotypes were found (25). Vitamin D-related gene variations are associated with vitamin D and circulating cytokine levels in children with T1D (25). A meta-analysis and reference lists of retrieved articles investigated the impact of vitamin D. The analysis included controlled trials and observational studies that evaluated the effect of vitamin D supplementation on the risk of developing type 2 diabetes. 1. Vitamin D supplementation in early childhood may provide protection against the development of type 1 diabetes studies (26). Research conducted by Hussein AG et al showed that the GG genotype of the CYP2R1 polymorphism and/or the CC genotype of the CYP27B1 polymorphism increases the risk of developing type 1 diabetes in Egyptian children (8). Research conducted by Nam HK et al has shown that polymorphisms in vitamin D metabolism may contribute to the susceptibility to type 1 diabetes in Korean children (10). According to American recommendations, infants and children should receive between 5 μg/day and 255 μg/day of additional vitamin D, especially if they have

limited sun exposure, live in northern areas, are exclusively breastfed, or have dark skin (27). Our research found that children who had vitamin D values within the reference values, 46.7% of them, live in the countryside. The question arises whether the place of residence, a different way of eating, and lifestyle have an influence in relation to rural and urban environments. However, no adequate evidence was found for this comparison.

CONCLUSION

The main goal of this research was to determine the influence of vitamin D concentration in children diagnosed with type 1 diabetes, taking into account the following parameters: gender, place of residence, negative or positive family history, comorbidities, and vitamin D concentration at the time of diagnosis. The research was conducted at the Department of Endocrinology and Metabolic Diseases of the Clinic for Children's Diseases, SKB Mostar. Since a lot of research supports the opinion that vitamin D can have a beneficial effect on the prevention of type 1 diabetes mellitus, it is important to determine the status of vitamin D and to start compensation in time if it is needed. Finally, it is important to note some facts, the research was conducted on a sample of 30 respondents, and the vitamin concentration was recorded at only one point in time. However, epidemiological evidence and observational studies suggesting that adequate vitamin D status is associated with a reduced risk of developing type 1 diabetes further support the concept of this research paper.

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ZNAČAJ ODREĐIVANJA KONCENTRACIJE VITAMINA D3 U BOLESNIKA SA ŠEĆERNOM BOLESTI TIP 1

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SAŽETAK

Uvod: Mnoga epidemiološka istraživanja pokazala su povezanost između nedostatka vitamina D i povećane incidencije dijabetesa tipa 1. Cilj: Cilj ovog istraživanja je utvrditi utjecaj vitamina D kod djece s novootkrivenom šećernom bolesti tip 1, uzimajući u obzir sljedeće parametre: spol, mjesto stanovanja, pozitivna/negativna obiteljska anamneza, pridružene bolesti te koncentracija vitamina D u trenutku otkrivanja bolesti. Ispitanici i metode: Istraživanje je provedeno retrospektivnom analizom medicinske dokumentacije pismohrane Klinike za dječje bolesti SKB Mostar. Istraživanjem je obuhvaćen uzorak od 30 djece s dijagnozom šećerne bolesti tip 1, liječenih na Odsjeku za endokrinologiju i bolesti metabolizma Klinike za dječje bolesti Sveučilišne kliničke bolnice Mostar. Rezultati: U istraživanju je sudjelovalo 30 ispitanika liječenih na Odsjeku za endokrinologiju i bolesti metabolizma. Uzorak sačinjava 40% (n=12) ispitanika muškog spola, a 60% (n=18) ispitanika ženskog spola. Nešto više od polovice ispitanika, odnosno njih 53,3% (n=16) je živjelo u gradu, dok je preostalih 46,7% (n=14) živjelo na selu. Statističkom obradom podataka se utvrdilo da među bolesnicima s novootkrivenom šećernom bolesti tip 1 značajno je više onih koji imaju pozitivnu obiteljsku anamnezu od bolesnika s negativnom anamnezom. Ispitanika s pozitivnom obiteljskom anamnezom je bilo 70%, dok je njih samo 30% imalo negativnu anamnezu. U ovom istraživanju je 26,7% (n=8) bolesnika s novootkrivenom šećernom bolesti tip 1 imalo pridružene bolesti, u odnosu na 73,3% bolesnika bez pridruženih bolesti (n=22). Bolesnici koji žive na selu imaju značajno veće vrijednosti koncentracije vitamina D3 u odnosu na one koji žive u gradu. Zaključak: 83,3% ispitanika s novootkrivenom šećernom bolesti tip 1 ima sniženu razinu vitamina D u trenutku otkrivanja bolesti. Brojne su studije pokazale poveznicu između nedostatka vitamina D i povećanog rizika za nastanak dijabetesa. Zbog svega navedenog preporučuje se nadoknada i kontrola vitamina D, osobito kod djece koja imaju rizik u vidu pozitivne obiteljske anamneze te pridruženih bolesti kao što je Hashimotov tireoiditis, celijakija od najranije dobi u svrhu prevencije.

Ključne riječi: Vitamin D, diabetes mellitus tip 1, šećerna bolest, djeca

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