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Original Research Paper

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EFFICACY OF VITAMIN D3 SUPPLEMENTATION IN DIABETIC CHILDREN: A COHORT PROSPECTIVE STUDY

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ABSTRACT Diabetes mellitus (DM) is a complex metabolic disorder characterized by chronic hyperglycemia due to defect from insulin secretion, insulin action, or both. Despite intensive diabetes management, less than a fifth of diabetic patients achieve the recommended HbA1c target. This cohort prospective design study was conducted in the pediatric endocrinology division of Haji Adam Malik Hospital Medan from March- October 2019. A total of 14 children were enrolled in this study. This study result showed increase of 25(OH)D level from 18.6±5.6ng/mL to 27.3±5.9ng/mL (p=0.00) and decrease of HbA1c level from 9.8%±1.9 to 7,0%±1.1 (p=0.00). This study found a negative correlation between the HbA1c value and 25(OH)D level (r-0.83;p=0.00). The management of DM with standard medication plus vitamin D supplementation showed a satisfactory result and is expected to become a routine recommendation in the management of children with DM.

KEYWORDS : Diabetes Mellitus, Children, Hba1c, Vitamin D

INTRODUCTION

Hemoglobin A1c (HbA1c) is one of the measurement methods that helps to achieve the expected glycemic control, besides measuring blood sugar (self monitoring blood glucose / SMBG), reporting of hypoglycemia events, type of treatment, patient age and quality of life.[1] From a study conducted by Diabetes Control and Complications Trial (2008) reported that poor glycemic control for 5 to 7 years as a teenager could lead to an increased risk of microvascular and macrovascular complications 6 to 10 years later.[2]At present the evidence shows that achieving good glycemic control can reduce complications from diabetes mellitus (DM). However, even with intensive diabetes management, less than one fifth of DM patients achieve the recommended HbA1c level target.[3]

A South East Asian Nutrition Surveys (SEANUT) study in Indonesia, Malaysia, Thailand and Vietnam in 2016 showed that in Indonesia only 5% of children with adequate 25 (OH) D levels (serum levels> 30ng / mL).[4] Vitamin D deficiency affects almost 50% of the population worldwide.[5] Besides functioning to regulate calcium metabolism, vitamin D also functions in immunomodulating T helper cells, and inhibits the production of inflammatory cytokines that can damage pancreatic cells and helps insulin secretion.[6,7,8]

One study conducted by Wulandari reported that there was a strong negative correlation between low vitamin D levels and high HbA1c in DM patients.[9] Then, one study conducted by Dehkordi (2018) reported that vitamin D supplementation for 12 weeks can reduce patients' HbA1c levels and it is hoped that the results of these studies can be recommendations for additional therapy in DM patients.[10]

The results of studies increasingly support that vitamin D deficiency is often related to autoimmune disease and poor glycemic control in DM patients.[11,12] This statement is in line with studies conducted by Wulandari (2014) type 1 DM patients who had vitamin D levels that were much lower than the comparison group.[9]

Although vitamin D supplementation as insulin adjunctive therapy in type 1 DM patients can help with residual β cell function, however, studies by Sharma (2017), and Madar (2013) did not get a significant decrease in HbA1c levels.[13,14] Therefore, more studies are needed to support the provision of vitamin D supplementation for DM patients. The purpose of this study was to determine the efficacy of vitamin D supplementation in reducing HbA1c level.

METHODS

This study was a cohort prospective study was conducted on diabetic children who were recruited from the pediatric endocrinology unit in H. Adam Malik General Hospital Medan, periods from May to October 2019. All patients were diagnosed with either DM type 1 or 2 are recruited consecutively. Informed consent was obtained from all participants. Patients with chronic kidney disease, chronic liver diseases, malnutrition, malabsorption disorders such as short bowel syndrome, previously receiving vitamin D supplementation or any drugs affecting vitamin D level, such as steroids, antiepileptics, methotrexate, INH (isoniazid), thiazides, antacids, calcium channel blockers, and anticonvulsants, were excluded. The health research ethical committee number 395/TGL/KEPK FK USU-RSUP HAM/2019 was obtained from medical faculty of Universitas Sumatera Utara and number LB.02.03/II.4/154/2019 was obtained from the clinical research unit of H. Adam Malik Hospital. The sample size in this study was calculated based on the sample size formula for testing hypotheses in a population of mean differences before and after treatment.

$$n = [\frac{(Z\alpha + Z\beta) \times s}{(X1 - X0)}]^2$$

The calculation was done using a 95% confidence level with minimal sample size was 13 patients.

History taking, physical examination, and anthropometry data were carried out and informed consent was obtained from the parents. Blood drawn (T0) for laboratory tests was carried out when patients came for treatment or were hospitalized. Blood tests included complete blood, blood sugar levels, HbA1c, 25 (OH) vitD levels, urea, creatinine, urinalysis, and c-peptide. 25(OH)D level was examined by CLIA (Chemiluminescent Immunoassay) method. Patients were given vitamin D3 2000IU per day for 3 months. Second blood tests (T1) were done after the administration of vitamin D3 supplementation in the third month by re-examining the HbA1c level and 25 (OH) vitD levels.

All data obtained will be recorded and tabulated. The

Saphiro-Wilk test was used for assessment of normality of data distribution. Because the data were normally distributed, t-paired test was used to compare differences before and after receiving vitamin D3. Pearson's correlation test was used to examined correlation between the independent and dependent variables ($p < 0.05$). Mann-Whitney test was used to value the relationship between vitamin D levels with either type 1 DM or type 2 DM w the ($p < 0.05$). Data processing was performed using Statistical Package for Social Sciences for Windows (SPSS) version 24.0, 2016 with $p < 0.05$ was significance, and 95% confidence interval.

RESULT

From May to October 2019, 14 subjects met the study's inclusion and exclusion criteria were collected. Data is presented in tabular form. 14 subjects included male 35,7% and female 64,3% with type 1 DM 85,7% and type 2 DM 14,3%. All characteristic data from the research sample was listed in Table 1.

In this study, we found that all diabetic patients both type 1 and type 2 diabetes with vitamin D deficiency or insufficiency (listed in table 2). The levels of HbA1c, c-peptide and vitamin-D in the first month (T0) before receiving vitamin D supplementation and HbA1c levels with vitamin D in the third month (T1) after the administration of vitamin D supplementation were then analysed. The result of the t-dependent test found that 25(OH)D level increased significantly after supplementation of vitamin D ($p < 0.05$) accompanied by significant decrease in HbA1c ($p < 0.05$) (listed in table 3).

From the Pearson correlation test, we found that there was a strong negative correlation between 25 (OH) D and HbA1c levels both before the intervention (T0) was given with $r = -0.93$ ($p = 0.00$) and after vitamin D supplementation (T1) with $r = -0.64$ ($p = 0.01$) (listed in table 4). We found that either type 1 or type 2 DM was in vitamin D deficiency or insufficient status. Therefore, the Mann-Whitney test obtained results that stated that the actual levels of vitamin D had no relationship with which type of DM (listed in table 5).

DISCUSSION

The incidence of DM varies greatly. The highest incidence of type 1 DM is found in Finland which is 43/100,000 and the lowest incidence is found in Japan 2.4 / 100,000 and China 0.1/100,000 for children aged 15 years. Indonesia does not yet have the right DM incidence rate so that by referring to neighbour countries such as Singapore and Malaysia who have similar ethnic and cultural backgrounds, the estimated incidence of DM in children in Indonesia is 0.3 / 100,000. The peak age of incidence of type -1 DM in children is at the age of 5-6 years and 11 years.[15] Although type 1 diabetes is the most common case in children and adolescents, the number of children and adolescents with type 2 diabetes has also increased in recent years.[16] On study in Sweden reported the use of c-peptide to classified types of diabetes. Mostly children in c-peptide level between 0.2 -0.99 nmol/L were type 1 DM and c-peptide $\geq$ 1.0 nmol/L had predictive value for type 2 DM as 0.46 (95%CI 0.37 – 0.58).[17] The proportion of diabetic patient in this study was found most in type 1 DM was 85.7% with the age ranged between 4-17 years old and c-peptide range between 0,1-7,9 with all type 1 DM were below 1 ng/dL.

HbA1c is formed as a result of glucose binding to hemoglobin permanently with an estimated erythrocyte life span of 120 days. Therefore, HbA1c describes the state of glycemia for 4 - 12 weeks. HbA1c is believed to be the most useful parameter in evaluating metabolic control and has a close relationship with microvascular and macrovascular complications.[17] The recommended HbA1c target is $\leq$7%.[18] In addition, one of the criteria for diagnosis of diabetes mellitus is the HbA1c value $\geq$ 6.5%.[19] The mean HbA1c level while diagnosed with diabetes in this study was 9.8% $\pm$ 1.9. This level indicated poor glyce mic control.

According to the Endocrine Society, the term vitamin D deficiency when level of 25(OH)D are below 20 ng/ml (50 nmol/L) and vitamin D insufficiency when level of 25(OH)D are 21-29 ng / ml (52.5 - 72 , 5 nmol / liter).[20] Researchs in the United States, Canada and Europe explained that 20-100% of elderly people suffer from vitamin D deficiency and around one billion people worldwide experience vitamin D deficiency or insufficiency (Deluca HF, 2018). A South East Asian Nutrition Surveys (SEANUT) study in Indonesia, Malaysia, Thailand and Vietnam in 2016 showed that in Indonesia only 5% of children had adequate 25(OH)D levels (serum levels> 30ng / mL).[4]

Effects of vitamin D on immune responses can be through various complex mechanisms. Interaction of vitamin D with antigen presenting cell (APC) and T cells produced suppressive responses and down regulator immune responses. The effect of vitamin D began noticed since the discovery of vitamin D receptors on lymphocytes, which acted as anti-proliferation through the production of cytokines by T cells, had been found. Vitamin D binds to the DNA chain. Vitamin D inhibits the production of Th1, IL2 and INF-γ media tors in cell transcription processes thereby inhibiting damage from pancreatic β-cells.[21] A study conducted by Savastio et al for 6 years on type 1 DM patients reported that the average of pediatric and adolescent patients with type 1 DM had vitamin D deficiency.[22] In this study, vitamin D deficiency or insufficiency was found in all diabetic patients therefore we stated that levels of 25(OH)D had nothing to do with the type of diabetes.

The presence of vitamin D receptors (VDR) in pancreatic β cells is the origin of the working knowledge of vitamin D in glycemic control. Its mechanism of action is through the VD3-VDR complex which binds to the RXR and then forms the VD3-VDR-RXR-DNA polymerase complex which then binds to the insulin promoter gene and modulates the expression of the gene. In addition, the action of vitamin D also helps the influx of calcium thereby increasing insulin exocytosis.[6]

Several studies had shown that there is a strong relationship between low vitamin D levels and high HbA1c in both type 1 and type 2 DM patients.[23-28] Then, several intervention studies conducted by Dehkordi (2018) reported that vitamin D supplementation could reduce patients' HbA1c levels and it is expected that the results of these studies can be the recommendation for additional therapy in DM patients.[10,29,30] Although many studies had revealed significant effects and relationships, studies by Sharma (2017) and Madar (2013) did not get a significant decrease in HbA1c levels after vitamin D supplementation.[13,14] Research conducted by Savastio reported that vitamin D supplementation had improved the body's metabolic status and glycemic control significantly so it needs to be considered in additional therapy in diabetic patients.[22] In this study, supplementation of vitamin D 2000 IU for 3 months had significantly increased 25(OH)D levels and an increase in 25(OH)D level was negatively correlated with the decrease of HbA1c values.

CONCLUSION

All children with type 1 and type 2 diabetes are accompanied by vitamin D deficiency. There is a strong negative correlation between 25(OH)D and HbA1c levels. Giving vitamin D3 supplementation at a dose of 2000 IU per day for 3 months can significantly increase levels of 25(OH)D diabetic children. In this study, supplementation of vitamin D3 combination with standard therapy will help reduce HbA1c in diabetic children.

Table 1. Subject characteristics

Parameters	n = 14
Age (years),median(min-max)	9 (4 – 17)
Gender (n, %)	
• Boy	5 (35,7)
• Girl	9 (64,3)
Nutritional status (n, %)	
• Severe wasting	1 (7,1)
• Wasting	4 (28,6)
• Normal	7 (50)
• Overweight	1 (7,1)
• Obesity	1 (7,1)
Types of DM	12 (85,7)
Type 1 DM(n,%)	2 (14,3)
Type 2 DM(n,%)	

Table 2. HbA1c, c-peptide, and 25(OH)D levels in the first month (T0) and third months after recieving vitamin D supplemention

Parameters	n = 14 (T0)	n = 14 (T1)	Referal normal range
25(OH)D(ng/mL),mean(SD)	18,6 (5,65)	27,3 (5,9)	30-40
Normal (n.%)	-	6 (42,9)	
Insufisiensy (n,%)	6 (42,9)	7 (50)	
Deficiency (n,%)	8 (57,1)	1 (7,1)	
Types of DM			
Type 1 DM(n,%)	12 (85,7)	-	-
Type 2 DM(n,%)	2 (14,3)	-	-
HbA1c (%), mean (SD)	9,8 (1,9)	7,0 (1,1)	4 – 5,6
C-peptide (ng/ml), median (min-max)	0,35 (0,1-7,9)	-	0,9 – 7,1

Table 5.3. HbA1c and 25(OH)D levels before and after vitamin D supplementation (t-paired test)

Parameters	Suplementasi Vit-D		p
	Before	After	
25(OH)D, mean(SD)	18,6 (5,65)	27,3 (5,9)	0.000
HbA1c, mean(SD)	9,8 (1,9)	7,0(1,1)	0.000

Table 5.4. Correlation between HbA1c and 25(OH)D before (T0) and after supplementation (T1)

Parameters	25(OH)D	
	r	p
HbA1c (T0)	-0.83	0.00
HbA1c (T1)	-0.64	0.01

Tabel 5.5. Relationship between 25(OH)D level and Type 1 or Type 2 DM

Parameters	25(OH)D	
	n	p
Type 1 DM	12	0,201
Type 2 DM	2	

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