

Original Article

Effect of vitamin D supplementation on glycemic control in type 1 diabetes mellitus



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ABSTRACT

Diabetes mellitus is a group of metabolic diseases with high prevalence, mortality and morbidity characterized by prolonged high blood glucose concentrations resulting from defects in insulin secretion, insulin action, or both. This study aimed to assess the role of vitamin D supplementation in glycemic control in uncontrolled type 1 diabetes with vitamin D deficiency. It is a prospective study between 1st of October 2022 to 31st of July 2023, where ninety patients (male: female ratio 1:1) with uncontrolled type 1 diabetes and vitamin D deficiency attended The Specialized Center for Endocrinology and Diabetes in Baghdad Government-Iraq, their ages between 5-18 years were followed for 10 months to assess their Hemoglobin A1c (HbA1c) and serum calcium after correction of vitamin D level with therapeutic doses of vitamin D. The findings of the study had shown that 41.1% of the patients had vitamin D insufficiency and 58.9% with deficiency regardless sex and age. All the obese children and 66.4% of the overweight had vitamin D deficiency with significant correlation with BMI ($P < 0.001$). The severity of vitamin D was also related to duration of disease diagnoses ($P < 0.001$). Good glycemic control occurs in patients with vitamin D levels $> 50 \text{ ng/ml}$ ($P < 0.01$). In 14.5% of the patients after 6 months, their vitamin D levels again became deficient, so re-check was needed after 6 months from the end of the loading therapy. Vitamin D deficiency among the patients of diabetes mellitus type 1 was high and was closely related to glycemic control. The level of vitamin D was negatively related to the body weight and the duration of the disease. Additionally, the findings of the study have demonstrated therapeutic dose of vitamin D has the potential to manage glucose levels.

1. Introduction

Diabetes mellitus is a group of metabolic diseases characterized by prolonged high blood glucose concentrations. The cause of high blood glucose “also known as hyperglycemia” is the result of defects in insulin secretion, insulin action, or both. Diabetes mellitus contributes to a

considerable increase in morbidity and mortality, which can be reduced by early diagnosis and treatment [1, 2].

Direct medical expenditures such as inpatient care, outpatient services, and nursing home care are astronomical, and indirect costs such as disability, work loss, and premature mortality are equally high. It is

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estimated that 10.5% of the US population is living with diabetes. In 2020, the total prevalence of diabetes in the United States in all ages was 34.2 million people. Of these, 26.9 million are diagnosed and 7.3 million are undiagnosed [1, 2].

The American Diabetic Association (ADA) estimates that 10% of people with diabetes have type 1 diabetes and 5.2% of all newly diagnosed cases of diabetes were type 1 [3]. The primary defect in type 1 diabetes is pancreatic β -cell destruction, usually leading to absolute insulin deficiency and resulting in hyperglycemia, polyuria (excessive urination), polydipsia (excessive thirst), polyphagia (excessive hunger), unexpected weight loss, dehydration, electrolyte disturbance, and diabetic ketoacidosis (DKA) [4, 5]. T1DM has two forms: immune-mediated and idiopathic. Immune-mediated diabetes mellitus results from an autoimmune destruction of the β -cells of the pancreas, the only cells in the body that make the hormone insulin. Idiopathic T1DM refers to forms of the disease that have no known etiology. Although only a minority of individuals with T1DM fall into this category, of those who do, most are of African or Asian ancestry. Although at this time, there is no known cure for T1DM [6, 7] but evidences indicates that appropriate glycemic control would reduce the risk of T1DM-related morbidity and mortality by appropriate insulin and nutritional regimen. Some factors and supplementation could improve glycemic control of diabetic patients [8]. One of the supplements which are suggested that could improve glycemic control is vitamin D. There are also evidences regarding the role of vitamin D in the pathogenesis of T1DM and recent review studies indicated that vitamin D supplementation both in prenatal and postnatal periods reduce the risk of T1DM [9].

Vitamin D deficiency and insufficiency are a problem across the globe, in the United States, 50% of children ages 1 to 5 and 70% of children ages 6 to 11 have vitamin D deficiency [10]. Epidemiologic, genetic, and basic studies indicate a potential role of vitamin D in the pathogenesis of certain systemic and organ-specific autoimmune diseases [11]. Vitamin D is closely related to the occurrence of autoimmune diseases and

plays an important role in the pathogenesis of diabetes and glycemic control by inhibiting inflammatory and autoimmune responses and promoting insulin synthesis, secretion, and sensitivity [12]. In addition, the enzyme 1- α hydroxylase, which is important for the synthesis of calcitriol (an active form of vitamin D), was found to be present in pancreatic β -cells which stimulate insulin synthesis and release [13].

Very few foods naturally contain vitamin D, a vital fat-soluble vitamin. When exposed to UV radiation, the skin's endogenous synthesis produces vitamin D, accounting for 80–90% of the body's needs. This is one of the main sources of vitamin D. Lower skin tone prevents the synthesis of vitamin D. A person with lighter skin may get their daily dose of vitamin D from the sun in around 15 minutes, while someone with darker skin may require up to three hours. Melanin reduces the synthesis of vitamin D but absorbs damaging UV rays, shielding cells from sun exposure-induced DNA damage [14, 15]. Additionally, foods like egg yolks, red meat, liver, and oily fish (salmon, mackerel, and sardines) naturally contain vitamin D. Vitamin D may also be purchased as a dietary supplement and added to a variety of meals and beverages, such as milk and certain juices. Both the vitamin D that is absorbed from food and supplements and the vitamin D that is made by the skin is biologically inert. It must be activated by hydroxylation twice in the body—first into 25(OH)D (calcidiol) by the liver, and again into 1,25(OH)₂D (calcitriol) by the kidney [16].

Vitamin D deficiency has become a global pandemic, especially in those with metabolic syndrome and obesity, including in areas that receive adequate sunlight and this would increase the global burden of diseases [17]. Because vitamin D insufficiency is so common, governments, legislators, healthcare professionals, and people should be aware of this and prioritize preventing it for the sake of public health [18]. The primary biomarker of vitamin D status at the moment is the serum concentration of 25(OH)D. It represents both endogenously generated vitamin D and vitamin D from diet and supplementation. Twenty-five days is a rather long circulation

half-life for 25(OH)D in serum. Contrary to 25(OH)D, circulating 1,25(OH)₂D has a short half-life (measured in hours), and parathyroid hormone, calcium, and phosphate closely control blood levels, making it a poor indication of vitamin D status overall. Usually, 1,25 (OH)₂D levels do not drop until a severe case of vitamin D insufficiency [19, 20]. The unit of measurement for the normal range of 25-hydroxy vitamin D is nanograms per milliliter or ng/mL. Vitamin D insufficiency is defined as a level of 25-hydroxyvitamin D (25 OH D) of less than 30 ng/mL and less than 20 ng/ml for deficiency, according to the Endocrine Society and the World Medical Association (WMA). A preferable range of 40 to 60 ng/mL is suggested. The Endocrine Society advises 400–1000 International Units (IU) every day for newborns under one-year-old, 600–1000 IU for children and adolescents aged one to eighteen, and 1500–2000 IU for all people in order to maintain a normal level of blood vitamin D [21-23]. Recommended treatment for vitamin D-deficient patients 1–18 years of age is as follows [24-26]: -2000 IU/day of vitamin D2 or D3 for at least 6 weeks or -50,000 IU of vitamin D2 once weekly for at least 6 weeks (better compliance). When the serum 25(OH)D level exceeds 30 ng/mL, provide maintenance treatment of 600-1000 IU/day

2. Materials and Methods

It is a prospective study between the 1st of October 2022 to the 31st of July 2023, where ninety patients (1:1 male to female ratio was selected) ages between 5-18 years with uncontrolled type 1 diabetes (HbA1c >7%) and their serum 25(OH)vit D level less than 30ng/ml attended The Specialized Center for Endocrinology and Diabetes in Baghdad Government-Iraq, were followed for 10months to assess their glycemic controls after treatment with vitamin D 50000IU weekly for 16 weeks in addition to their routine insulin therapy. Vitamin D insufficiency (vitamin D level 20-29ng/ml) and deficiency (<20ng/ml) criteria depend on the WHO and Endocrine Society guidelines. When the serum 25(OH)D level exceeds 30 ng/mL, the patients provided maintenance treatment of 1000 IU/day. All patients gave

their or their guardians' informed consent prior to inclusion.

Serum total 25(OH) D3 level was measured using "Enzyme-Linked Fluorescent Assay" in Mini Vidas immuno-assay analyzer and Glycosylated Hemoglobin measured using High-performance gel chromatography technique "HPLC BIO-RAD D10".

Exclusion criteria were a history of liver disease, abnormal renal function, and current use of vitamin D, celiac disease, and hypothyroidism. Using a questionnaire, the medical history of the patients and anthropometric characteristics (weight, height and body mass index (BMI)) as well as data about the duration of T1DM, presentation, treatment and glycemic control of the disease were recorded. Before treatment with vitamin D, serum vitamin D, Hba1c and serum calcium were measured and reassessed every 3months after treatment. Means of serum vitamin D, Hba1c and serum calcium before and after treatment with vitamin D3 were compared.

Data were entered into the Statistical Package for Social Science (SPSS) program for Windows version 20 to generate the general characteristics of the study. Quantitative variables were summarized by finding mean $\pm$ SD. Statistical analysis Differences between patients were tested with the independent t-test, x2 test and C-test to identify the potential risk factors. A two-tailed P-value of less than 0.05 was considered to be statistically significant.

3. Results

Ninety patients completed the study with male to female ratio 1:1 being selected. Table 1 shows baseline characteristics of the diabetic patients where mean ages in male group were 11.3 $\pm$ 4.5 years and in female group were 9.3 $\pm$ 4.2 years.

It has been shown that 3.3% of the patients were obese (BMI $\geq$ 95th %) and 36.7% were overweight (BMI=85th-94th %). Mean duration of the patients diagnosed with type 1 diabetes was 3.2 $\pm$ 2.1 years in male patients and 2.4 $\pm$ 1.9 years in female patients. 41.1% of the patients their 25-hydroxyvitamin D levels

were 20-29ng/ml and 58.9% of the patients their 25-hydroxyvitamin D levels were less than 20ng/ml with no significant differences in the prevalence between vitamin D deficiency and insufficiency in the diabetic patients (P-value=0.09).

Mean serum calcium was 8.6 ± 0.9 mg/dl in male patients and 8.2 ± 0.4 mg/dl in female patients. Mean HbA1c was high in males and females with no significant correlation with sex (P-value=0.1).

Table 1. Baseline characteristics of the type 1 diabetic patients

Variables	Male	Female	Total%
Mean age $\pm$ SD years	11.3 $\pm$ 4.5	9.3 $\pm$ 4.2	
	No. %	No. %	
BMI according to CDC growth charts	2	1	3
-obesity (BMI $\geq$ 95 th %)	4.5	2.2	3.3
-overweight	15	15	33
BMI=85 th -94 th %	40	33.3	36.7
-normal weight	25	29	54
BMI=5 th -84 th %	55.5	64.5	60
Mean duration of diabetes $\pm$ SD	3.2 $\pm$ 2.1	2.4 $\pm$ 1.9	
	No. %	No. %	Total%
25-ydroxyvitamin D level	19	18	37
- 20-29 ng/mL	42.2	40	41.1
- <20ng/ml	26	27	53
	57.8	60	58.9
Mean serum Ca (mg/dl) $\pm$ SD	8.6 $\pm$ 0.9	8.2 $\pm$ 0.4	
Mean Hba1c $\pm$ SD %	11.5 $\pm$ 2.3	10.9 $\pm$ 1.7	

Table 2 shows that there was no significant correlation between vitamin D deficiency and insufficiency with sex and age, (P-value= 0.08 and 0.06 respectively). All of the obese patients (BMI $\geq$ 95th %) and 66.7% of the overweight patients (BMI=85th-94th %) had vitamin D deficiency with significant correlation (P-value <0.001). Duration of diagnoses of diabetes negatively affects vitamin D levels with P-value <0.001. Mean serum calcium was lower than normal in both vitamin D deficit and insufficient group.

Table 3 shows that only 10.3% of the diabetic patients who have got vitamin D level 30-50ng/ml after treatment with vitamin D supplements got good glycemic control (HbA1c $\leq$ 8%) while those with vitamin D level >50ng/ml, 68.8% of them got good glycemic

control with significant correlation (P-value<0.01) and 35.6% of the patients got vitamin D level >50ng/ml after 16 weeks of treatment.

Table 2. Baseline characteristics by 25-hydroxy vitamin D

Variables	Level of 25 (oh) vitamin D - 20-29 ng/mL - <20ng/ml	
Age	10.2 $\pm$ 2.5	11.3 $\pm$ 2.7
Sex (Male/Female)	19/18	26/27
	No. %	No. %
BMI according to CDC growth charts	0	3
-obesity (BMI $\geq$ 95 th %)	0	100
-overweight	11	22
(BMI=85 th -94 th %)	33.3	66.7
-normal weight	26	28
(BMI=5 th -84 th %)	48.1	51.9
-Total no. of the patients	37	53
Mean duration of diabetes $\pm$ SD	1.9 $\pm$ 0.6	3.6 $\pm$ 0.8
Mean serum Ca (mg/dl) $\pm$ SD	8.9 $\pm$ 0.4	8.2 $\pm$ 0.5
Mean Hba1c $\pm$ SD %	9.8 $\pm$ 1.8	10.6 $\pm$ 1.9

Table 3. Mean HbA1c $\pm$ SD values after 16 weeks of treatment with vitamin D

Level of vitamin D (ng/mL)	HbA1c			
	$\leq$ 8% No. %	>8-10% No. %	>10% No. %	Total No. %
30-50ng/ml	6 10.3	23 39.7	29 50	58 64.4
>50ng/ml	22 68.8	6 18.7	4 12.5	32 35.6

In Table 4, no significant changes in the mean serum calcium level between patients with vitamin D level 30-50ng/ml and those with vitamin D > 50ng/ml (p-value=0.08)

Table 4. Mean serum calcium $\pm$ SD after treatment with vitamin D

Level of vitamin D	Mean serum Ca (mg/dl) $\pm$ SD
30-50ng/ml	8.6 $\pm$ 0.6
>50ng/ml	8.9 $\pm$ 0.8

In Table 5, 14.4 % of the diabetic patients whose vitamin D level was normal became vitamin D insufficient after 6 months of

maintenance doses (1000 IU/day) of vitamin D.

Table 5. Vitamin D levels 6months after daily maintenance doses of vitamin D

Level of vitamin D	Patients	
	No	%
-30-50ng/ml	45	50
->50ng/ml	32	35.6
- 20–29 ng/mL	13	14.4

4. Discussion

In this study, we investigated the outcome of vitamin D treatment on glycemic control in type 1 diabetic patients with vitamin D deficiency. The selected patients were those with poor glycemic control and low vitamin D levels. Their ages were between 5-18 years with mean ages in male patients being 11.3 ± 4.5 years and in female patients being 9.3 ± 4.2 years with male to female ratio being 1:1. In Table 1, 3.3% of the patients were obese and 36.7% were overweight. Researchers at the Johns Hopkins Bloomberg School of Public Health discovered in a recent study that Americans with type 1 diabetes were obese or overweight at almost the same high rates as those without the disease [27, 28].

The link between childhood/youth obesity and an increased T1D incidence is ascertained (higher BMI percentiles are positively associated with incident T1D among adolescents, with approximately 25% greater risk observed for each incremental standard deviation in BMI) [29]. It has been shown that the prevalence of overweight and obesity in youth with type 1 diabetes ranges between 15.3% and 36.0% [29]. Type 1 diabetes patients who are overweight may be caused by a number of intricate causes. The main factor thought to be responsible for weight gain in type 1 diabetics is intensive insulin treatment [30], Nonetheless, their lifestyle decisions, behavioral patterns, psychological issues, and fear of hypoglycemia might all have an impact. The development of overweight and obesity is also influenced by independent variables, including age, sex, and the length of the illness [31].

Table 1 demonstrates that among diabetic individuals with poor glycemic control, there

were no significant differences between vitamin D insufficiency and deficiency (P-value=0.09). Bedowra's research demonstrates that in type 1 diabetes, where the majority of patients were female and the median duration of the disease was 2.5 years, vitamin D deficiency is more prevalent than vitamin D insufficiency [32]. It has been shown that vitamin D insufficiency is more common where most of sample studied were males newly diagnosed with diabetes [33]. Mean serum calcium was on lower normal in both vitamin D deficit and insufficient patients and this is due to not only decrease serum vitamin D but also increase in glucose blood level, resulting in a significant decrease in the concentration of the serum calcium [34].

Table 2 shows that there was no significant correlation among vitamin D deficiency, insufficiency, sex and age. Many studies found that vitamin D deficient (vitamin D level <20ng/ml) in females with diabetes than in males which may be due to decreased time spent outside, and higher incidence of vitamin D deficiency in teens ages than in younger age groups which may be due to faster growth spurt during puberty and longer duration of disease diagnoses [35, 36]. Other studies found that there is no relation between vitamin D deficiency and age or sex of diabetic patients [37]. In our study, duration of diagnoses of diabetes negatively affects vitamin D levels and this goes with Bassam et al study [38] and Levgeniia Burlaka et al study [39]. Obese and overweight children had more sever vitamin D deficiency (table 2) and this result was in agreement with previous research [35, 40].

In Table 3, vitamin D levels>50ng/ml correlate with better glycemic control than patients with a vitamin D level of 30-50ng/ml (P-value<0.01). Different studies from various regions have investigated the effectiveness of vitamin D supplement therapy on glycemic control and level of HbA1c in type 1 diabetic patients and almost all of them indicated that vitamin D could improve glucometabolic status [41, 42] and mean level of vitamin D was higher in the good glycemic group (70.96 ± 22.66 ng/ml) than in the poor glycemic group (54.81 ± 19.98 ng/ml) [43]. A therapeutic dose of 50000IU/week can be given safely for

16 weeks without fear of hypercalcemia (table 4) or other side effects as tolerable upper limit of daily dose of vitamin D in children up to 10000 IU/day [44].

In Table 5, 14.5% of the diabetic patients in whom vitamin D levels were normal after finishing loading doses of vitamin D supplement became deficit after 6 months of maintenance doses (1000 IU/day) of vitamin D. This may cause poor adherence with the maintenance doses, inadequate maintenance dose as some authors recommend 2000-4000 IU/day [45-47] or inadequate sun exposure. Alternatively, consider referral to an appropriate specialist to exclude pathological causes. So, timely retesting every six months can confirm adequate treatment and prevent potential toxic over-treatment. Routine checking of vitamin D levels in non-high-risk groups is not recommended [48-50].

5. Conclusion

Vitamin D deficiency and insufficiency are highly prevalent among pediatric diabetic patients and it had a role in the pathogenesis of type 1 diabetes and glycemic control. Therefore, screening for vitamin D deficiency and supplementation of children with low vitamin D levels should be warranted especially in diabetic patients with additional risk factors like obesity, long duration with diabetes, celiac disease, dark skin child and those with indoor lifestyle. A higher level of 25(OH) vitamin D associated with good glycemic control and timely retesting every six months can confirm adequate treatment and prevent potential toxic over-treatment.

Conflict of Interests

All authors declare no conflict of interest.

Ethics approval and consent to participate

No human or animals were used in the present research. The authors have adhered to ethical standards, including avoiding plagiarism, data fabrication, and double publication.

Consent for publication

All authors read and approved the final manuscript for publication.

Informed Consent

The authors declare not used any patients in this research.

Availability of data and material

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Authors' contributions

Conceptualization: Mohammed Shaker Al-Awady.

Data curation: Besma Mohammed Ali.

Formal analysis: Besma Mohammed Ali.

Investigation: Mohammed Shaker Al-Awady.

Methodology: Mohammed Shaker Al-Awady.

Project administration: All authors.

Resources: All authors.

Validation: Besma Mohammed Ali.

Visualization: All authors.

Writing-original draft: All authors.

Writing-reviewing & editing: All authors.

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