

DOI: 10.4274/jarem.galenos.2021.3947

J Acad Res Med 2021;11(2):143-8

# Relationship Between the Levels of 25-hydroxyvitamin D at Presentation and the Clinical, Laboratory and Follow-up Data of Children and Adolescents with Type-1 Diabetes Mellitus

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**Cite this article as:** Karamık G, Araslı Yılmaz A, Aycan Z, Savaş Erdeve Ş, Çetinkaya S. Relationship Between the Levels of 25-hydroxyvitamin D at Presentation and the Clinical, Laboratory and Follow-up Data of Children and Adolescents with Type-1 Diabetes Mellitus. J Acad Res Med 2021;11(2):143-8

## ABSTRACT

**Objective:** This study aimed to assess the relationship of 25-hydroxyvitamin D [25(OH)D] levels at presentation with the clinical, laboratory and follow-up data of children and adolescents with type-1 diabetes mellitus.

**Methods:** Patients who had available follow-up data and were diagnosed to have type-1 diabetes mellitus in our clinic between 2009 and 2015 were included. Patient files were screened for data regarding presentation, history/family history and clinical, laboratory and follow-up data. Data were also assessed in the context of threshold values for sufficiency, insufficiency or deficiency of 25(OH)D.

**Results:** The mean age was 8.62±14.19 years. Type-1 diabetes mellitus was diagnosed as diabetic ketoacidosis in 53.9% of the patients. The mean 25(OH)D level was 18.90±11.07 ng/mL at the time of diagnosis. The mean time to subcutaneous insulin therapy through the resolution of ketosis/diabetic ketoacidosis in the group with vitamin D deficiency was significantly longer than vitamin D insufficient and sufficient groups (p=0.020). The mean 25(OH)D levels were lower in patients diagnosed with moderate and severe diabetic ketoacidosis (p=0.020). Insulin doses at discharge were significantly lower in patients with a mean 25(OH)D level of 10-20 ng/mL (p=0.039). The relationship of vitamin D groups with HbA1c and insulin doses in the follow-up period was not significant.

**Conclusion:** This pilot study assessed the clinical, laboratory and follow-up data and the honeymoon status on month 2 (±1). We found that 25(OH)D levels affected clinical features at the time of diagnosis but not during follow-up.

**Keywords:** 25-hydroxyvitamin D, type-1 diabetes mellitus, children, adolescence, ketoacidosis

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**Presented in:** This study was presented at the 22<sup>nd</sup> National Pediatric Endocrinology and Diabetes Congress, 18-22 April 2018, Antalya, Turkey.

**Received Date:** 12.11.2020 **Accepted Date:** 02.03.2021

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## INTRODUCTION

Type-1 diabetes mellitus (T1DM) is an autoimmune disorder whose incidence increases because of beta cell destruction. Its pathogenesis involves autoimmunity, genetics and environmental factors. Although the causes of T1DM have not been fully elucidated, genetic factors in human leucocyte-antigen complexes and environmental factors, such as diet or viral infections, are likely implicated in the T1DM pathogenesis (1). The incidence of autoimmune disorders, such as multiple sclerosis, inflammatory bowel disease, rheumatoid arthritis and T1DM, is high in northern countries, and the frequency of vitamin D deficiency in people living in these countries is high; as such, vitamin D is highly related to the immune system and autoimmune disorders. The EURODIAB Work Group reported that the risk of T1DM development decreases by 33% in children who receive vitamin D supplementation compared with those who have no supplementation (2). Type-1 helper, type-2 helper and regulatory T-cells participate in the interaction between vitamin D and the immune system. Vitamin D may slow down the process of autoimmune insulinitis in T1DM (3,4).

Our study aimed to assess the relationship of 25-hydroxyvitamin D [25(OH)D] levels at presentation with the clinical, laboratory and follow-up data of children and adolescents with T1DM. We also determined the effects of vitamin D on the T1DM pathogenesis.

## METHODS

### Study Population

Dr. Sami Ulus Gynecology Obstetrics and Child Health and Diseases Training and Research Hospital Ethics Committee ethical approval was obtained for the retrospective review of the cohort of patients diagnosed with T1DM (approval number: 2016/73799008). A total of 115 patients who had positive diabetes-associated autoantibodies and were diagnosed with T1DM in accordance with the 2014 American Diabetes Association Diabetes Mellitus Diagnosis and Classification criteria between 2009 and 2015 were included. Their 25(OH)D levels were measured at presentation, and their follow-up data were collected for at least 2 years. The following data were extracted from patient records: Age, gender, physical examination and laboratory findings at presentation, diagnosis at presentation (hyperglycaemia, ketosis and ketoacidosis), time to the resolution of ketoacidosis, insulin doses at discharge (U/kg/day), insulin doses and honeymoon status in the first control visit (on month  $2\pm 1$ ), mean insulin doses per year during follow-up and HbA1c levels.

### Acquisition and Definition of Data

Diabetic ketoacidosis (DKA) was diagnosed on the basis of the following criteria (5): Plasma glucose level  $\geq 200$  mg/dL, venous pH  $< 7.3$  or  $\text{HCO}_3^- < 15$  mEq/L and total ketone bodies  $> 5$  mmol/L. DKA was classified according to pH and  $\text{HCO}_3^-$  as follows (6): Mild DKA, pH  $< 7.3$  and  $\text{HCO}_3^- < 15$  mmol/L; moderate

DKA, pH  $< 7.2$  and  $\text{HCO}_3^- < 10$  mmol/L; and severe DKA, pH  $< 7.1$  and  $\text{HCO}_3^- < 5$  mmol/L.

Metabolic control was assessed in terms of mean insulin doses per year, which was the arithmetic mean of HbA1c levels measured at 3-month interval during follow-up: HbA1c  $< 7.5\%$ , good metabolic control; 7.6-9%, moderate metabolic control; and  $> 9.1\%$ , poor metabolic control (7). Honeymoon status was defined as an insulin requirement of  $< 0.5$  U/kg/day in the first control visit (on month  $2\pm 1$ ) (8).

Serum 25(OH)D levels were measured and classified as follows: Deficient,  $< 20$  ng/mL; insufficient, 21-29 ng/mL; and sufficient,  $> 30$  ng/mL (9,10). All the patients were initially given 2000 IU/day vitamin D3 replacement therapy for 6 weeks at discharge. After the supplementation therapy, our patients were prescribed to have 1000 IU/day vitamin D. The relationship of 25(OH)D level with T1DM clinical features at the time of diagnosis and follow-up data was investigated.

### Statistical Analysis

Data were analysed by using SPSS version 15.0 and expressed as n (%), mean  $\pm$  standard deviation (SD) or median (minimum-maximum) as appropriate. SD scores (SDS) were calculated by subtracting the patient's value from the mean value of that age and dividing by the SD value determined for that age. A chi-square test was conducted to assess the relationship between two categorical variables. Clinical and laboratory values were given as descriptive statistics. Student's t and Mann-Whitney U tests were performed to compare parametric and non-parametric data. For quantitative data, One-Way ANOVA was carried out to compare categorical variables with three or more categories in case of normal distribution. Kruskal-Wallis test was used in case of skewed distribution. Results with  $p < 0.05$  were considered statistically significant.

## RESULTS

A total of 115 children and adolescents with T1DM were included in this study. T1DM was diagnosed in the prepubertal period of 59.1% of the patients. The mean age was  $8.62\pm 4.19$  years, whilst most patients (41.9%) were 10-14 years old. Of the patients, 53.9% were girls. The patients' demographics and laboratory data are summarised in Table 1. The mean body weight, height and body mass index-SDS values were found to be normal at the time of presentation, in the first control visit (on month  $2\pm 1$ ) and in the final control visit. However, the lowest values were detected at the time of presentation. The mean 25(OH)D level was lower in girls than in boys ( $p=0.020$ ). The phosphor and alkaline phosphatase (ALP) levels were lower in girls than in boys. However, age-adjusted ALP levels were within normal ranges in all cases.

A comorbid autoimmune disorder was detected in 23.4% of the patients (including Hashimoto thyroiditis in 18 cases and celiac disease in 8 cases). When autoantibodies were considered, positive anti-islet antibodies were found in 72.1% of the patients, positive anti-glutamic acid decarboxylase (anti-GAD) antibodies

were detected in 69.5% of the patients, and positive anti-insulin antibodies were observed in 4.3% of the patients. The most common antibodies were anti-islet plus anti-GAD antibodies, which were found to be positive in 32.2% of the patients.

T1DM was diagnosed as DKA in 53.9% of the patients, hyperglycaemia in 25.2% of the patients and ketosis in 20.9% of the patients (Table 2). Of the patients presenting with DKA, 79% were 10-14 years old. Furthermore, 27.4% had mild DKA, 33.9% had moderate DKA, and 38.7% had severe DKA. The mean time to subcutaneous insulin therapy via the resolution of ketosis and DKA was 14.48 h. The mean insulin doses were 0.59 U/kg/day at discharge and 0.55±0.27 U/kg/day on month 2±1 after discharge. In addition, 52.2% of the patients were in the honeymoon phase in the first control visit (on month 2±1) after discharge.

No significant differences were observed between clinical presentation and vitamin D groups (p=0.774). DKA was detected in 55.1%, 50% and 56.2% of the patients in the deficient, insufficient and sufficient groups, respectively. Additionally, the rates of severe

DKA in the deficient, insufficient and sufficient groups were 36.8%, 33.3% and 44.4%, respectively (p=0.314).

The following results of the mean time to subcutaneous insulin therapy via the resolution of ketosis/DKA were found: 16.89 h (range: 4-53 h) in the group with vitamin D deficiency, 9.70 h (range 1-20 h) in the group with vitamin D insufficiency and 13.21 h (range 3-36 h) in the group with sufficient vitamin D levels. This parameter was significantly longer in the group with vitamin D deficiency than vitamin D insufficient and sufficient groups (p=0.020). No significant relationship was observed between vitamin D groups and follow-up data (Table 3).

The mean 25(OH)D level was 17.68 ng/mL in patients in the honeymoon phase in the first control visit (on month 2±1). In cases without honeymoon status, the mean 25(OH)D level was 20.34 ng/mL, which was not significantly different from that of the patients in the honeymoon phase (p=0.213). Vitamin D replacement was given to the patients with a low 25(OH)D level. The assessment of the mean 25(OH)D levels in the metabolic control groups

**Table 1. Patients' anthropometric measurements and laboratory data at presentation**

	Total (n=115)	Girl (n=62)	Boy (n=53)	p value
Weight-SDS, mean, (min-max)	-0.49±1.18 [-3.50-(+2.88)]	-0.63±1.24 [-3.50-(+2.05)]	-0.32±1.08 [-2.92-(+2.88)]	0.154
Height-SDS, mean, (min-max)	-0.02±1.16 [-3.05-(+3.18)]	-0.07±1.15 [-3.05-(+3.18)]	0.14±1.17 [-2.95-(+2.26)]	0.328
BMI-SDS, mean, (min-max)	-0.75±1.41 [-6.20-(+3.16)]	-0.88±1.54 [-6.20-(+1.89)]	-0.60±1.24 [-3.83-(+3.16)]	0.287
Pre-puberty, n (%)	68 (59.1%)	41 (%66.1)	27 (%50.9)	0.102
Puberty, n (%)	47 (40.9%)	21 (%33.9)	26 (%49.1)	
25(OH)D, ng/mL, mean, (min-max)	18.90±11.07 (3.00-61.00)	15.98±10.16 (3.00-60.00)	22.32±11.21 (6.90-61.00)	0.020*
Glucose, mg/dL, mean, (min-max)	412.96±162.88 (106-855)	404.69±160.37 (106-780)	422.62±166.77 (118-855)	0.560
C-peptide, ng/mL, mean, (min-max)	0.55±0.62 (0.03-3.60)	0.56±0.70 (0.03-3.60)	0.54±0.51 (0.07-2.44)	0.880
HbA1c, %, mean, (min-max)	12.11±2.36 (5.20-16.40)	12.32±2.41 (5.20-16.40)	11.87±2.30 (5.50-16.10)	0.310
pH, mean, (min-max)	7.23±0.16 (6.70-7.55)	7.21±0.16 (6.70-7.55)	7.26±0.14 (6.93-7.48)	0.106
HCO <sub>3</sub> , mmol/Lt, mean, (min-max)	12.83±7.54 (0.60-29.00)	11.90±7.67 (1.10-29.00)	13.92±7.30 (0.60-29.00)	0.152
Calcium, mg/dL, mean, (min-max)	9.65±0.46 (8.40-10.70)	9.59±0.49 (8.40-10.70)	9.71±0.43 (8.80-10.50)	0.200
Phosphor, mg/dL, mean, (min-max)	4.19±1.11 (1.40-8.80)	3.87±0.93 (2.20-6.20)	4.54±1.19 (1.40-8.80)	0.010*
Alkaline phosphatase, U/Lt, mean, (min-max)	262.74±113.39 (117-840)	241.42±81.79 (117-483)	288.94±139.55 (121-840)	0.040*
Albumin, g/dL, mean, (min-max)	4.31±0.42 (3.20-5.40)	4.27±0.43 (3.20-5.10)	4.35±0.40 (3.40-5.40)	0.306
TSH, µU/mL, mean, (min-max)	2.35±2.36 (0.46-23.60)	2.31±1.47 (0.46-7.55)	2.39±3.11 (0.62-23.60)	0.865

25(OH)D: 25-hydroxyvitamin D, SDS: standard deviation score, TSH: thyroid stimulating hormone, BMI: body mass index, min: minimum, max: maximum  
\*Statistically significant

stratified according to the mean HbA1c level in the 1<sup>st</sup> and 2<sup>nd</sup> years revealed no significant differences amongst the groups ( $p=0.784$  and  $p=0.834$ ).

After the patients with acidosis were stratified according to 25(OH)D levels, the mean 25(OH)D levels were lower in the patients diagnosed with moderate and severe DKA ( $p=0.020$ ; Table 4).

In the patients stratified into two groups according to their 25(OH)D levels, the time to subcutaneous insulin therapy via the resolution of ketosis/ketoacidosis was 16.89 h in patients with a mean 25(OH)D level of  $<20$  ng/mL. By comparison, this parameter was 11.03 h in patients with a mean 25(OH)D level of  $>20$  ng/mL. The time to resolution of ketosis/ketoacidosis was significantly longer in patients with a mean 25(OH)D level of  $<20$  ng/mL ( $p=0.020$ ). Additionally, insulin doses at discharge were significantly lower in patients with a mean 25(OH)D level of 10-20 ng/mL ( $p=0.039$ ).

## DISCUSSION

Although sunlight is a major source of vitamin D, individual factors, genetic variation and environmental factors may alter vitamin D levels. Blood 25(OH)D level represents the stored vitamin D from cutaneous synthesis and dietary intake (11). However, no consensus has been obtained on deficient or sufficient vitamin D levels. Different studies have revealed varying threshold levels. For instance, the optimal vitamin D

level in children is 20 ng/mL (3). Furthermore, regional and geographic variations have been found in studies evaluating vitamin D levels in patients with T1DM. In a study on 88 patients with newly diagnosed T1DM, Pozzilli et al. (12) found that the mean 1,25(OH)D level in diabetic patients is lower than that in the controls. They also observed that vitamin D level had no correlation with age, gender, season at diagnosis and HbA1c levels. In a diabetes incidence study in Sweden, Littorin et al. (13) observed that mean 25(OH)D levels at presentation and on year 8 are significantly lower in 459 patients with T1DM than in the controls. In our study, the majority of the patients with T1DM had deficient/insufficient mean 25(OH)D levels when the groups were compared on the basis of their vitamin D levels. The mean 25(OH)D levels were  $<30$  and  $<20$  ng/mL in 86% and 60% of the patients, respectively. In addition, the mean 25(OH)D levels were  $<20$  and  $<10$  ng/mL in 70.9% and 30.7% of the girls, respectively. The mean 25(OH)D level was lower in girls than in boys. Furthermore, vitamin D deficiency/insufficiency was more common in the former than in the latter. Consistent with previous findings, our results revealed that low vitamin D levels in this age group might be due to poor dietary habits in the adolescence period and the accelerated growth rate in puberty. Consequently, their vitamin D requirement increased.

Several studies on the relationship between acidosis and vitamin D have suggested that a sufficient vitamin D level protects against DKA, particularly in cases induced by infection (14). Studies have also demonstrated that chronic metabolic acidosis decreases 1-alpha-hydroxylase levels, thereby transforming 25(OH)D to 1,25(OH)D; by contrast, other studies have shown that chronic metabolic acidosis increases 1,25(OH)D levels (15,16). In an Italian study on 58 patients with T1DM, 25(OH)D level is lower in the patient group than in the controls; furthermore, vitamin D levels are lower in patients presenting with ketoacidosis than in patients without ketoacidosis (17). In our study, the mean 25(OH)D level was significantly higher in 17 cases with mild ketoacidosis than in cases with moderate or severe ketoacidosis. According to vitamin D deficiency/insufficiency/sufficiency, the time to subcutaneous insulin therapy through the resolution of ketosis/ketoacidosis was significantly longer in patients with a mean 25(OH)D level of  $<20$  ng/mL. This finding suggested that 25(OH)D levels could be associated with ketoacidosis at presentation, and 25(OH)D levels might affect insulin synthesis and secretion mechanisms. Therefore, vitamin D levels likely influenced data at presentation, but they did not affect the subsequent process. However, further studies with a larger sample size should be conducted.

Aljabri et al. (18) investigated the effects of vitamin D replacement on patients with T1DM and vitamin D deficiency. They gave vitamin D and calcium supplement to patients with vitamin D deficiency and assessed the mean HbA1c and 25(OH)D levels after 12 weeks. They found that vitamin D positively affects the metabolic control of patients with diabetes. Similarly, Svoren et al. (19) and Giri et al. (20) observed that

**Table 2. Clinical features at the time of diagnosis and follow-up**

	Total (n=115)
<b>Clinical presentation at diagnosis</b>	
DKA, n, (%)	62 (53.9%)
Hyperglycaemia, n, (%)	29 (25.2%)
Ketosis, n, (%)	24 (20.9)
Time to resolution of ketosis/ketoacidosis, h, mean, (min-max)	14.48±10.59 (1-53)
Mean insulin doses at discharge, U/kg/day, mean, (min-max)	0.59±0.29 (0-1.80)
Mean insulin doses in the first control visit (on month 2±1), U/kg/day, mean, (min-max)	0.55±0.27 (0.07-1.80)
Honeymoon present, n, (%)	60 (52.2%)
<b>First year control</b>	
HbA1c, %, mean, (min-max)	10.26±2.51 (5.50-15.90)
Insulin dose, U/kg/day, mean, (min-max)	0.56±0.24 (0.00-1.44)
<b>Second year control</b>	
HbA1c, %, mean, (min-max)	7.03±1.17 (5.20-12.90)
Insulin dose, U/kg/day, mean, (min-max)	0.67±0.24 (0.00-1.33)
25(OH)D: 25-hydroxyvitamin D, DKA: diabetic ketoacidosis, min: minimum, max: maximum	

**Table 3. Relationship of 25-hydroxyvitamin D levels with follow-up data**

Total (n=115)	Deficient (n=69) <20 ng/mL	Insufficient (n=30) 20-30 ng/mL	Sufficient (n=16) >30 ng/mL	p value
25(OH)D, ng/mL, mean, (min-max)	11.97±4.04 (3.00-19.30)	23.85±2.89 (20.20-29.70)	39.52±10.90 (30.50-61.00)	0.001*
Time to the resolution of ketosis/ketoacidosis, h, mean, (min-max)	16.89±11.47 (4-53)	9.70±5.99 (1-20)	13.21±10.71 (3-36)	0.020*
Insulin doses at discharge, U/kg/day, mean, (min-max)	0.58±0.28 (0.05-1.40)	0.56±0.26 (0.31-1.29)	0.67±0.38 (0.00-1.80)	0.487
Insulin doses at first control visit (on month 2±1), U/kg/day, mean, (min-max)	0.52±0.26 (0.07-1.31)	0.54±0.23 (0.24-1.22)	0.68±0.37 (0.19-1.80)	0.104
Honeymoon present	37 (543.47%)	18 (60%)	5 (31.2%)	0.162
Honeymoon absence	312 (456.63%)	12 (40%)	11 (68.8%)	
<b>HbA1c at year 1, n, (%)</b>				
Good (<7.5%)	10 (14.5%)	4 (13.3%)	1 (6.3%)	0.693
Moderate (7.5-9%)	19 (27.5%)	5 (14.7%)	7 (43.8%)	
Poor (>9%)	40 (58%)	21 (70%)	8 (50%)	
<b>HbA1c at year 2, n, (%)</b>				
Good (<7.5%)	49 (721.10%)	24 (820.80%)	9 (6056.3%)	0.329
Moderate (7.5-9%)	167 (234.56%)	45 (136.86%)	56 (337.35%)	
Poor (>9%)	3 (4.4%)	1 (3.4%)	1 (6.72%)	
Insulin dose at year 1, U/kg/day, mean, (min-max)	0.53±0.24 (0.00-0.17)	0.48±0.66 (0.25-1.27)	0.53±0.82 (0.32-1.44)	0.118
Insulin dose at year 2, U/kg/day, mean, (min-max)	0.66±0.27 (0.00-1.24)	0.69±0.24 (0.27-1.33)	0.66±0.14 (0.47-0.97)	0.871

25(OH)D: 25-hydroxyvitamin D, min: minimum, max: maximum, \*Statistically significant

**Table 4. Relationship of 25-hydroxyvitamin D levels with ketoacidosis**

Mean 25(OH)D level according to acidosis severity, ng/mL, (min-max)	p value
Mild acidosis (n=17)	0.020*
Moderate acidosis (n=21)	
Severe acidosis (n=24)	

25(OH)D: 25-hydroxyvitamin D, min: minimum, max: maximum, \*Statistically significant

25(OH)D deficiency is associated with poor metabolic control. In our study, 60% of the patients had poor metabolic control, as indicated by their mean HbA1c level in the 1<sup>st</sup> year. Conversely, 71.3% of the patients had good metabolic control, as shown by their mean HbA1c level in the 2<sup>nd</sup> year. According to vitamin D deficiency, insufficiency and sufficiency, mean HbA1c levels and metabolic control were comparable in our study. Although glycaemic control following vitamin D replacement could not be addressed because of our retrospective study design, our data suggested that vitamin D could regulate glycaemic control because of its protective features and positive effects on beta cell function and insulin sensitivity.

### Study Limitations

Our study had some limitations. Firstly, this study was retrospective and had relatively few patients. We could not assess the exact effect of vitamin D replacement therapy on clinical outcomes because vitamin D treatment could be affected by a number of factors, such as patient compliance, season, baseline vitamin D level and dietary intake. Secondly, the follow-up period might not be long enough. Lastly, a control group consisting of healthy children in the same age group was lacking.

### CONCLUSION

This pilot study assessed the 25(OH)D levels at the time of diagnosis in the context of the clinical, laboratory and follow-up data of patients with T1DM. We found that vitamin D levels affected the severity of clinical presentation, time to the resolution of ketoacidosis and insulin doses at discharge, but these levels had no effect on follow-up data. However, the measurement of vitamin D levels at the time of diagnosis and replacement therapy might contribute to the honeymoon status of 52.2% of the patients in their control visit on month 2±1. As such, prospective studies on this topic should be further performed.

**Ethics Committee Approval:** Dr. Sami Ulus Gynecology Obstetrics and Child Health and Diseases Training and Research Hospital Ethics Committee ethical approval was obtained for the retrospective review



of the cohort of patients diagnosed with T1DM (approval number: 2016/73799008).

**Informed Consent:** Retrospective study.

**Peer-review:** Externally peer-reviewed.

**Author Contributions:** Surgical and Medical Practices - G.K., A.A.Y.; Concept - G.K., Z.A., Ş.S.E., S.Ç.; Design - G.K., Z.A., Ş.S.E., S.Ç.; Data Collection and/or Processing - G.K., A.A.Y.; Analysis and/or Interpretation - G.K., S.Ç.; Literature Search - G.K., A.A.Y., S.Ç.; Writing - G.K., S.Ç.

**Conflict of Interest:** The authors have no conflict of interest to declare.

**Financial Disclosure:** The authors declared that this study has received no financial support.

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