Title:

The Effects of Vitamin D Supplementation on Glycemic Control in Children with Type 1 Diabetes Mellitus in Gaza Strip, A Randomized Controlled Trial.

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Running title:

Vitamin D Supplementation and Glycemic Control Improvement among Type 1 Diabetic Children.

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Abstract

Objective: To screen for vitamin D deficiency, and to examine the effects of vitamin D supplementation on glycemic control among children with Type 1 Diabetes Mellitus (T1DM).

Material and Methods: A randomized clinical trial including 80 children (40 interventions and 40 controls) who were diagnosed with T1DM. Vitamin D status and glycated hemoglobin (HbA1c) were assessed initially for both groups. The intervention group was on (2000 IU/day) of vitamin D_3 for 3 months while the control group did not receive any type of supplements throughout the intervention period. Vitamin D and HbA1c were measured at the baseline and the end of the study. Differences in mean±SD of vitamin D and HbA1c were assessed before and after the study.

Results: A high prevalence of vitamin D deficiency (43.8%) and insufficiency (52.5%) was found among children with T1DM. Mean baseline serum 25-hydroxyvitamin D (25(OH)D) (ng/ml) increased from 14.76±3.71 to 12.46±4.35 and 38.79±16.86 to 14.88±4.73 in both the intervention and control groups, respectively. Mean baseline HbA1c (%) was 10.23±1.95 in the intervention group and 9.86±2.19 in the control group. After vitamin D supplementation for three months, mean HbA1c (%) was 9.20±1.50 in intervention and 10.28±1.77 in the control group without statistically significant difference $P>0.05$ between groups.

Conclusions: Our study revealed that in T1DM children, vitamin D deficiency coincided with poor glycemic control. The levels of HbA1c showed no statistically significant difference between children who received vitamin D supplementation and those who have not received it regarding glycemic control, whereas the results were clinically significant.

Keywords: Vitamin D Supplementation, Glycemic Control, Type 1 Diabetes Mellitus, Gaza Strip, Randomized Controlled Trial.

1. Introduction

Type 1 diabetes mellitus (T1DM) is an immune-mediated disease characterized by diminished insulin secretion due to damage to islets of Langerhans in the pancreas, which eventually results in high levels of glucose in the blood (Katsarou et al., 2017). According to World Diabetes Foundation, in Palestine, 4.4% of diabetic patients are diagnosed with T1DM, while 95.3% are diagnosed with type 2 diabetes (T2DM) (World Diabetes Foundation, 2020).

Vitamin D, also known as calciferol, exists in two major forms, namely vitamin D_2 or ergocalciferol and vitamin D_3 or cholecalciferol, which are mainly found in plant and animal products, respectively (Busta, Alfonso, & Poretsky, 2011; Griz, Bandeira, Gabbay, Dib, & Carvalho, 2014). Cholecalciferol can also be synthesized in the skin through ultraviolet B radiation (Busta et al., 2011). The inactive forms of vitamin D are transported to the liver where they are hydroxylated and converted into 25-hydroxyvitamin D (25(OH)D) or calcidiol. Thereafter, calcidiol is converted to the biologically active form of the vitamin, 1,25-dihydroxy vitamin D ($1,25(OH)_2D$) or calcitriol (Mitri & Pittas, 2014).

In recent years, the extra-skeletal effects of vitamin D (25(OH)D) have raised considerable interest since specific receptors have been found in many tissues and systems, including pancreatic β cells and immune cells. 25(OH)D deficiency represents a major health problem since it has been related to cardiovascular, inflammatory, autoimmune diseases, cancer, and T1DM (Savastio et al., 2016).

Observational studies have reliably provided evidence that T1DM patients with acceptable glycemic control have higher 25(OH)D levels than T1DM with lesser glycemic control (Al Sawah, Compher, Hanlon, & Lipman, 2016; Lamichhane et al., 2015). Additionally, it has been specified by some of the research-based studies that there is a strong connection between the deficiency of vitamin D and the incidence of T1DM (Al-Agha & Ahmad, 2015; Elhamalawi, 2015; Savastio et al., 2016).

In interventional studies of T1DM children and adults, repletion of vitamin D in deficient individuals improved HbA1c in a period of 12 weeks. Participants were more likely to achieve HbA1c < 7.8% if they had higher 25(OH)D levels on week 12 than on baseline, especially if 25(OH)D levels were exceeded 51 nmol/l (Aljabri, Bokhari, & Khan, 2010; Hafez, Hassan, Musa, Atty, & Azim, 2017; Mohammadian,

Fatahi, Zaeri, & Vakili, 2015; Nwosu & Maranda, 2014; Shih, Mittelman, Pitukcheewanont, Azen, & Monzavi, 2016).

According to the Food and Drug Administration (FDA), The Institute of Medicine's (IOM) recommended Upper Limit (UL) for chronic vitamin D intake for infants (children less than 1 year of age) is 25 mcg/day (1,000 IU/d), and for children age 1 year and older the recommended UL is 50 mcg/day (2,000 IU/d) (Institute of Medicine Standing Committee on the Scientific Evaluation of Dietary Reference Intakes, 1997).

Despite a large amount of evidence from observational and experimental studies supporting the effects of vitamin D on glucose metabolism and the immune system, results from clinical studies remain inconsistent, which makes it impossible to recommend vitamin D supplementation for the treatment of T1DM. Therefore, this study aimed to screen for vitamin D deficiency and to examine the effects of vitamin D supplementation on glycemic control among children with T1DM. This is the first randomized controlled trial that studied the effects of vitamin D supplementation on glycemic control among T1DM children in the Gaza Strip, Palestine.

2. Materials and Methods

2.1 Study design

The study design was an experimental, randomized controlled trial.

2.2 Study setting

The study was conducted at the endocrinology outpatients' clinic at Al-Rantisi Pediatric Hospital in Gaza Strip.

2.3 Study Sample

After getting the ethical approval from the Palestinian Ethical Committee (Helsinki Ethics Committee) (PHRC/HC/273/17), and the Informed Consent from parents of children, data were collected for 3 months, starting from October 2017 to January 2018. In this period, 80 children who were less than 14 years old were diagnosed with T1DM which was indicated through fasting blood glucose level greater than 126 mg/dl or HbA1c cut point of ≥6.5% (American Diabetes Association, 2010), and had vitamin D deficiency which indicated by its levels of less than 12 ng/ml (Sullivan, 2019), were recruited from endocrinology outpatients' clinic at Al-Rantisi Pediatric Hospital in Gaza Strip.

2.4 Eligibility Criteria

2.4.1 Criteria for children with T1DM:

2.4.1.1 Inclusion criteria for children with T1DM:

1- Children (4-14 years of age) of both gender, with a T1DM.

2- Not on vitamin D supplementaition.

2.4.1.2 Exclusion criteria for children with T1DM

1. Age ≤ 4 or more than14 years old
2. Patients with T2DM
3. Children had received vitamin D supplements

2.5 Sampling

A stratified random sampling technique was applied to assign children with the previously mentioned criteria into two groups. The first group is the interventional (experimental) group that received vitamin D supplements (2000 IU/day) and the second group is the control group that did not receive any supplements. Both groups

were on their regular diet and treatment. According to previous studies and after the direct supervision from the treating pediatrician and endocrinologist, the best preparation and dosage of vitamin D was used (According to FDA the recommended dose for children age 1 year and older is 2,000 IU/day). The two groups were defined as follows:

Group A: is the interventional group that supplemented with vitamin D tablets containing 2000 IU once time daily with a meal, for 3 months of intervention.

Group B: is the control group, that did not receive any type of supplements during the intervention period.

Concerning the laboratory investigations; vitamin D status was assessed by measuring the concentration of 25-hydroxyvitamin D (25(OH)D) in the children's serum. Levels of 25(OH)D were interpreted as deficiency (≤20 ng/ml or ≤50 nmol/L), insufficiency (21–29 ng/ml or 52.5-72.5 nmol/L), and sufficiency (30-100 ng/ml ng/ml or 75-250 nmol/L). The glycated hemoglobin levels are defined based on the control of diabetes, as good control (HbA1c<7.8%), moderate control (HbA1c:7.8%-9.9%), and poor control (HbA1c>9.9%) (Aljabri et al., 2010).

2.6 Tools of Data Collection

Children's health assessment structure interview sheet was used to collect data. It was constructed by the researchers based upon relevant literature. The questionnaire consisted of three parts:

Part I: Children's socio-demographic characteristics

This part was aimed to collect socio-demographic characteristics for both interventions, and control groups before the intervention such as age, gender, number of family members, and level of education.

Part II: Children's current health history

It covered the history of the discovery of diabetes, duration of diabetes, type of insulin, family history of diabetes, and periodic test for diabetes. This part had been used before the intervention for both the intervention and control groups.

Part III: Children's laboratory investigations

This part addressed HbA1c and vitamin D status that were investigated and recorded before and after the interference for both interventions, and control groups.

2.7 Statistical analysis

Data was entered and statistically analyzed using SPSS (statistical package for social sciences) version 26 database for windows 10. Descriptive statistics were used to summarize the socio-demographic characteristics of subjects. Numerical data like 25-OHD levels, and HbA1c, were presented as mean (SD) or median (IQR) based on their normality distribution. Categorical data were presented as frequency (percentage). The chi-square test was used for categorical data comparison. Analysis of quantitative data between two groups was done using unpaired t-test. Pearson correlation coefficients between continuous variables were used as a measure of association. A p-value <0.05 was considered statistically significant.

3. Results

In our study, 83 children were found eligible. Three children did not meet the inclusion criteria and 80 children were randomized to the two groups (intervention and controls). Eighty children adhered to protocol. Data of 80 children were analyzed (Figure 1).

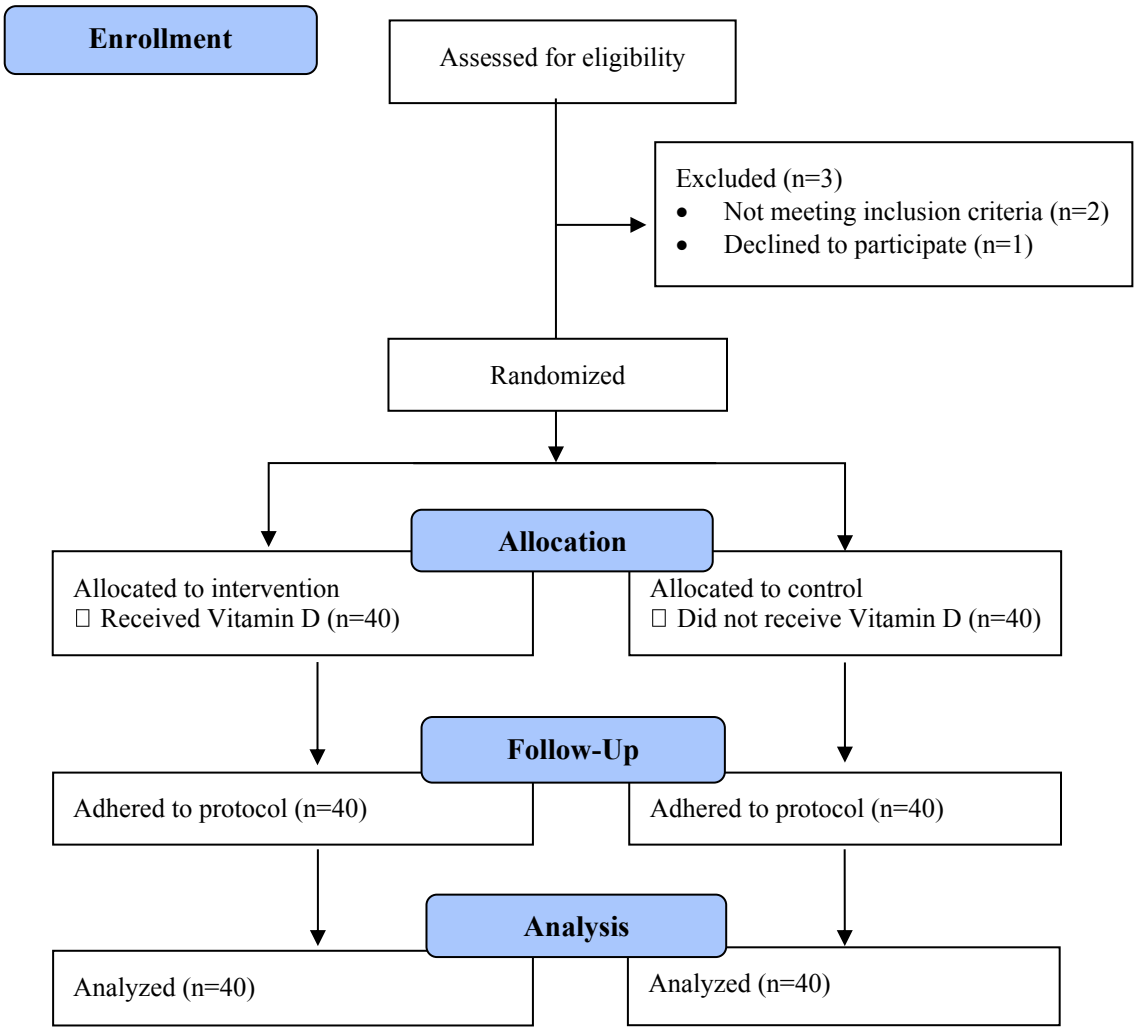

Figure 1. CONSORT Flow Diagram.

Table 3. 1 General characteristic of the studied population.

Characteristics		Intervention group (n=40)	Control group (n=40)	*P*-value
Gender				
Male		22 (27.5)	18 (22.5)	0.371
Female		18 (22.5)	22 (27.5)	
Educational Level				
Kindergarten		6 (7.5)	6 (7.5)	
Elementary		24 (30.0)	24 (30.0)	1.000
Intermediate		10 (12.5)	10 (12.5)	
First-degree relative of TIDM				
Yes		7 (8.8)	8 (10.0)	0.775
No		33 (41.3)	32 (40.0)	
Self-monitoring of blood glucose				
Yes		39 (48.8)	38 (47.5)	0.556
No		1 (1.3)	2 (2.5)	
Vitamin D categories (baseline)				
Vitamin D deficiency		10 (12.5)	25 (31.3)	
Vitamin D insufficiency	n (%)	30 (37.5)	12 (15.0)	**0.001**
Vitamin D sufficiency		0 (0.0)	3 (3.8)	
Vitamin D categories (follow up after 3 months)				
Vitamin D deficiency		1 (1.3)	13 (16.3)	
Vitamin D insufficiency		2 (2.5)	19 (23.8)	**0.001**
Vitamin D sufficiency		37 (46.3)	8 (10.0)	
HbA1c categories (baseline)				
Good glycemic control		0 (0.0)	5 (6.3)	
Moderate glycemic control		12 (15.0)	11 (13.8)	0.069
Poor glycemic control		28 (35.0)	24 (30.0)	
HbA1c categories (follow up after 3 months)				
Good glycemic control		2 (2.5)	2 (2.5)	
Moderate glycemic control		18 (22.5)	8 (10.0)	**0.054**
Poor glycemic control		20 (25.5)	30 (37.5)	
Age (years)		8.98±3.00	9.10±2.77	0.256
Duration of TDIM (years)		3.43±2.58	5.15±3.69	**0.030**
25-H vitamin D (Baseline)		14.76±3.71	12.46±4.35	0.169
25-H vitamin D (follow up after 3 months)	Mean ± SD	38.79±16.86	14.88±4.73	**0.001**
HbA1c (Baseline)		10.23±1.95	9.86±2.19	0.306
HbA1c (follow up after 3 months)		9.20±1.50	10.28±1.77	0.324
Mean difference of HbA1c levels		-1.03±0.217	0.423±0.217	**0.001**

In our study, 80 children were found eligible and were randomized into two groups (40 intervention and 40 controls). Table 3.1 showed the homogeneous matching in the general characteristics of both intervention and control groups. This is noticeable in the percentage of male and female participants was 27.5% & 22.5% for intervention group while 22.5.% & 27.5% for the control group respectively, there was no

statistically significant difference between the two groups P=0.371. The elementary level of education was 30.0% in both intervention and control groups respectively with no statistically significant difference between the two groups. Regarding the family history of TIDM, most of the study population had no first-degree relative of TIDM with 41.3% and 40.0% in intervention and control groups respectively P=0.775. The majority of the study population had compliance to self-monitoring of blood glucose with 48.8% for intervention and 47.5% for control groups. The mean age of the intervention group was (8.98±3.00 years) and the controls were (9.10±2.77 years), there was no statistically significant difference between the two groups P=0.256.

In relation to vitamin D status, the mean level of vitamin D (Baseline) was higher in the intervention group (14.76±3.71 ng/ml) compared to controls (12.46±4.35 ng/ml) (P=0.169). Vitamin D (Baseline) was deficient in 12.5% of the intervention group compared to 31.3% in the controls. While 37.5% of the intervention group had an insufficient level of vitamin D compared to 15.0% only among the controls (P=0.001). Three months of supplementation of vitamin D caused a significant rise in serum vitamin D levels to a sufficient range among the intervention group with a mean serum level of (38.79±16.86 ng/ml). Vitamin D (follow up after 3 months) was sufficient in 46.3% of the intervention group compared to 10.0% in the controls (P=0.001). The participants of the intervention and controls had poor glycemic control at baseline level with mean levels (10.23±1.95) and (9.86±2.19) respectively, the difference was not statistically significant (P> 0.05). After vitamin D supplementation for three months, 25.0% of the intervention group had poor glycemic control, while 37.5% of the controls had poor glycemic control with a statistically significant difference (P=0.054). Moreover, the mean levels of HbA1c before vitamin D supplementation and after three months follow-up had decreased from 10.23±1.95 to 9.20±1.50 among the intervention group. On the other hand, the mean levels of HbA1c before vitamin D supplementation and after three months follow-up had increased from 9.86±2.19 to 10.28±1.77 among the controls.

Furthermore, the mean difference of HbA1c in the intervention group was -1.03±0.217, while in the control group was 0.423±0.217, with a statistically significant difference detected between children in both groups P=0.001.

Table 3. 2 shows that there were statistically significant differences in the mean of glycosylated hemoglobin and vitamin D deficiency and sufficiency between intervention and control groups at 12 weeks (P< 0.05). Whereas, there was no statistically significant difference in the mean of glycosylated hemoglobin and vitamin D insufficiency between both groups at 12 weeks (P>0.05).

Table 3. 3 Glycosylated hemoglobin levels according to vitamin D categories among children with T1DM and non-diabetic control groups.

Vitamin D categories	HbA1c	Case Mean±SD	Control Mean±SD	*P*-value
Vitamin D deficiency	**Baseline**	10.70±0.00	10.04±1.60	**0.030**
	Follow-up	10.60±0.00	10.35±1.20	
	Mean change	-0.10±0.00	0.31±1.18	
Vitamin D insufficiency	**Baseline**	14.35±1.20	9.71±2.64	0.394
	Follow-up	10.30±2.55	10.13±2.23	
	Mean change	-4.05±1.34	0.42±1.10	
Vitamin D sufficiency	**Baseline**	9.99±1.75	9.91±2.09	**0.016**
	Follow-up	9.10±1.46	10.54±1.50	
	Mean change	-0.89±1.37	0.63±1.65	

Figure 3. 1 show that 25-H vitamin D levels negatively correlated with HA1c after 3 months follow up (r=-0.305, P=0.006).

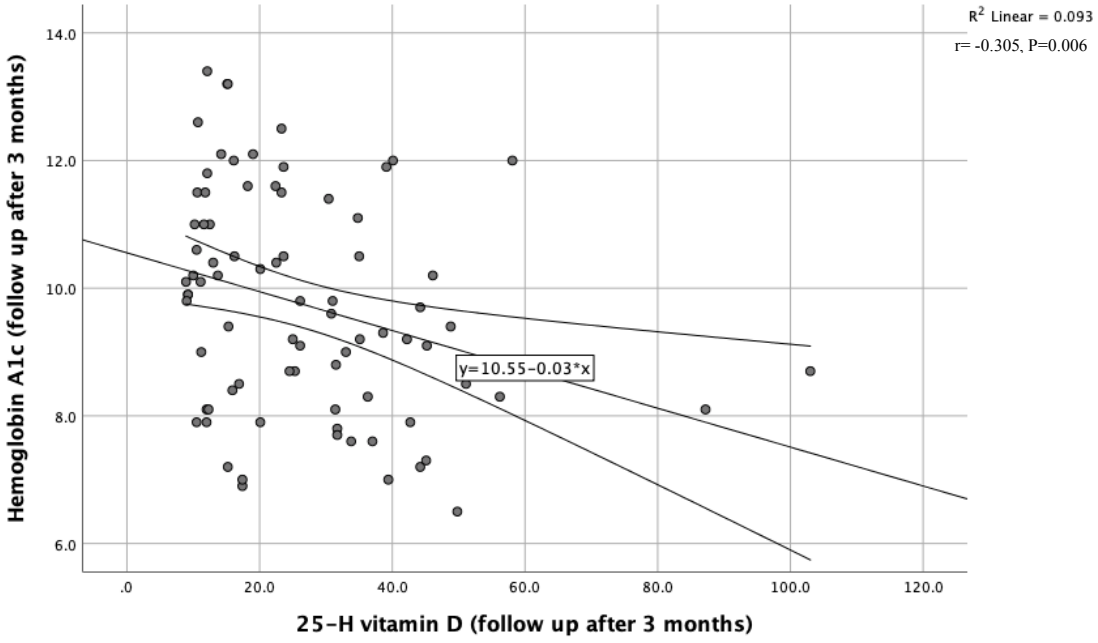

Figure 3. 1 25-H vitamin D serum levels in relation to glycemic control (%HbA1c) in children with T1DM group.

4. Discussion

The study aimed to investigate the status of vitamin D and to examine the effects of vitamin D supplementation on glycemic control in children with T1DM. The study was conducted on a homogeneous sample, who were matched in age, sex, and means of HbA1c, and 25(OH)D at the start point in both intervention and control groups. Children in the present study were ≥ 4 years of age with a mean age of 8.98±3.00 and 9.10±2.77 years old in intervention and control groups respectively.

It was found that 43.8% of the patients had vitamin D deficiency, 52.5% had insufficiency and only 3.8% were vitamin D sufficient. This high prevalence of vitamin D deficiency and insufficiency in patients with T1DM was previously reported in the Gaza strip. In the Islamic University of Gaza, Elhamalawi et al. enrolled 44 children with T1DM to assess their vitamin D levels and concluded that 11.4 % were vitamin D deficient and 45.5% were vitamin D Insufficient (Elhamalawi, 2015).

In the current study at the start point, mean levels of diagnostic HbA1c were 10.23±1.95 and 9.86±2.19 in both intervention and control groups respectively and most of the children in both groups had vitamin D deficiency and insufficiency. While after 3 months HbA1c mean in the intervention group was 9.20±1.50 compared with 10.28±1.77 in the control group. These findings were in the same line with El-Sayed et al. (2019) in their study on children aged above 2 years in Egypt observed that there was a greater incidence of T1DM with lower levels of vitamin D (El-Sayed, Abd El Raaouf, & Laimon, 2019). As well as in Mohammadian and Aljabri studies, a reduction in the mean reduction in mean HbA1C among the vitamin D deficient group was observed (Aljabri et al., 2010; Mohammadian et al., 2015).

According to the present study, although there was no statistically significant difference between children who received vitamin D supplementation and those who have not received it regarding glycemic control, the result was clinically significant. This can be explained as vitamin D may act directly on β cell, promoting insulin secretion and regulating calcium homeostasis or through a peripheral action, increasing the insulin sensitivity of target cells, or regulating the activation of several calcium-dependent enzymes involved in glucose metabolism (Gabbay, Sato, Finazzo, Duarte, & Dib, 2012). Moreover, a recent study in Egypt concluded that supplementation of vitamin D for 3 months in vitamin D deficient T1DM patients revealed that better glycemic control was achieved (Hafez et al., 2017).

On the other hand, Bizzarri et al. found that vitamin D supplementation was ineffective in improving glycemic control in children with T1DM of recent onset, their study was not confirmed the protective effect of vitamin D supplementation on β cells function in recent-onset diabetes (Bizzarri et al., 2010). Moreover, Walter et al. as well as a meta-analysis conducted by George et al. in Scotland observed no significant improvement in HbA1c% or fasting blood glucose in those treated with vitamin D supplementation compared with those who received placebo concluding that there was insufficient evidence of the beneficial effect of vitamin D supplementation as a means of improving glycemic control in children and adolescents with T1DM (George, Pearson, & Witham, 2012; Walter et al., 2010).

On one hand, the lack of statistical significance might be explained by our small sample size, while on the other this might be explained by the higher vitamin D dose eventually required in this subset of the population. There is still no consensus about the best dose of supplementation (Holick et al., 2011).

In this study, although most of the patients were consuming vitamin D, at the endpoint only 45/80 had sufficient 25OHD levels, according to the Endocrine criteria. Surely, lifestyle variables, as clothing, outdoor sports activities, and food choice can impact 25OHD levels. These variables were not investigated and this represents a limitation of this study. A prospective case-control double-blind study must be planned to see if vitamin D supplementation produces better metabolic control of T1DM in children. Despite the limits of this work, a 25OHD deficiency correction program should be considered.

Our study was limited by number due to the high price of laboratory investigations, and the short duration of the study. The role of Vitamin D as an immunomodulator needs to be further researched in T1DM patients, preferably in a larger sample size and for a longer duration.

5. Conclusions

Our study revealed that in T1DM children vitamin D deficiency coincided with poor glycemic control. A high prevalence of vitamin D deficiency (43.8%) and insufficiency (52.5%) was found among children with T1DM. The HbA1c% showed no statistically significant difference between children who received vitamin D supplementation and those who have not received it regarding glycemic control, whereas the results were clinically significant.

Acknowledgment

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Approval

Ethical approval was obtained from the Palestinian Ethical Committee (Helsinki Ethics Committee) (PHRC/HC/273/17) to carry out the study in Gaza Strip. The formal letter of request was obtained from the Palestinian Ministry of Health to facilitate the task of the researchers.

Conflict of interest

All the authors declare no conflict of interest.

Author's Contribution

All the authors have accepted responsibility for the entire content of this submitted manuscript and approved submission. Heba AbdAllah Al Sarraj and Ashraf Jaber Shaqaliah set the study design. Heba AbdAllah Al Sarraj and Heba Mohammed Arafat recruited the patients, collected the samples, and supplemented the patients with vitamin D. Ashraf Jaber Shaqaliah, Ohood Mohammed Shamallakh, and Kholoud Mohammed Shamallakh performed the laboratory assessment, Ohood Mohammed Shamallakh, and Heba Mohammed Arafat the statistical analysis. Heba AbdAllah Al Sarraj wrote the original draft preparation. Heba Mohammed Arafat, Ohood Mohammed Shamallakh, and Kholoud Mohammed Shamallakh wrote, reviewed the research. All authors have read and agreed to the published version of the manuscript.

Availability of data and materials

The datasets analyzed during the current study are available from the corresponding or first author on reasonable request.

This randomized controlled trial was registered in the ClinicalTrials.gov, Protocol Registration and Results System (PRS) (ClinicalTrials registration number: (-----).

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