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The Association between 25-(OH)D Level and Metabolic Control Status in Children with Type 1 Diabetes Mellitus at Dr. M. Djamil General Hospital Padang

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A R T I C L E I N F O

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A B S T R A C T

Background: Type 1 diabetes mellitus (T1DM) is an autoimmune disease causing the destruction of pancreatic beta cells. This is an incurable condition, but with good metabolic control, an optimal quality of life can be achieved. Glycated hemoglobin (HbA1C) is still considered a reliable parameter of metabolic control. Studies showed vitamin D has a role in controlling glycemic homeostasis in children with T1DM. Calcidiol or 25-(OH)D is the best parameter to determine the level of vitamin D in the blood. This study aimed to evaluate the association between 25-(OH)D with metabolic control status in T1DM children at Dr. M. Djamil General Hospital Padang. **Methods:** A cross-sectional study was conducted on 43 pediatric patients with T1DM from July 2019-January 2021. Serum levels of 25-(OH)D were measured by direct CLIA method and classified into deficiency (≤ 20 ng/mL) and insufficiency (21–30 ng/mL). The HbA1C levels were calculated using the HPLC method and classified into good (<7%), adequate (7-8%), and poor (>8%) control. The Chi-square test and ANOVA were used for data analysis. The P-value of < 0.05 was considered statistically significant. **Results**: The majority of respondents were girls (53.5%), with 90.7% having a good nutritional status. The mean age at diagnosis was 11.25±2.85 years, and had been known to suffer from T1DM for 2.95±1.74 years. All respondents had abnormal levels of 25-(OH)D (100%), i.e., insufficiency (28%), deficiency (72%), poor (65.1%) metabolic control, and 96.4% of respondents with poor metabolic control had a deficiency of 25-(OH)D. (P-value <0.001). **Conclusion:** T1DM patients who have poor metabolic control have very low levels of 25-(OH)D.

1. Introduction

Diabetes mellitus is a chronic autoimmune, metabolic disease caused by impaired insulin production or insulin action disorders. The destruction of pancreatic beta cells by an autoimmune process results in the body not being able to produce insulin at all or can still produce insulin in small amounts.[1,2] The prevalence is estimated at 1-3 per 100,000 per year in China, Asia, and South America, 10-20 per 100,000 per year in Southern European countries and the United States.[3] According to the Indonesian Pediatric Society (IDAI), in 2018, the incidence of T1DM in Indonesia was 1,220 children.[4]

Vitamin D is a fat-soluble vitamin that plays a role in controlling glycemic homeostasis. Vitamin D is produced with the help of Ultraviolet B (UVB). It is estimated that 1 billion people in the world have vitamin D deficiency or insufficiency.[5,6] Vitamin D deficiency is more common in children with T1DM than in the general population. The action of vitamin D on insulin production depends on the presence of Vitamin D Receptor (VDR), 1-α hydroxylase expression in pancreatic cells, Vitamin D Receptor Element (VDRE), which is found in the insulin gene, and 1,25 dihydroxy vitamin D which plays a role in insulin gene

transcription.[7]

This study aimed to evaluate the association between 25-(OH)D with metabolic control status in children with T1DM at Dr. M Djamil General Hospital Padang.

2. Methods

A cross-sectional study was conducted on 43 pediatric patients with T1DM in the pediatric ward and polyclinic of Dr. M Djamil General Hospital Padang from July 2019 - to January 2021, by consecutive sampling method.

The inclusion criteria were patients with T1DM aged 1 to 18 years old who agreed to participate in this study. Meanwhile, the exclusion criteria were children with other diseases that affect vitamin D levels. Children with severe acute nutritional disorders were on vitamin D3 supplementation 3 weeks prior to the study, and children with impaired kidney and liver function also were excluded.

A blood level of 25-(OH)D was measured by direct Competitive Chemiluminescence Immunoassay (CLIA) method, and a level ≤ 30 ng/mL was considered abnormal, ≤ 20 ng/mL as a deficiency, and 21–30 ng/mL as an insufficiency. Metabolic control was assessed by the level of Glycated hemoglobin (HbA1C). HbA1C level was measured by High-Performance Liquid Chromatography (HPLC) method and was classified into good (<7%), adequate (7-8%), and poor (>8%) metabolic control. Statistical analysis was performed using the IBM SPSS Statistics software. Numerical data analysis was performed using the ANOVA test, and categorical data using the Chi-square test. A normality test by Shapiro-Wilk was conducted previously. P-value of <0,05 was considered significant.

3. Results

There were 43 subjects with T1DM. Table 1 showed that the average age of the respondents was 14.28±3.08 years. The majority of respondents were girls (53.5%), with 90.7% of respondents having a good nutritional status. The mean age at diagnosis was 11.25 ± 2.85 years, and the length of time known to have T1DM was 2.95 ± 1.74 years. More than half of the respondents had a family history of DM type 2. Almost all respondents did blood sugar checks independently 4 times/day (97.7%) and received an average insulin dose of 1.14±0.12 IU/kg BW/day.

Table 2 showed that more than half of the respondents had poor metabolic control. All respondents had abnormal 25-(OH)D levels, which were dominated by vitamin D deficiency.

Table 1. Subject characteristics

Characteristics	f (%)	Mean±SD
Age (years)		14.28±3.08
Gender		
Boys	20 (46.5)	
Girls	23 (53.5)	
Nutritional status		
Normal	39 (90.7)	
Underweight	4 (9.3)	
Age at diagnosis (years)		11.25±2.85
Length of time known to have T1DM (years)		2.95±1.74
Family history of T2DM		
Yes	22 (51.2)	
None	21 (48.8)	
Frequency of blood sugar monitoring/day		
< 4 times	1 (2.3)	
≥ 4 times	42 (97.7)	
Insulin dosage (IU/kg BW/day)		1.14±0.12

Table 2. The characteristics of respondents based on laboratory results

Characteristics	f (%)	Mean±SD
Hemoglobin (g/dl)		12.97±1.73
Leukocytes (/mm^3)		11,102.33±7,444.20
Platelets (/mm^3)		326,465.12±115,479.2
Urea (mg/dl)		20.05±10.00
Creatinine (mg/dl)		0.55±0.18
AST (U/L)		19.74±6.84
ALT (U/L)		21.12±6.80
HbA1C		
Good metabolic control Adequate metabolic control Poor metabolic control	11 (25.6) 4 (9.3) 28 (65.1)	
Vitamin D Status		
Normal Abnormal	0 43 (100,0)	
Deficiency Insufficiency	31(72) 12 (28)	

Table 3 shows the mean of 25-(OH)D levels and HbA1C. The mean 25-(OH)D levels were 16.49±5.21, with the lowest level being 8,4 ng/ml and the highest being 28,8 ng/ml. The lowest HbA1C level was 3,5%, and the highest level was 17,9%. Respondents with the highest HbA1C levels (17.9%) had the lowest 25-(OH)D levels of all respondents i.e., 8.4 ng/ml, while those with the lowest HbA1C levels (3.5%) had 25-(OH) D levels of 22.3 ng/ml. Respondents with the highest levels of vitamin D (28.8 ng/ml) had HbA1C levels of 7.2%.

Table 3. Average levels of 25-(OH)D and HbA1C in children with T1DM

Variable	Mean±SD	Min-Max
Level of 25-(OH)D (ng/ml)	16.49±5.21	8.40-28.80
HbA1C (%)	9.52±3.23	3.50-17.90

Table 4 showed that the mean 25-(OH)D levels were lower in poor metabolic control. Based on the results of the one-way ANOVA statistical test, p-value <0.001, it can be concluded that there was an association in the mean levels of 25-(OH)D with metabolic control status in children with T1DM (p<0.05).

The results of this study found that all respondents had abnormal levels of 25-(OH)D; thus, the chi-square test could not be carried out because there were zero cells in the chi-square table; thus, the variable of vitamin D status (normal and abnormal) was being converted to vitamin D status (deficiency and insufficiency) and then being analyzed.

Based on table 5, it can be concluded that the incidence of vitamin D deficiency was found in respondents who had poor, adequate, and good metabolic control, 96.4%, 50%, and 18.2%, respectively. There was a statistical relationship between vitamin D status and metabolic control status in children with T1DM (p<0.001).

Table 4. Relationship of mean 25-(OH)D levels with metabolic control in children with T1DM

HbA1C Level	N	25-(OH)D levels (Mean±SD)	P-value
Good metabolic control	11	21.35±4.75	<0,001*
Adequate metabolic control	4	20.95±5.72	
Poor metabolic control	28	13.94±3.30	

*one-way ANOVA test

Table 5. Relationship between abnormal vitamin D status and metabolic control status in children with T1DM

Metabolic Control	Vitamin D Status		Total	P-value
	Deficiency (f/%)	Insufficiency (f/%)		
Poor	27 (96.4)	1(3.6)	28 (65.1)	<0.001**
Adequate	2 (50)	2(50)	4 (9.3)	
Good	2 (18.2)	9(81.8)	11 (25.6)	
Total	31 (72)	12(28)	43 (100.0)	

**Chi-square test

4. Discussion

In this study, respondents with type 1 DM were in the age range of 1-17 years. According to the International Diabetes Federation (IDF), more than 1.1 million children and adolescents aged <20 years worldwide suffer from T1DM.[8] According to the Indonesian Pediatric Society (IDAI) 2003-2009, T1DM is often found in the age group of 10-14 years, with 60% girls and 28.6% boys.[9,10] Al Zahrani et al. conducted a retrospective study in Saudi Arabia on children with T1DM showed an average HbA1C level of 9.6% ± 1.9%. Vitamin D deficiency was found in 63.3% of boys and 67% of girls.[11] The mean insulin dose was 1.01±0.25 for boys and 1.04±0.23 for girls11, while in the current study, the mean insulin dose was 1.14±0.12 IU/kg/day.

The relationship between T1DM and vitamin D deficiency is a causal relationship. Autoimmunity is the cause of the development of T1DM, and vitamin D deficiency can cause immune system disorders that lead to autoimmune diseases. A research hypothesis suggests that low serum 25-(OH)D levels are a consequence of diabetes. Diabetes mellitus can cause complications related to autoantibodies that will lead to polymorphisms in VDR and VDBP. Patients with type 1 diabetes mellitus have vitamin D deficiency due to gene polymorphisms in VDR and VDBP.[12,13]

In this study, it was found that more than half of the sample (51.2%) had a family history of type 2 diabetes mellitus. Epidemiological studies show the risk of developing T1DM is 8-15 times greater when a first-degree relative has diabetes and twice the risk when a second-degree relative has diabetes.[14]

In this study, it was found that most of the subjects (65.1%) had poor metabolic control. A study conducted by Al-Agha found that 66% of the subjects had poor glycemic control, with HbA1C levels above 9%.[15] Alkharashi et al. in Saudi Arabia also found 70% of children with T1DM had low levels of 25-(OH)D i.e., 11% of children with T1DM had severe vitamin D deficiency, 30% had a moderate deficiency, 29% had a mild deficiency, and 30% had normal vitamin D levels. Alkharasi's study found a significant relationship between vitamin D deficiency and HbA1C levels. Lower vitamin D levels were found mostly in girls and occurred due to lack of sun exposure (<10 minutes/day, p<0.001).[16] The subjects in this study were mostly girls and became one of the risk factors for vitamin D deficiency.

Diabetes mellitus causes chronic hyperglycemia, which will increase oxidative stress and lead to an increase in HbA1c levels. Vitamin D can cause a decrease in oxidative DNA damage in diabetic patients. Increased levels of vitamin D could lead to a decrease in the percentage of HbA1c levels in diabetic patients.[17] Diabetes mellitus is associated with chronic inflammation, which will increase cytokines and cause insulin resistance and impaired glucose homeostasis.[18] Vitamin D can decrease proinflammatory chemokines in vivo and in vitro as well as cytokine expression, which will have implications for the pathogenesis of type 1 diabetes mellitus.[19]

Vitamin D can inhibit the differentiation and maturation of dendritic cells and neutralize Fas expression, thereby preventing pancreatic cell apoptosis.[20,21] Vitamin D can inhibit the production of inflammatory interleukins (IL-2, IL-12, TNF α, IFN γ) and stimulate the production of anti-inflammatory cytokines (IL-4, IL-10, TGF). Thus, vitamin D has an immunomodulatory, anti-inflammatory, and anti-apoptotic effect on pancreatic cells.[18,19]

Of all respondents with abnormal levels of 25-(OH)D, 12 (28%) had insufficiency, and 31 (78%) had vitamin D deficiency. A total of 65.1% had poor metabolic control, 25.6% had good metabolic control, and 9.3% had adequate metabolic control. Al-Agha in Jeddah, Saudi Arabia, reported the same incidence i.e., 66% of children had vitamin D deficiency and had poor

metabolic control.[15] A study by Ferraz et al. in Brazil reported 82.4% of patients with poor metabolic control had a vitamin D deficiency.[22] A study conducted by Giri et al. in Liverpool showed that 41.1% of respondents had vitamin D deficiency and the average HbA1C level was 8.9±3.5%, then the subjects were re-examined after vitamin D administration. There was a decrease in the incidence of vitamin D deficiency ($p<0.001$).[23]

Because this study is a cross-sectional study, data sampling is only done once. To determine a causative relationship between levels of 25-(OH)D and metabolic control status required a case-control study.

5. Conclusion

Levels of 25-(OH)D in all respondents were within an abnormal range. More than half of the respondents had poor metabolic control status. There was an association in the mean levels of 25-(OH)D with metabolic control status in children with T1DM ($p<0.05$). There was a statistical relationship between vitamin D status and metabolic control status in children with T1DM ($p<0.001$).

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