Available online www.ijpras.com

International Journal of Pharmaceutical Research & Allied Sciences, 2019, 8(3):204-211

Research Article

ISSN : 2277-3657
CODEN(USA) : IJPRPM

Association between Vitamin D Status and Type 1 Diabetes Mellitus in Saudi Adolescents

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ABSTRACT

Background: Nowadays, the deficiency of vitamin D (VD) is a health problem worldwide, that affects many people including adolescents who have type 1 diabetes mellitus (T1DM). However, the role of VD in autoimmune diseases such as T1DM has been a recent interest. Aim: This study was designed to assess the VD deficiency prevalence in Saudi adolescents with or without T1DM. Methods: In this case-control study, 49 T1DM and 49 control (non-DM) (N=98), age and gender-matched were enrolled. The study was carried out from May to September 2017 at King Abdulaziz University Hospital (KAUH). After obtaining the consent form, the blood samples were withdrawn to determine fasting blood glucose (FBG) and glycosylated hemoglobin (HbA1c) in blood and VD (25OHD) in serum. Statistical analysis was made by SPSS version 22. Results: Data showed that 25OHD levels were significantly lower in adolescents with T1DM compared to the controls (49.5 ± 26.9 nmol/L vs 67.96 ± 30.03 nmol/L). In the T1DM adolescents, VD was deficient in 44.9%, insufficient in 36.7%, and sufficient in 18.4% as compared with 34.7% (deficient), 26.5% (insufficient), and 42.86% (sufficient) in non-DM adolescents. Overall, VD was deficient and insufficient in 81.6% of the T1DM adolescents and 61.2% of non-DM adolescents, respectively. Considering sex, females showed higher significance between T1DM and non-DM groups in overall groups, and in all VD level subgroups, males showed significance ($p<0.05$) in only overall groups and in insufficient VD levels. The data showed an inverse correlation between HbA1c and FBG values with VD concentration. While there was no correlation between both glycemic parameters with VD in non-DM group. Conclusion: The VD deficiency prevalence in T1DM Saudi adolescents was relatively high particularly in females. Therefore, screening for VD status and supplementation in early young age should be warranted.

Key words: *VD deficiency, Adolescents, Type 1 diabetes mellitus, Glycemic control.*

INTRODUCTION

T1DM is one of the autoimmune diseases that occurs in the pancreas. T1DM can affect any age of community, particularly children and adolescents, which represent almost 90% of afflicted population. [1, 2] Previously, the estimated incidence of T1DM per 100,000 of Saudi children and young ages was 27.5 in the eastern region. [3] and 29 in the northwest area of KSA. [4] Recently, the International Diabetes Federation (IDF) has considered KSA as one of the highest rates of T1DM incidence for ages between 0-19 years. [5] The molecular mechanism of T1DM is unclear but it may be related to many factors such as genetics and environment. [6] The destruction of pancreatic insulin production that is immune-mediated, leads to the induction of T1DM disease. Previous literature has illustrated the important role of VD in immune system modulation and its impact on T1DM onset. [7]

The VD is very important for bone growth and accretion during childhood and adolescence stages. In the last decade, perceiving VD effects and its role in the functioning of body tissues, systems, and organs have substantially been improved. VD is considered deficient, when 25-hydroxy VD (25-OHVD) value is <30 nmol/L in circulation. [8] VD function of in the body goes through two mechanisms, one by an endocrine that regulates calcium absorption and the other by an autocrine that facilitates gene expression. [9] The low level of VD has been embroiled in many chronic diseases such as autoimmunity DM, bone mineral disease, and cancer.

[10] A lot of evidence has revealed that 1,25(OH)2D3 is closely related to the occurrence of autoimmune diseases. [11, 12] Some studies reported a connection between β-cell dysfunction and insulin resistance that consequently leads to the incidence of T1DM with deficiency of VD in adult population. [13, 14] A recent study confirmed that vitamin D has an important role in the inflammation and immune response inhibition, enhancing insulin synthesis and secretion, as well as enhancing insulin sensitivity. [15] The prevalence of VD deficiency in children and adolescents with T1DM is higher compared to the general population. [16, 17] In a review study, it has been revealed that the deficient levels of circulated VD have a potency on the incidence, progression, and complications of T1DM disease. [18] Many previous studies, carried on youth in different countries, reported that the deficiency of VD is still a prevalent and unrecognized health problem. [19] In Middle East, many studies reported that there is low VD concentration in serum across many regions, ages, and genders. [20-22]
This work aimed to explore the relationship between the VD level in serum and the incidence of T1DM in Saudi adolescents.

MATERIAL AND METHODS

Subjects:

A total of 49 established T1DM adolescents (12-18-year-old) were recruited from the Pediatric Endocrine Clinic at KAUH. In addition, 49 control (non-DM) adolescents were recruited. The control adolescents group included outpatients of non-diabetic units, who were randomly selected and matched according to age, gender, and ethnicity. This study was undertaken between May 7, 2017 and September 30, 2017. The control adolescents who had problems in bones, kidneys, liver, endocrinopathies, other autoimmune diseases or any other diseases that might influence VD metabolism were excluded. These procedures were approved by the Faculty of Medicine's Ethical Committee, KAU (Protocol Reference No. 205.16). The written consent was obtained from the parents or guardians of the adolescents before starting the work.

Samples collection and processing:

Before withdrawing the blood samples, all adolescents were told to rest in the seating position for 15 min to allow the calibration of blood components' concentrations. Then, approximately 3 ml of venous blood samples were drawn after the participants' fasting for at least 8-10 hours. One ml of each sample was kept in a tube containing EDTA for FBG and HbA1c tests. The rest of blood samples were centrifuged at 3000 rpm for 10 minutes for the serum separation. Then, the serum was frozen at -80°C for subsequent analyses.

Total VD test:

The serum total VD level was measured by ADVIA Centaur ®immunoassay System (SIEMENS, USA). Literature has recommended the following cutoff points to categorize the VD status for adolescents, based on serum VD values to: sufficiency (>75 nmol/L); insufficiency (51–74.5 nmol/L); and deficiency (<50 nmol/L).[23-25]

Fasting blood glucose (FBG):

The FBG was measured by Dimension Vista® System (SIEMENS, Germany), expressed as mg/dl.

Glycosylated hemoglobin (HbA1c):

The percentage of HbA1c was determined by monoclonal antibody agglutination method (Siemens DCA Vantage analyzer).

Statistical analyses:

They were performed using (SPSS), version 22 (SAS Institute Inc., Cary, NC, USA). ANOVA and t-test were applied for comparing average values. In addition, the correlation coefficient was used to evaluate the relationship between HbA1c and FBG values and VD levels. The resulted values were represented as mean ± SD, and p-value less than 0.05 was considered statistically significant.

RESULTS

In this study, 49 T1DM and 49 control (non-DM) adolescents were selected as the participants. The participants' characteristics have been described in Table (1). The subjects' mean age in the T1DM group was 14.52 ± 2.06 years, and that of non-DM group was 13.92 ± 2.03 years with the p-value of 0.435. The percentages of both sexes were almost equal in both adolescent groups. The average duration of diabetes in T1DM adolescents was 4.6±3.7 years. The average serum VD concentration of the total T1DM adolescents was significantly (p=0.002) lower than that of the non-DM control group (49.5 ± 26.9 nmol/L vs 67.96 ± 30.03 nmol/L) (see Table. 2). In the total T1DM adolescents, the deficiency percentage was 44.9% (22/49), the insufficiency percentage was 36.7%

(18/49), and both the deficiency and insufficiency percentages was 81.6% (40/49), while in the non-DM adolescents, the deficiency percenrage was 34.7% (17/49), the insufficiency percentage was 26.5% (13/49), and both the deficiency and insufficiency percentage was 61.2% (30/49). The differences between total T1DM and non-DM adolescents in the deficient and sufficient subgroups was statistically significant at p-values 0.002 and 0.045, respectively. While differences were not significant in the insufficient level of VD (p=0.507) (Table 2).

The serum VD levels in both adolescent groups according to the gender distribution are shown in Table (3), which shows the differences in VD levels based on the sex of the participants. The deficiency of VD was significant in both genders between the two groups, with higher significance in females at the p-value of 0.007 than males at the p-value of 0.028. The female adolescents showed significant differences with different p-values in all VD levels between T1DM and non-DM groups. While male adolescents showed significant differences (p=0.03) only at insufficient VD level with no significance at deficient or sufficient levels of the vitamin D (Table 3), no significant difference was detected based on sex in each adolescent group.

The linear correlation between the VD value in serum and HbA1c (%) in T1DM adolescents group is shown in Figure (1). The data showed an opposite correlation (r= -0.542, p<0.01) between the HbA1c values with VD while showed no correlation between VD and HbA1c in non-DM group ($r = 0.137$; $P = 0.09$).

In addition, the data detected a negative correlation between the FBG values and VD concentration in T1DM adolescents (Fig. 2) (r= -0.369, $P < 0.01$), while no correlation existed between VD and FBG in non-DM group ($r = 0.095$; $P = 0.15$).

Table 1: Characteristics of T1DM and non-DM study participants

	Non-DM (n=49)	T1DM (n= 49)	P-value
Gender Male	24 (50.0 %)	24 (50.0 %)	0.98
Female	25 (50.0 %)	25 (50.0 %)	
Age (years)[a]	13.92±2.03	14.52±2.08	0.435
12-14 y	23 (46.9%)	19 (38.8%)	0.414
15-18 y	26 (53.1%)	30 (61.2%)	
Duration of Diabetic (Y)	4.6±3.7	N/A	

[a] Values are expressed as mean ± SD. The p-value of less than 0.05 was statistically significant.

Table 2: Serum levels of VD in T1DM and non-DM adolescents

Vit. D levels	Non-DM	T1DM	p-value
Overall	67.96±30.27	49.5±26.9	0.002
Deficient nmol/L	37.14±9.64	23.23±11.02	0.002
%	34.7%	44.9%	
Insufficient nmol/L	62.48±7.7	62.19±5.72	0.207
%	26.5%	36.7%	
Sufficient nmol/L	94.68±23.27	82.96±5.59	0.045
%	42.86%	18.4%	

Values are expressed as Mean±SD, when *P*-value less than 0.05 was statistically significant.

Table 3: Serum VD levels in T1DM and non-DM based on gender

Vit D levels	Non-DM		T1DM			
	Male	Female	Male	Female	*P1	**P2
Overall	71.29±34.95	66.47±28.8	51.28±25.19	43.81±27.7	0.028	0.007
Deficient	38.9±8.5	31.1±7.2	33.48±7.3	26.05±11.8	0.09	0.045
Insufficient	56.8±6.6	66.0±6.3	61.78±4.7	62.71±5.3	0.03	0.025
Sufficient	92.9±18.5	85.3±8.8	89.9±9.5	80.7±2.1	0.056	0.045

Values are expressed as Mean±SD when P-value less than 0.05 was statistically significant.

*P1 value for males (non-T1DM and T1DM). **P2 value for females (non-T1DM and T1DM).

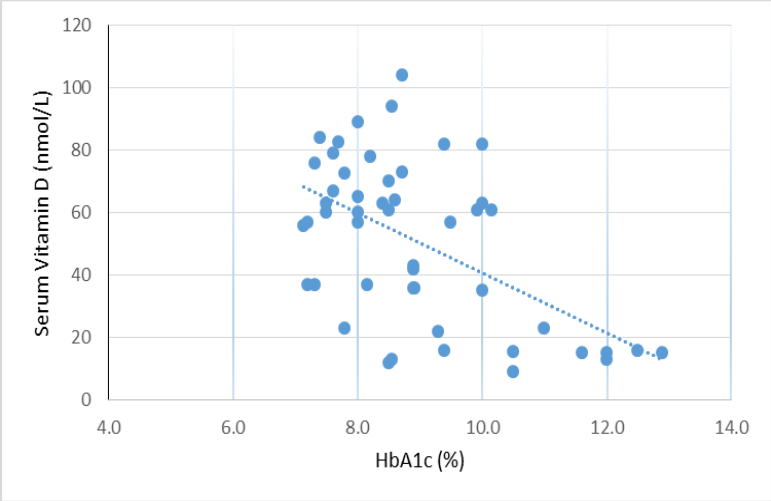

Figure 1: Linear correlation between VD (nmol/L) value in serum and HbA1c (%) in T1DM adolescent group.

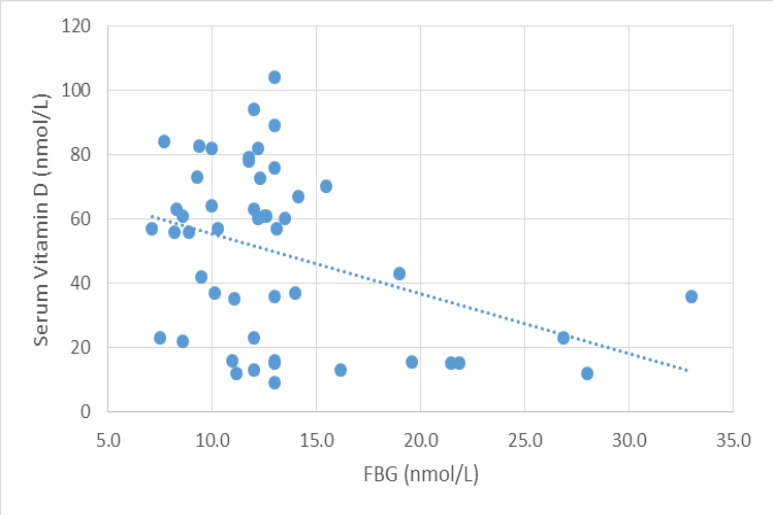

Figure 2: Linear correlation between VD (nmol/L) value in serum and FBG in the T1DM adolescent group.

DISCUSSION

Previously, VD was known to be essential for normal skeletal architecture and maintenance of mineral homeostasis. Recently, it has been increasingly recognized for its potency as prodifferentiative potent antiproliferative and immunomodulatory activities. [11, 12, 26] VD, known as an immunomodulator, can prevent the occurrence and development of T1DM in non-obese diabetic (NOD) mice, also it is effective against apoptosis in human pancreatic islets *in vitro.* [27] It also inhibits the differentiation and maturation of dendritic cells with the promotion of apoptosis. Moreover, it prevents transformation of dendritic cells into antigen-presenting cells, which is the first step of the immune response. [18] Mice showed impairment in both glucose tolerance and islet function gene transcription when they underwent diet-induced hypovitaminosis D. [28] A recent review illustrated the role of vitamin D in pancreatic disease (T1DM and T2DM) as well as pancreatic cancer. [29]

Many observational studies detected a significantly high prevalence of 25-OHVD deficiency in T1DM patients compared to non-DM. [7, 14, 30-39] In Switzerland, a cross-sectional study detected VD deficiency percentages of 60-84% in T1DM children [30] while it was 58% against 32% in control children in North India. [31]. In Turkey, 28-43 of 100 children and young adults with T1DM were VD-deficient [32] and in another region in Turkey, the percentage of VD deficiency and insufficiency was 38% in similar age groups. [33] While in an American cross-sectional study, the 25-OH D deficient and insufficient percentages were 15% and 61%, respectively in T1DM patients and these deficient levels were inversely associated with age. [34] Recently, the V-deficiency percentage was 75.3% in Iranian diabetic children (1-15 y). [14] Furthermore, in the Middle East, the V-deficiency prevalence varied between 77% and 91.67% even in sunny countries. In a recent study in

Jeddah, it was found that 77% of diabetic children and adolescents (1-18 y) had low concentration of VD in total. [35] In a cross-sectional study in Riyadh, low concentration of VD was detected in 84% of T1DM Saudi children. [36] Some cross-sectional Egyptian studies showed that VD deficiency varied from 70% to 91.67% in similar age groups. [37, 38] In Qatar, VD deficiency was high with a percentage of 90.6% in T1DM children versus 85.3% in control children. [39] Otherwise, 84% of 216 Kuwaiti children with T1DM were deficient in VD value compared to 77 % in non-DM children. [7] This work mentioned that 81.6% of T1DM adolescents had low values of VD, while 36.7% of them had insufficient VD values. The percentage of VD deficiency in this workgroups was within the average of hypovitaminosis D in Arab's T1DM adolescents. These variations in vitamin D deficiency levels are probably related to the direct impact of geographic and latitude environments. [35] The low VD values that occurred among T1DM patients, maybe due to the presence of a pre-existing VD insufficiency status that played a role of contributing factor in the development of T1DM. [35]

The differences that were previously reported about VD deficiency in adolescents with T1DM can also be due to various causes. One of them may be related to the occurrence of a malabsorptive state among those groups of adolescents. [35] A reasonable suggested mechanism to explain the association between VD deficiency and DM is the urinary loss of VD binding protein (VDBP), which is subsequent to the reduced availability of megalin or low-density lipoprotein-related protein 2 (LRP2), together with proteinuria. The megalin is considered as a receptor of many ligands, including VDBP, which encourages the production of 1,25(OH)2VD, the most active form of VD, followed by reabsorption of complex VDBP-25OHD via megalin endocytic receptor. [40] The fact that VD can prevent islet cell death has been evidently described. [27] So, there is a direct link between hypovitaminosis D, beta-cell impairment, and insulin resistance. [41] On the other hand, some cases like severe ketoacidosis may have transiently lower 25OHD levels in children with new-onset T1DM. [42] The supplementation of VD can improve glycemic control. [17] Furthermore, there is a linkage between HbA1c and VD that may occur because of the influences of vitamin D on insulin production from beta-cells and its actions. [43, 44] The current work has detected a strong negative association between HbA1c and VD values in T1DM adolescents. These results confirmed previous studies in children. A recent study identified that 66% of T1DM and VD deficient Saudi children were poorly controlled HbA1c (>9%). [35] The association between HbA1c values and 25OHD levels in established T1DM children was recently reported. [44] The reduced levels of 25(OH)VD in serum had a close relationship with improper metabolic control among diabetic patients. [34, 45]

This work indicated higher deficiency levels of VD among girls compared to boys. A recent study on T1DM children and early adolescents found that 61.5% of girls had inadequacy of VD, whereas only 38.5% of boys showed VD deficiency. [35] In spite of that, a similar study confirmed that girls have more tendency to cope up with the deficiency of VD in comparison to boys. [46]

One of the strongest points of this study was the determination of VD values in matched groups of both T1DM and control adolescents. There were some limitations like a deep need to carry out this research point based on a molecular mechanism.

CONCLUSION

The T1DM adolescents had lower VD in circulation than the controls. Furthermore, in this group, the VD values in serum were significantly lower in females than in males. Whether low VD is a risk factor or consequence of T1DM is still to be deeply researched.

ACKNOWLEDGMENTS

The authors would like to express their thanks and appreciation to King Abdulaziz University of Science and Technology for the financial support to the project of the research (number 1-17-00-009-0024).

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