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Assessment of Vitamin D Status and Study the Effect of Supplementation of Vitamin D on Type 1 Diabetic Children in Egypt

Hamdy A. Ibrahim[1,*], Mohamed R. E. Aly[1], Odette W. Hindy[2], Ayman El Baz[3], Ayda K. Kelany[4]

[1] Chemistry Department, Faculty of Science, Port Said University, 42522 Port Said, Egypt

[2] Biochemistry Department, Faculty of Medicine, Cairo University, Cairo, Egypt

[3] Department of Basic Medical Sciences, Faculty of Medicine, University of Ibn Sina for Medical Sciences, Amman, Jordan

[4] Department of Genomic Medicine, Cairo University hospitals, Cairo University, Cairo, Egypt

***Corresponding author: mrea34@hotmail.com**

ABSTRACT

Background: A pancreatic B-cell loss autoimmune condition known as type 1 diabetes (T1D). T1D is a significant global health concern as its prevalence rises by 2% to 5% globally each year. It is indicated that a vitamin D (Vit D) deficit increases the likelihood of developing T1D. Since large interventional trials have failed to clearly demonstrate a benefit, the role of supplementation of Vit D and the ideal Vit D dose are now up for discussion. The aim of the present study to assess vitamin D deficiency in children with type 1 diabetes with laboratory assessments and studying the effect of Vit D supplementation on glycemic control. **Subjects & Methods:** A prospective research was carried out to assess how supplementation of Vit D affected young individuals with T1D. In this research, 60 children divided to two groups, 40 T1D children with a mean age of 7.9 years ±2.7 SD, and their levels of Vit D less than 20ng/ml, and healthy 20 children participated in this study as control group, from Abo-Elrish Pediatric Hospital, Cairo University. Chemiluminescence immunoassay was utilized to assess the serum 1,25-Dihydroxyvitamin D levels of each sample. Serum calcium (total), serum parathyroid hormone (PTH), serum phosphorus, serum alkaline phosphatase (ALP) was evaluated; serum fasting, P.P., random glucose and glycated hemoglobin (HbA1c%) levels were also assessed for both groups, supplementation was added by 4000 IU/ day Vit D for 3 months to patient's group only. Results: Before supplementation, blood levels of vitamin D were considerably lower in diabetes participants in comparison to the control group (9.3±1.4Vs 59.2 ± 18.7ng/ml $p < 0.0001$).

While after supplementation of Vit D, levels of 1,25- Dihydroxyvitamin D were improved in contrast to that before (9.3± 1.4 Vs 38.7±4.2ng/ml $p < 0.0001$). There was also improvement in the glycemic evaluated by HbA1c% and serum glucose after supplementation 10.5±1.3 Vs 5.2±0.8% and 231.8±11.0 Vs 89.6±7.7mg/dl respectively $p<0.0001$) for HbA1c% and glucose before and after supplementation respectively.

Conclusion: It would seem crucial to implement a global public health intervention which incorporates supplementation of Vit D in particular risk groups to prevent severe Vit D insufficiency.

Key Words:

Vitamin D deficiency, Type 1 diabetes mellitus, parathyroid hormone, HbAlc%, pancreatic B-cell, supplementation

1. INTRODUCTION

Vitamin D deficiency was reported to be a risk factor in the development of T1D. The data that was currently accessible on children and teenagers demonstrate that hypovitaminosis D was common and is an increasing by approximately 2% to 5% worldwide every year and becoming a global health problem [1]. Due to its relatively abundant circulating levels, long half-life (2–3 weeks), and resistance to variations in PTH levels, blood concentration of 1,25- Dihydroxyvitamin D was generally utilized to assess the whole-body Vit D state [2].

It is widely acknowledged that a deficiency of Vit D can lead to adult osteomalacia and childhood rickets. Nutritional rickets practically eliminated from developed nations once Vit D was identified and dietary supplements with Vit D were introduced [3]. Lately, Vit D state was defined as sufficiency, serum 1,25- Dihydroxyvitamin D > 20ng/ml insufficiency, serum 1,25- Dihydroxyvitamin D 12-20ng/ml, and deficiency, serum 1,25- Dihydroxyvitamin D < 12ng/ml according to the "Global Consensus Recommendations on Prevention and Management of Nutritional Rickets". Additionally, this agreement defines toxicity as serum 1,25- Dihydroxyvitamin D levels greater than 100ng/ml, hypercalcemia, hypercalciuria, and suppressed PTH [4]. Other scientific organizations as Wadi El Nile hospitals, on the other hand, have established the threshold for Vit D adequacy at > 30ng/ml [5].

Recent studies showed that supplementation of Vit D alleviated disease symptoms in T1D patients. However, a few randomized controlled trials (RCTs) demonstrated the clinical effect of Vit D treatment with inconsistent findings. This article aimed to evaluate the effect of Vit D supplementation in T1D, which is helpful to develop an adjuvant therapy for T1D (6). Thus, more long time and large-scale studies are required to evaluate the role of Vit D supplementation in T1D. Further studies are needed to establish the duration of therapy, the optimal dose, the appropriate form of Vit D [VD3, alfacalcidol (1a-OHD3), 25-OHD3, 1,25(OH)2D3] or its analogs to elucidate the conclusion (7)

The objective was to evaluate how Vit D supplementation affected Egyptian children with T1D, which was useful for adjuvant therapy.

2. SUBJECTS AND METHODS

For determining the impact of supplementation of Vit D on individuals with Type 1 Diabetes Mellitus (T1DM) who have previously received proof of other elements, prospective research was conducted [8].

This study included 60 participants of outpatients who visit Abo-Elrish Pediatric Hospital, Cairo University, from May 2017 to November 2018, classified into 40 children had T1DM with low vitamin D (13 males and 27 females) and 20 healthy children (control group) (14 males and 6 females). They had age ranged from 4-14 years (8.4 ± 3.0).

Everyone who participated signed a permission form after receiving full information. Patients who had T1D and 1,25- Dihydroxyvitamin D levels more than 30ng/ml following the experiment were not included in the study. Outpatients with serum 25 (OH) D less than 30ng /ml and had type 1 Diabetes Mellitus were chosen as cases or patient group. Others who had 1,25- Dihydroxyvitamin D levels more than 30ng/ml without diabetic history, they were chosen as control group. Exclusion criteria (a) bone metabolism disorders (b) uncontrolled hypo or hyperthyroidism (c) cases with chronic liver disease and cases allergic to Vit D supplementation components.

Samples collection and analysis

After three months of supplementation with 4000 IU/day of Vit D (cholecalciferol 500 IU/drop) for the patient's group exclusively, laboratory assessments were examined firstly for the diabetic and control groups. Glycated hemoglobin (HbA1c), fasting glucose (FG), 1,25- Dihydroxyvitamin D, phosphorus, magnesium, total calcium, alanine aminotransferase (ALT), and aspartate aminotransferase (AST), all these parameters using serum except HbA1c using 20 µl whole blood. Fasting blood glucose (mg/dl) using Enzymatic Colorimetric Method with catalog number. GL 13 20. Serum calcium (mg/dl); magnesium (mg/dl), phosphorus (mg/dl), and alkaline phosphatase ALP (U/l) levels were measured by using Colorimetric Method with catalog numbers. CA 12 10, MG 16 10, E-BC-K245-M and MBS011598 respectively, while parathyroid hormone (PTH) (Pg/ml), ALT and AST (U/l) were validated by Elisa kit. Serum Vit D ng/ml quantities and glycosylated hemoglobin (Hb_{A1c} %) were assessed utilizing chemilum-inescence immunoassay through Siemens Dimension X pand plus apparatus.

Statistical analysis

All results were expressed as the mean ± standard division (SD). Data were analyzed using one-way variance analysis (ANOVA), using the social sciences statistical package (SPSS) program, version 18 followed by the least significant difference (LSD) to compare meaning among groups. Variance was deemed significant when P was ≤ 0.05 (9).

3. RESULTS

In our study, before Vit D supplementation, biochemical parameters measured for patients and compared to controls **(Table 1),** Vit D25, Ca (Total), HbA1c, ph, Alp, PTH and glucose were a highly significant differences between two groups (p= < 0.0001). On the other hand, Mg, AST and ALT were nonsignificant differences. After Vit D supplementation, biochemical parameters measured for patients and compared to controls **(Table 2),** Vitamin D25, Hb_{A1c}, ph, Alp and PTH were significant differences between two groups. On the other hand, no significant differences between the two studied group in Mg, AST, Ca (Total), and glucose and ALT.

The status of Vit D before supplementation, in comparison to after supplementation was revealed in mean values ± SD of vitamin D were (9.3 ± 1.4 Vs 38.7± 4.2 p< 0.0001) respectively. The laboratory and clinical features of the examined subjects before and after Vit D treatment of the studied cases were shown in **table 3,** also, it showed enhancement in the glycemic control evaluated by Hb_{Alc}, % and serum glucose mg/dl mean ± SD of their values were (10.5 ± 1.3Vs5.2 ± 0.8% p <0.0001, and 231.8 ± 11.0Vs89.6 ± 7.7mg/dl p <0.0001) respectively. Healthy group was near in mean values ± SD to values after supplementation mean values ± SD 4.5 ± 1.4 VS 5.2 ± 0.8% and 88.1 ± 10.1 Vs 89.6 ± 7.7mg/dl respectively **(Table 3).**

The correlation between Vit. D and HbAlc before and after supplementation were (r = - 0.8 p < 0.0001 Vs r = 0.1p = 0.4) were shown in **(Table 4,5)** respectively; negative correlation with high significant before versus positive correlation with no significant after supplementation. In serum glucose the correlation at the two before and after supplementation were (r = - 0.9, p < 0.0001Vs r = - 0.03, p = 0.8) respectively, that showed negative correlations before, after supplementation and the significant in before while insignificant after supplementation **(Table 4,5)** There was also improvement in Ca (Total) mg/dl after supplementation in comparison to that before, the correlations were (r = 0.8, p < 0.0001 Vs r = 0.3, p = 0.03) respectively, that showed positive association between Ca (total) and Vit D with highly significant before supplementation and insignificant after supplementation.

4. DISCUSSION

Vitamin D plays a fundamental role in regulating calcium and phosphorus homeostasis and, in particular, the pathways involved in bone mineralization and bone mass acquisition. As Vit D deficiency is believed to act a direct function in inducing immune-mediated B-cell destruction and calcium-mediated dysfunction that results in the development of clinical Diabetes, Vit D levels must be minimal at the moment of diagnosis (10). Vit D deficiency has been confirmed to be closely related to pancreatic b-cell destruction and T1D. Thus, more longtime and large-scale studies are required to evaluate the role of Vit D supplementation in T1D (7).

Studies that have evaluated intake of Vit D from the diet and/or supplements in relation to the risk of islet autoimmunity and type 1 diabetes, have produced mixed results. In addition to the dietary intake, several factors modify serum 1,25- Dihydroxyvitamin D concentration including genetic factors and the amount of sunlight. Therefore, it may be challenging to determine whether higher intake of Vit D from the diet or supplements has resulted in an improved vitamin D status, especially if the amount of recommended supplementation has been low (11).

In the present study, a significant low mean value of Vit D in diabetic group compare to control group as shown in table 1 $P < 0.0001$. While after supplementation of Vit D there was improvement of Vit D in diabetic group in comparison with diabetic group before supplementation with significantly high $P<0.0001$ shown in table 3. Azab et al observed a significant difference was observed between Vit D deficient diabetic cases and those with normal vitamin D level regarding serum calcium, phosphorus, alkaline phosphatase, and serum parathyroid hormone levels (all $P < 0.01$) (12).

Recently, a retrospective study demonstrated that treatment of Vit D3 improved the glycemic control, for the mean hemoglobin A1c (HbA1c) was 73.5 ± 14.9 mmol/mol and 65 ± 11.2 mmol/mol ($P < 0.001$) before and after Vit D3 administration for 3 months (13). There is a controversy regarding glycemic control and Vit D supplementation. Some studies have reported an improvement in glycemic control after Vit D supplementation in patients with DM1 (14). Also, Panjiyar et al demonstrated that T1D patients with Vit D3 supplementation lowered HbA1c, fasting blood glucose (FBG) and mean blood glucose (MBG) level (15). Although some authors as Hafez et al described an improvement in glycemic levels (15), others as Bizzarri et al did not agree (16).

De Melo et al suggest that Vit D is generally not recommended for the management of hyperglycemia in T1DM patients, although we have found a subgroup that might benefit from this approach. We also found an association between Vit D and HbA1c in our regression model. Nevertheless, additional studies are necessary in order to confirm our results (17).

Most of the patients who denied Vit D supplementation admitted a lack of knowledge and a lack of personal motivation to initialize Vit D supplementation. These justify the continuation of efforts to increase public awareness on Vit D benefits. Moreover, irregular supplementation and a too-low Vit D daily dose were the most frequent errors in supplementation. To prevent ineffective Vit D

supplementation, medical professionals should motivate their patients for regular and adequate supplementation (18).

5. CONCLUSIONS

Given the significant insufficiency, a connection between autoimmune disorder and deficiency of Vit D has been established. We claim that given the prevalence of deficiency of Vit D in children with T1D, its possible health impacts, and the simplicity of its treatment, pediatric endocrinologists must think about routinely screening their T1D cases for insufficiency or deficiency of Vit D. Correcting Vit D insufficiency in people with T1D has the potential to have a large positive impact on their health because Vit D supplements are affordable and widely available.

Table (1): Studied parameters before vitamin D supplementation among control and diabetic groups.

Variables	control group (n=20)	diabetic group (n=40)	P value
1,25-Dihydroxyvitamin D ng/ml	59.2±18.7	9.3±1.4	<0.0001
Ca (Total) mg/dL	9.1±1.0	5.7±1.2	<0.0001
Hb_{A1c}%	4.5±1.4	10.5±1.3	<0.0001
ph mg/dL	4.4±1.3	7.5±2.4	<0.0001
Alp U/L	373.7±65.4	503.9±11.5	<0.0001
Mg mg/dL	1.9±0.4	1.8±0.3	0.1
PTH pg/mL	34.7±11.6	72.2±5.5	<0.0001
AST U/L	25.5±7.5	23.9±7.7	0.4
ALT U/L	29.9±9.1	25.2±9.8	0. 1
Glucose mg/dl	88.1±10.1	231.8±11.0	<0.0001

Table (2): Studied parameters after vitamin D supplementation among control and diabetic groups.

Variables	control group (n=20)	diabetic group (n=40)	P value
1,25- Dihydroxyvitamin D ng/ml	59.2±18.7	38.7±4.2	<0.0001
Ca (Total) mg/dL	9.1±1.0	8.6±0.9	0.1
HbA1c%	4.5±1.4	5.2±0.8	0.01
ph mg/dL	4.4±1.3	5.3±0.9	0.001
Alp U/L	373.7±65.4	433.0±45.9	<0.0001
Mg mg/dL	1.9±0.4	2.0±0.3	0.4
PTH pg/mL	34.7±11.6	50.0±7.1	<0.0001
AST U/L	25.5±7.5	22.8±5.3	0.1
ALT U/L	29.9±9.1	25.9±7.9	0.1
Glucose mg/dl	88.1±10.1	89.6±7.7	0.5

Table (3): Effect of vitamin D supplementation on studied parameters among studied cases.

Variables	Before supplementation n=40	After supplementation n=40	P value
1,25- Dihydroxyvitamin D ng/ml	9.3±1.4	38.7±4.2	**<0.0001**
Ca (Total) mg/dL	5.7±1.2	8.6±0.9	**<0.0001**
HbA1c%	10.5±1.3	5.2±0.8	**<0.0001**
ph mg/dL	7.5±2.4	5.3±0.9	**<0.0001**
Alp U/L	503.9±11.5	433.0±45.9	**0.001**
Mg mg/dL	1.8±0.3	2.0±0.3	**<0.0001**
PTH pg/mL	72.2±5.5	50.0±7.1	**<0.0001**
AST U/L	23.9±7.7	22.8±5.3	**0.5**
ALT U/L	25.2±9.8	25.9±7.9	**0. 7**
Glucose mg/dl	231.8±11.0	89.6±7.7	**<0.0001**

Table (4): Correlation between Vit D and other tests before Supplementation.

Variable	r	P value
1,25- Dihydroxyvitamin		
Weight	0.6	**<0.0001**
Height	0.3	**0.02**
BMI	0.3	**0.02**
Ca (Total) mg/dL	0.8	**<0.0001**
HbA1c%	-0.8	**<0.0001**
ph mg/dL	-0.5	**<0.0001**
Alkaline phosphatase U/L	-0.7	**<0.0001**
Mg mg/dL	0.3	**0.01**
PTH pg/mL	-0.8	**<0.0001**
AST U/L	0.2	**0.2**
ALT U/L	0.2	**0.05**
Glucose mg/dl	-0.9	**<0.0001**

Table (5): Correlation between Vit D and other tests after Supplementation.

Variable	r	P value
Vit D25(OHD		
Weight	0.6	**<0.0001**
Height	0.3	**0.02**
BMI	0.3	**0.02**
Ca (Total) mg/dL	0.3	**0.03**
HbA1c%	0.1	**0.4**
ph mg/dL	-0.2	**0. 2**
Alkaline phosphatase U/L	-0.1	**0. 2**
Mg mg/dL	0.2	**0. 2**
PTH pg/mL	-0.3	**0.01**
AST U/L	0.2	**0.05**
ALT U/L	0.2	**0.05**
Glucose mg/dl	-0.03	**0.8**

6. Recommendations

The study recommend that Vit D will eventually be employed as an adjuvant treatment to enhance T1DM patients' quality of life.

7. Conflict of interest

There are no competing interests.

8. Fund

No particular grant organizations in the public, commercial, or nonprofit sectors was awarded to this research.

9. Data availability

In the endocrinology clinic affiliated to Abu Al-Rish children's Hospital, Faculty of Medicine, Cairo University. All cases data were taken from children suffering from type1 diabetes and deficiency in vitamin D. The children's medical history was followed up.

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