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Araştırma / *Research Article*

Significant Vitamin D Deficiency in Children and Adolescents With Type 1 Diabetes Mellitus: A Cross- Sectional Study

Didem Gülcü Taşkın
Hasan Önal
Atilla Ersen
Erdal Adal

Tip 1 Diabetes Mellituslu Çocuk ve Ergenlerde Anlamlı D Vitamini Eksikliği: Kesitsel Bir Çalışma

ABSTRACT

Objective: *Considering the fact that individuals with type 1 diabetes mellitus (T1DM) have multiple risk factors, vitamin D sufficiency in childhood in this population is of particular concern. The aim of this study is to assess vitamin D status of T1DM patients in childhood with respect to their age groups.*
Method: *A total of 212 type 1 diabetic children between ages of 1.5-18 years were screened for serum 25-hydroxyvitamin D [25(OH)D] levels from 29 December 2009 to 13 April 2010. Four age groups were copnstructed [<5 years (n: 13), 5-11 years (n: 66), 11-14 years (n: 65), >14 years (n: 68)], and those groups were compared according to 25(OH)D status. Vitamin D sufficiency, insufficiency, and deficiency were defined as 25(OH)D ≥30 ng/mL, 21-29 ng/mL, and ≤20 ng/mL, respectively. Body mass index of patients, HbA1c levels and daily insulin doses were recorded.*
Results: *Vitamin D sufficiency rate was 34.9%, and deficiency rate was 42,9%. Vitamin D levels significantly decreased iwith aging; only 16.2% of >14 year-old patients had 25(OH)D levels of >30 ng/mL.*
Conclusion: *We found that vitamin D deficiency is prevalent among type 1 diabetic children in our study, and especially adolescent diabetic patients were of special concern. Future studies are needed to verify our data and for a possible supplementation regimen for these patients.*

Keywords: *Type 1 Diabetes mellitus, vitamin D, childhood*

ÖZ

Amaç: *Tip 1 diabetes mellitus (T1DM) hastası bireylerin çoklu risk faktörlerine sahip olduğu gerçeği göz önüne alındığında, bu popülasyondaki D vitamini yeterliliğinin çocukluk çağında özel bir önemi vardır. Bu çalışmanın amacı, çocukluk çağındaki T1DM hastalarının vitamin D durumunu yaş grupları göz önüne alınarak değerlendirmektir.*
Yöntem: *1,5-18 yaşları arasındaki toplam 212 diyabetik çocuk 29 Aralık 2009 ila 13 Nisan 2010 tarihleri arasında serum 25-hidroksivitamin D [25(OH)D] seviyeleri için tarandı. Yaş gruplarına göre dört grup oluşturuldu [<5 yaş (n: 13), 5-11 yaş (n: 66), 11-14 yaş (n: 65), >14 yaş (n: 68)] ve bu gruplar 25(OH)D durumuna göre karşılaştırıldı. D vitamini yeterliliği, yetersizliği ve eksikliği sırasıyla 25 (OH) D ≥30 ng/mL, 21-29 ng/mL ve ≤20 ng/mL olarak tanımlandı. Hastaların vücut kitle indeksi, HbA1c düzeyleri ve günlük insülin dozları kaydedildi.*
Bulgular: *D vitamini yeterlilik oranı% 34,9, eksiklik oranı% 42,9 idi. Yaş ilerledikçe D vitamini düzeyi önemli ölçüde azaldı; > 14 yaşındaki hastaların yalnızca % 16,2'sinde 25 (OH) D> 30 ng/mL idi.*
Sonuç: *Çalışmamızda, D vitamini eksikliğinin Tip 1 diyabetik çocuklarda yaygın olduğunu bulduk ve özellikle ergen diyabetic hastalarda daha dikkat çekici idi. Verilerimizi doğrulamak ve bu hastalar için olası bir takviye rejimini için ileri çalışmalara gereksinim vardır.*

Anahtar kelimeler: *Tip 1 diyabet, D vitamini, çocukluk çağı*

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Hasan Önal
S.B.Ü. Kanuni Sultan Süleyman Eğitim ve Araştırma Hastanesi, Pediatrik Endokrinoloji ve Metabolizma Kliniği
İstanbul - Türkiye
hasanonal@hotmail.com
ORCİD: 0000-0001-9676-7086

D. Gülcü Taşkın 0000-0002-2746-3799
S.B.Ü. Kanuni Sultan Süleyman Eğitim ve Araştırma Hastanesi Pediatri Kliniği İstanbul - Türkiye

A. Ersen 0000-0002-2404-170X
S.B.Ü. Okmeydanı Eğitim ve Araştırma Hastanesi, Pediatri Kliniği İstanbul - Türkiye

E. Adal 0000-0003-4930-8447
S.B.Ü. Kanuni Sultan Süleyman Eğitim ve Araştırma Hastanesi, Pediatrik Endokrinoloji ve Metabolizma Kliniği İstanbul - Türkiye

INTRODUCTION

Vitamin D insufficiency constitutes a largely unrecognized epidemic in Turkey. Given the negative impact of vitamin D insufficiency and type 1 diabetes mellitus (T1DM) on prognosis, vitamin D status seems to be a critical issue throughout childhood in diabetic population.

Type 1 diabetes mellitus has been widely declared to result from the autoimmune destruction of insulin-producing β cells in the pancreas. Genetic and, as yet undefined, environmental factors act together to precipitate the disease [1]. Vitamin D, besides displaying effects in calcium and bone metabolism, has potent effects on cell proliferation, differentiation and immune system via receptors [2]. Recent evidence suggests a role for vitamin D in the pathogenesis and prevention of diabetes mellitus [2]. Actually, vitamin D deficiency predisposes individuals to type 1 and type 2 diabetes, and receptors for its activated form "1α,25-dihydroxyvitamin D3" have been identified in both beta cells and immune cells [4]. Some authors have proposed that vitamin D involves in the development of T1DM due to its modulation of immune system [5]. Vitamin D upregulates tolerogenic dendritic lymphocytes, whose roles include moderation of the autoimmune response [6]. Low serum levels of 25-hydroxyvitamin D [25(OH)D] are associated with a deficit of tolerogenic lymphocytes, allowing a more intense and protracted attack of killer T-lymphocytes on pancreatic islet cells [6,7].

Besides, results of vitamin D intervention studies on diabetes are still equivocal. Some biological evidence has speculated a potential influence of vitamin D on glucose homeostasis. Vitamin D exerts its effects on the presence of specific vitamin D receptors on pancreatic β-cells, expression of 1-α-hydroxylase enzyme in pancreatic β-cells. The presence of a vitamin D response element in the human insulin gene promoter, stimulates expression of insulin receptor, and enhances insulin-mediated in vitro glucose transport [8,14].

Furthermore, low vitamin D levels also seem to be a predictive value in foreseeing macrovasculer complications of diabetic patients [15,16]. This interference may be related to the effects of vitamin D on renin–angiotensin system, blood pressure, endothelial function, vascular endothelial growth factor and chronic inflammation [17-20].

Taking all these data collectively, although contradictory investigations also present, vitamin D status seems to be a significant concern in diabetic population in both progression and prognosis of T1DM. Up to date, studies examining vitamin D insufficiency in childhood with T1DM have been somewhat limited in our country. We herein aimed to evaluate vitamin D status and highlighted vitamin D deficiency in type 1 diabetic children due to a global concern in Turkey.

MATERIAL and METHODS

The population of this cross-sectional study consisted of 212 outpatient pediatric patients (51.9% female, 48.1% male) diagnosed with T1DM between ages of 1.5-18 years. They were investigated by screening serum 25(OH)D values from December 29, 2009 to April 13, 2010 in the Pediatric Endocrinology and Diabetes Department of the Ministry of Health Bakırköy Maternity and Children Research and Training Hospital. Four age groups were constituted : <5 years (n: 13), 5-11 years (n: 66), 11-14 years (n: 65), >14 years (n: 68).

The patients using medication for any other disorder, and individuals who had diagnosis of rickets or any chronic diseases such as neurological, cardiac, renal, or hepatic disorders were excluded from our study. Use of an anticonvulsant therapy was also an exclusion criterion. The study protocol was approved by the Ethics and Research Committee of the Ministry of Health Bakırköy Maternity and Children Research and Training Hospital and written informed consent was obtained from every participant.

Blood samples were obtained from all individuals for the measurement of 25(OH)D levels. Samples were stored at -70 C until analyzed and 25(OH)D values were measured using Biosource RIA kit International (Netherlands). The limit values of the kit for 25(OH)D ranged from 7.5 to 75 pg/mL. Since reports have shown seasonal changes in plasma vitamin D levels in individuals, dependent on season-related duration of exposure to sunshine per day, we conducted our

study in a limited period to minimize the seasonal effect on vitamin D status. Vitamin D sufficiency, insufficiency, and deficiency were defined based on 25(OH)D levels as ≥30 ng/mL, 21-29 ng/mL, and ≤20 ng/mL, respectively [21-23].

Median hemoglobin A1c (HbA1c) levels in the previous year, body mass indexes (BMIs) and daily insulin doses in all the individuals were recorded. Serum HbA1c levels were analyzed by Cobas Integra 400 device and normal reference values ranged between 4.5, and 6 percent.

Statistical significance was assessed for discrete variables by X2 analysis and for continuous variables by ANOVA, as appropriate. Qualitative variables were summarized as numbers and percentages. Correlations between the measured variables in each group were analyzed using Pearson's correlation method. Logistic regression analysis was performed for risk analysis between the groups. Statistical significance was set at p-value < 0.05.

RESULTS

The study group was composed of 212 T1DM patients (51.9% female, 48.1% male) between ages of 1.5-18 years. Mean BMI of the patients (28.6±7.5 kg/m^2), duration of diabetes (45.54±38.9 months), HbA1c level (8.92±2) and daily insulin dose (0.86±0.27 U/kg) were determined.

Vitamin D sufficiency, insufficiency, and deficiency rates were 34.9%, 22.2% and 42.9% respectively. We found significantly decreased median levels of 25(OH)D in regards to age groups with aging. Respective percentages of patients had 25(OH)D>30 ng/mL levels as follows: <5 years :53,8%; 5-11 years, 47% ; 11-14 years: 38.5% ; and > 14 years : 16.2%. We found a negative correlation between only BMI and age (r=-0.29, p: 0.01 r=0.32, p: 0.03) with vitamin D levels rather than HbA1c, daily insulin dose and gender. Although daily insulin doses didn't differ, serum HbA1c levels were statistically significantly different between age groups (Table 1).

Odds ratio was 3.43 in late adolescent period in evaluation of risk factors for vitamin D deficiency (≤ 20 ng/ml). Odds ratio was 0.36 for vitamin D deficiency in comparison of females to males (Table 2). Odds ratio was 0.15 in females to males for vitamin D deficiency in late adolescent group (Table 3).

Table 1. Comparison of diabetic patients in regards to age groups.

Age group	<5 years	5-11 years	11-14 years	>14 years	p
Number	13	66	65	68	0,75
Gender					
Male (n)	5	13	29	35	
Female (n)	8	33	36	33	
Median age	3,28±1,1	8,48±1,5	12,7±0,8	15,83±1	0,001
Vitamin D level					
≤ 20 ng/ml	15,4%	37,9%	29,2%	66,2%	
21-29 ng/ml	30,8%	15,2%	32,3%	17,6%	
≥30 ng/ml	53,8%	47,0%	38,5%	16,2%	
Hb A1c	9,41±2,2	8,39±1,8	9,43±2,1	8,84±2,0	0,028
Insulin (IU/kg/day)	0,74±0,1	0,81±0,3	0,89±0,2	0,91±0,2	0,073

Table 2. Logistic regression analysis for risk factors of hypovitaminosis D in whole group.

	B (SE)	OR	C.I. 95 %	p
Age of diagnosis	0,086 (0,08)	1,08	0,92-1,28	0,31
Duration of diagnosis	0,012 (0,008)	1,01	0,99-1,07	0,13
BMI	-0,019 (0,03)	0,98	0,91-1,05	0,60
Gender	-1,00 (0,33)	0,36	0,19-0,70	0,002
Age (late adolescent)	1,23 (0,47)	3,43	1,34-8,75	0,01
HbA1c	-0,028 (0,07)	0,97	0,83-1,27	0,71
Insulin (IU/kg/day)	-0,37 (0,61)	0,68	0,20-2,30	0,54

C.I. coefficient interval, OR; Odds ration Hosmer and Lemeshow test p=0,8

Table 3. Logistic regression analysis for risk factors of hypovitaminosis D in late adolescent group.

	B (SE)	OR	C.I. 95 %	p
Age of diagnosis	0,205 (0,26)	1,22	0,73-2,06	0,43
Duration of diagnosis	0,018 (0,02)	1,01	0,97-1,06	0,43
BMI	0,016 (0,06)	1,01	0,89-1,15	0,80
Gender	-1,86 (0,64)	0,15	0,04-0,54	0,004
HbA1c	0,079 (0,13)	1,08	0,83-1,41	0,56
Insulin (IU/kg/day)	0,69 (1,18)	1,99	0,19-20,5	0,56

C.I.; coefficient interval, OR; Odds ration, Hosmer and Lemeshow test p=0,7

DISCUSSION

Vitamin D deficiency and diabetes mellitus are currently two common conditions of intense interest, since they are widely prevalent across all ages and there may be possible interactions between these diseases in regard to etiology or prognosis.

The rates of vitamin D deficiency in T1DM patients vary in a large range from 15% to 90.6 % in different studies [24-27]. Tunc et al. [28] found the rates of 28% for deficiency, 43% for insufficiency and 29% for normal levels of vitamin D in diabetic adolescents in Turkish population. In another study from Turkey, Mutlu et al. [29] found the rate of 21.7% for vitamin D deficiency in type 1 diabetic patients. Our data also verified vitamin D deficiency with the rate of 42.9% and insufficiency of 22.2% in our study group, but only 34.9% of our T1DM adolescents had normal levels of vitamin D. Besides, differences between these studies may depend on season, BMI, gender or age ranges of individuals. Notably, we found the median levels of 25(OH)D were significantly decreased in regards to age groups with aging; 53.8% of cases aged <5 years, %47 of cases aged 5-11 years, %38,5 of cases aged 11-14 years and %16,2 of cases aged >14 years had 25(OH)D levels of >30 ng/mL. It was interesting to observe that late adolescent period was the most risky group about vitamin D deficiency and female gender in this period had higher risk than males in our study group.

It has been hypothesized that vitamin D may have a therapeutic role in T1DM via its immune-modulatory properties, thereby contributing favourably to the pathogenesis of T1DM. But, questions persist about the optimal level of 25 (OH)D to prevent the risk of developing diabetes mellitus. However, whether vitamin D may influence secretion and mechanism of action of insulin is a controversial issue. Although some studies found no association between serum 25(OH) D levels and parameters of insulin mechanism of action, others have shown positive the presence of associations [30]. Svoren et al [24] found an association between metabolic control of T1DM and vitamin D level. From Turkey, Tunc et al. [28] proposed a weak correlation between daily insulin needs and serum vitamin D levels, but Mutlu et al. [29] didn't find any correlation between both HbA1c and insulin doses and serum vitamin D levels. Actually observational studies support a potential role of vitamin D in the pathogenesis or morbidity of T1DM, but larger-scale prospective randomized control studies are not available to support the therapeutic role of vitamin D in preventing or postponing the disease [30-33]. In our study group, we didn't find any association between HbA1c and daily insulin dose with vitamin D levels in regards to age, duration of disease, BMI and gender; even in the late adolescents with the vitamin D deficiency rate was higher.

We herein have showed that vitamin D deficiency was prevalent in our T1DM patients and especially late adolescency deserved a special concern. Critical questions are a) 'which level should be considered as optimal level of 25(OH)D in T1DM, b) whether supplementation with vitamin D or its analogs have a therapeutic role in prevention or treatment of T1DM, and this supplementation is presently needed or not? Larger-scale long-term clinical trials are needed to clarify these issues.

Ethics Committee Approval: The study protocol was approved by the Ethics and Research Committee of the Ministry of Health Bakırköy Maternity and Children Research and Training Hospital (296/2010-10.15-296).
Conflict of Interest: None.

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Informed Consent: Approvals are available for all patients in our article.

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