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ORIGINAL ARTICLE

Vitamin D Level of Children with Diabetic Ketoacidosis in Pediatric Intensive Care Unit

Pediatrik Yoğun Bakım Ünitesindeki Diyabetik Ketoasidozlu Çocukların D Vitamini Düzeylerinin Değerlendirilmesi

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ABSTRACT

Aims: Vitamin D deficiency is a risk factor for autoimmune diseases such as diabetes mellitus. This study aimed to investigate the association between diabetic ketoacidosis (DKA) and vitamin D levels and the impact of vitamin D on the duration of DKA and pediatric intensive care unit length of stay in Turkish pediatric patients.
Methods: The study was a retrospective study conducted between January 2014 and March 2018. The study population was children younger than 18 years old admitted to the pediatric intensive care unit (PICU) with DKA.
Results: The study included 130 patients, 51.5%(n=67) of whom were females. We found vitamin D deficiency in 39.2% (n=51) and vitamin D insufficiency in 33.1% (n=43) of the patients. Most of the patients with severe acidosis had low vitamin D levels (44/59) and % 45.8 of them (27/59) had vitamin D deficiency. Duration of diabetic ketoacidosis, length of pediatric intensive care unit stay, and hospitalization stay were longer in patients with low vitamin D levels but not statistically significant (?).
Conclusions: This study is the first study evaluating the association between vitamin D and diabetic ketoacidosis in Turkey. Although there is no association between vitamin D deficiency and the duration of diabetic ketoacidosis and the severity of acidosis, vitamin D deficiency is substantially common in patients with diabetic ketoacidosis.

Keywords: Child; diabetic ketoacidosis; diabetes mellitus; intensive care unit; pediatrics; vitamin D;

ÖZ

Amaç: Vitamin D eksikliği, diabetes mellitus gibi otoimmün hastalıkların gelişimi için bir risk faktörüdür. Bu çalışma, çocuk hastalarda Diyabetik ketoasidoz (DKA) ile serum D vitamini düzeyleri arasındaki ilişkiyi ve D vitamininin DKA süresi ve çocuk yoğun bakım ünitesinde kalış süresine etkisini araştırmayı amaçlamıştır.
Metot: Çalışma, Ocak 2014-Mart 2018 tarihleri arasında yürütülen retrospektif bir çalışmadır. Çalışma popülasyonu DKA tanısı ile çocuk yoğun bakım ünitemizde (ÇYBÜ) takip edilen 18 yaş altı çocuklar oluşturmaktadır.
Bulgular: Çalışmaya 130 hasta dahil edildi ve bunların %51.5'i kızdı. Hastaların %39.2'sinde (n=51) D vitamini eksikliği, %33.1'inde (n=43) D vitamini yetersizliği olduğunu bulundu. Şiddetli asidozlu hastaların çoğunda D vitamini düzeyi düşük (44/59) ve % 45.8'inde (27/59) D vitamini eksikliği vardı. D vitamini düzeyi düşük olan hastalarda diyabetik ketoasidoz süresi, pediatrik yoğun bakımda kalış süresi ve hastanede kalış süresi daha uzundu ancak istatistiksel olarak anlamlı değildi.
Sonuç: Bu çalışma, Türkiye'de D vitamini ile diyabetik ketoasidoz ilişkisini değerlendiren ilk çalışmadır. D vitamini eksikliği ile diyabetik ketoasidoz süresi ve asidozun şiddeti arasında bir ilişki olmamasına rağmen, diyabetik ketoasidozlu hastalarda D vitamini eksikliği oldukça yaygındır.

Anahtar kelimeler: çocuk; diyabetik ketoasidoz; diabetes mellitus; pediatri; vitamin D düzeyi; yoğun bakım ünitesi

Introduction

Type 1 diabetes mellitus (T1DM), is an autoimmune disease characterized by hyperglycemia resulting from insulin deficiency (1). The incidence and prevalence of type 1 diabetes (T1DM) are increasing worldwide (2). Diabetic ketoacidosis (DKA) is an acute, life-threatening complication of diabetes mellitus that causes mortality and morbidity in children (3). Vitamin D level is associated with the risk of multiple autoimmune diseases such as multiple sclerosis, T1DM, and systemic lupus erythematosus (4). Vitamin D deficiency impairs beta-cell function, leading to glucose intolerance and predisposition to type 1 and 2 diabetes (5, 6). Supplementation of vitamin D in early childhood reduces the risk of developing T1DM (7, 8). Studies show that vitamin D deficiency contributes to the development of DKA and DKA also may reduce vitamin D levels (9-11). There are few studies evaluating vitamin D levels in DKA. This study aimed to investigate the mutual relationship between DKA and serum vitamin D levels and the impact of vitamin D on the duration of DKA and length of stay in the pediatric intensive care unit (PICU) in Turkish pediatric patients.

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Methods

This retrospective study was conducted at the pediatric intensive care unit and pediatric endocrinology departments of an education and training hospital in Ankara. This study was approved by the Institutional Ethics Committee (number E-21/06-196).

Study Design

The study was a retrospective study conducted between January 2014-March 2018. The study population was children younger than 18 years old admitted to our PICU with DKA. The PICU is a 16-bed, multidisciplinary, tertiary referral center in which 650 patients are followed up each year. Patients younger than one month and older than 18 years of age, and those who did not meet the diagnostic criteria for diabetic ketoacidosis (cases only acidosis or hyperglycemia) were excluded from the study. Laboratory data were retrospectively screened from electronic medical reports. Data included gender, age, weight, laboratory findings on admission including serum 25-hydroxyvitamin (25OHD), blood glucose, venous blood gas, serum, and urine ketone level, how many times patients applied to the hospital due to diabetic ketoacidosis (last admission were evaluated), medical management, duration of hospitalization, and medical outcomes. The diagnosis of DKA was made according to the clinical and laboratory results of the patients. DKA criteria are as follows: blood glucose level higher than 200 mg/dL a urine ketone level defined as moderate to large (+ to +++), and a venous pH <7.3 or serum bicarbonate (HCO3) <15 mmol/L (12). The severity of DKA is categorized as mild (venous pH<7.3 and/or HCO3 <15 mmol/L), moderate (venous pH<7.2 and/or HCO3<10 mmol/L), and severe (venous pH<7.1 and/or HCO3<5 mmol/L) according to the degree of acidosis (13).

In our study, Vitamin D status based on serum 25OHD is classified as follows; Vitamin D sufficiency (VDS) 20 to 100 ng/mL (50 to 250 nmol/L), vitamin D insufficiency (VDI) 12 to 20 ng/mL (30 to 50 nmol/L), vitamin D deficiency (VDD) <12 ng/mL (<30 nmol/L) (14).

Statistical Analysis

Statistical analysis was performed with the SPSS statistical package 18.0 version (Chicago, IL, USA). Descriptive statistics were given as mean±standard deviation (SD) or median with interquartile range (IQR); categorical variables were given as values and percentages. The Mann-Whitney U test and Student's test were used respectively to compare two groups of variables not normally distributed and normally distributed. The Pearson chi-square or Fisher's Exact test was used to evaluate categorical data. Correlations between 25OHD vitamin and ketoacidosis were performed by Spearman correlation analysis. A P value of < 0.05 indicated statistical significance.

Results

The study included 130 patients, 63 (48.5%) of them were males and 67 (51.5%) of them were females. The characteristics of the patients were demonstrated in Table 1. Most of the patients had polyuria and polydipsia (82.3%) and half of the patients had weight loss. None of the patients had a symptom of polyphagia. Of the patients, 87.7% (n=114) were newly diagnosed with T1DM. Of the patients, 12.3% (n=16) were previously diagnosed with T1DM. 13 of these patients were admitted to our hospital more than once due to diabetic ketoacidosis.

The vitamin D status of our patients was as follows; 39.2 % (n=51) had vitamin D deficiency (VDD) and 33.1 % (n=43) had vitamin D insufficiency (VDI). Vitamin D levels were sufficient in 27.7% of the patients. 72.3 % of the patients had low 25OHD levels (VDD+VDI).

Duration of acidosis, length of PICU, and hospitalization stay were longer in patients with low 25OHD compared to patients with VDS but were insignificant (respectively, p= 0.321, p=0.0897, and p=0.954). In the low 25OHD group, the mean pH and HCO3 levels were lower than in the VDS group. But these findings were not statistically significant (respectively, p=0.611 and p=0.147) (Table 3). 30 patients (%23.1) had mild acidosis, 41 patients (31.5%) had moderate acidosis, 59 patients (%45.5) had severe acidosis. Most of the patients with severe acidosis had low vitamin D levels (44/59) and % 45.8 of the patients (27/59) had vitamin D deficiency. But the correlation between the level of acidosis and 25OHD was not statistically significant (p= 0.262). Ten of the 13 patients who had DKA more than once were in the low 25OHD group, and 8 of them (8/10) were in the vitamin D deficiency group.

The Glasgow coma scale was similar in the low 25OHD and VDS group (14.8 vs 14.6, p=0,277). The mechanically ventilated two patients were in the vitamin D deficient group. Most of the patients who received HCO3-replacement were in the low 25OHD group (16/18, %60 of the total). The severity of dehydration was similar in two groups (low 25OHD group vs VDS). The patients' characteristics according to their vitamin D levels are demonstrated in Table 2.

Table 1. Patients' characteristics and laboratory variables

	(N %)	
Sex Female Male	67 (51.5%) 63 (48.5%	
	Mean (±standard deviation)	Median (IQR)
Age	10.6±4.7	11 (6-15)
Weight	29.8 ±15.8	
pH	7.07±0.14	7.1 (6.9- 7.19)
HCO_3 level, mmol/l	8.6 ±3.3	8.4 (6-11)
Lactate mg/dl	14.2 ± 6.6	13 (10-17.3)
25 (OH)D3 ng/ml	16.6 ± 9.9.8	14.4 (8.6-20.7)
Duration of acidosis (hours)	15..4 ± 11.1	14.5 (10.7-20)
Length of PICU stay (hours)	23.8 ±16.8	21 (16-27)
Length of hospitalization (days)	16.9 ± 5.8	17 (15-20)

HCO3: bicarbonate, PICU: pediatric intensive care unit,

Table 2. Patients' characteristics according to serum vitamin D status

	VDS N=36 (%27.7)	VDI N=43 (%33.1)	VDD N=51(%39.2)	Low 25OHD N=94 (%72.3)
Age (years)*	10.9±4.9	9.9±4.4	10.8±4.9	10.4± 4.7
25(OH)D_3 ng/ml*	28.8±9.7	16±2.4	8±2.1	11.7±4.5
pH*	7.08±0.14	7.09±0.14	7.05±0.14	7.07±0.14
HCO_3 level, mmol/l*	9.3±3.2	8.75±3.3	8.09±3.2	8.3±3.3
Lactate, mg/dl*	16.4±6.1	11±5.4	15.5±8.7	13.8±7.5
Duration of acidosis (hours)*	13.9±5.5	14.6±6.4	17.2±15.9	16±12.5
Length of PICU stay (hours)*	24.1±17	21.2±7.7	25.7±21.6	23.6±16.8
Length of hospitalization stay (days)*	16.9±6.6	16.6±5.2	17.3±5.7	17 ±5.4

HCO3: bicarbonate, PICU: pediatric intensive care unit, VDS: vitamin D sufficient, VDI: vitamin D insufficiency, VDD: vitamin D deficiency, 25OHD: 25-hydroxyvitamin
*mean±standard deviation

Table 3. Comparison of the parameters between the vitamin D sufficient group (VDS) and the vitamin D low group

	VDS (N=36)	Low 25OHD (N=94)	P*
Age (years)	10.9±4.9	10.4± 4.7	0.598
pH	7.08±0.14	7.07±0.14	0.611
HCO_3 level, mmol/l	9.3±3.2	8.3±3.3	0.147
Lactate	16.4±6.1	13.8±7.5	0.127
Duration of acidosis (hours)	13.9±5.5	16±12.5	0.321
Length of PICU stay (hours)	24.1±17	23.6±16.8	0.897
Length of hospitalization (days)	16.9±6.6	17 ±5.4	0.954

PICU: pediatric intensive care unit, 25OHD: 25-hydroxyvitamin

Parameters were expressed in mean ±standard deviation, *student t-test

Discussion

The relationship between vitamin D and T1DM has been found and several theories have been proposed in recent years (5-8,15). There are very few studies evaluating vitamin D levels in DKA (9-11,16). To the best of our knowledge, this is the first study evaluating vitamin D levels in patients with DKA in Turkey.

In Turkey, VDD has been reported as 86.6% for infants, 39.8% for children, and 63.5% for adults (17,18). Demiral et al. (19) found that VDD/VDI was 86.6% in patients with endocrine diseases. In this study, obesity and T1DM were found as risk factors (19). VDD was reported as 7-68% and VDI as 19-68% in recent epidemiological studies evaluating vitamin D levels in healthy children and adolescents in different regions of the World (20). In this study, 39.2% of the patients had VDD and 33.1% had VDI, similar to the rates in healthy children in Turkey. Studies have suggested that patients with T1DM have a higher prevalence of 25OHD deficiency and contribute to the pathogenesis of T1DM (5,6,21-23). In a study evaluating vitamin D levels in patients with diabetes in Turkey, VDI and VDD rates were similar to the rates in our study (24). In another study in Turkey, no significant difference was found between vitamin D levels in patients with T1DM and healthy controls (25), Unlike the literature, the fact that the rates of VDD and VDI in patients with DKA and T1DM are similar to the healthy group may be due to the high prevalence of VDD in our country (17).

In our study, most of the patients with severe acidosis had low 25OHD levels and the duration of DKA was longer in patients with low 25OHD (VDD+VDI) group compared to the VDS group. But the relationship between the level of acidosis/pH/HCO3 and 25OHD was not statistically significant. In previous studies, low bicarbonate levels were significantly associated with low 25OHD levels (9-11). In the study of Hyung et al. (10), spontaneous normalization of vitamin D levels was observed after the resolution of ketoacidosis while Devidayal et al. (11) did not observe this in their study. The mechanism underlying changes in vitamin D levels in acute metabolic acidosis is unclear. Some studies suggest that acidosis decreases 25OHD levels by inactivating 1 alpha-hydroxylase enzyme or by decreasing vitamin D binding protein (16,26-28). Vitamin D levels of our patients were not re-examined after acidosis resolved, and further studies are needed in this regard.

The effects of vitamin D on multiple immune cell lineages suggest that vitamin D may play important roles in immune-mediated disorders. (4). Iqbal et al. (16) concluded in their review that vitamin D deficiency and diabetic ketoacidosis were interrelated, and vitamin D deficiency contributed to DKA occurrence. The fact that 72.3% of the patients with diabetic ketoacidosis in our study had low vitamin D levels supports this review.

Vitamin D deficiency in critically ill children is associated with a high mortality rate (29-30). In our study, duration of acidosis, length of PICU, and hospitalization stay were longer in the low 25OHD group, but not statistically significant. Only 2 of our patients with VDD required mechanical ventilation. Recent studies have reported that VDD was associated with increasing severity of illness, longer PICU length of stay, and duration of hospital stay (29,30). However, Das et al. (31) have found no statistically significant relationship between VDD and length of hospital stay/ ventilation requirements/ duration of PICU stay/duration of ventilation.

The limitations of our study include its retrospective design and single-center nature, the absence of a control group, the limited number of patients, and the lack of assessment of vitamin D levels after the resolution of acidosis. Further studies with a larger sample of patients are needed to better understand the relationship between 25OHD levels and DKA.

Conclusion

To the best of our knowledge, this is the first study in Turkey evaluating the relationship between vitamin D and diabetic ketoacidosis. Although there is no relationship between vitamin D deficiency and diabetic ketoacidosis duration and severity of acidosis in patients with type 1 diabetes mellitus, which is one

of the three most common causes of chronic diseases in children and adolescents, it is noteworthy that 72.3% of the patients with diabetic ketoacidosis have vitamin D deficiency/insufficiency. These findings support that the vitamin D level should be screened to provide an opportunity for early diagnosis and treatment of VDD in patients with T1DM and healthy children with risk factors for VDD.

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