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Vitamin D Levels And Glycemic Control In Type 1 Diabetes Mellitus

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Abstracts:

Background: Type 1 diabetes is a chronic illness characterized by the body's inability to produce insulin due to the autoimmune destruction of the beta cells in the pancreas. Although onset frequently occurs in childhood, the disease can also develop in adults. Vitamin D deficiency is a major public health problem worldwide in all age groups, even in those residing in countries with low latitude**.** Recent studies reported a relationship between low vitamin D and the development of type 1 diabetes. Vitamin D supplementation especially in the early stages of life may reduce the risk of development of type 1 diabetes.

Aim of study: is to see the prevalence of vitamin D deficiency in type 1diabetes and relation with glycemic control.

Patients and methods: It is a cross sectional study for 6 months between 1st of October 2022 to 30th of March 2023, where one hundred thirty two patients with type 1 diabetes who attended The Specialized Center for Endocrinology and Diabetes in Baghdad Government-Iraq**,** there ages between 2-18 years were investigated for fasting blood glucose (FBG), Hemoglobin A1c (HbA1c) vitamin D and serum Calcium (S.Ca), in addition to anthropometric measures which standardized according to Center for Disease Control and Prevention (CDC) growth charts. Whether vitamin D deficit, insufficient or normal levels were depended on Endocrine Society definitions of vitamin D levels.

Results: 57.6% of the patients were older than 10 years and 59.8% of the diabetic patients were females**.** Body Mass Indexes for the diabetic patients were within normal limit according to CDC growth charts. Means HbA1c of the diabetic patients were higher in those older than 10 and in female patients (P-value=0.000 for both). Levels of vitamin D were deficit in 71.1% of the diabetic patients and insufficient in 22%, with no sex or age predominance (P-value=0.907 and 0.981 respectively). Serum calcium was normal in 64.4% of the diabetic patients and 55.3% of them had vitamin D deficiency. Glycemic control was poor at any serum vitamin D levels (normal or abnormal values) with no significant relation between vitamin D and HbA1c (P-value=0.943).

Conclusions: Most of type 1 diabetic patients were vitamin D deficit mainly females older than 10years.Poor glycemic control was seen at any vitamin D levels.

Key words: vitamin D deficiency, vitamin D insufficiency, type 1 diabetes mellitus, glycemic control.

Introduction:

Type 1 diabetes was formerly called insulin-dependent diabetes mellitus (IDDM) or juvenile diabetes. Type 1 diabetes is a chronic multifactorial illness characterized by the body's inability to produce insulin due to the autoimmune destruction of the beta cells in the pancreas which will lead to low or absent levels of endogenously produced insulin and dependence on exogenous insulin to prevent development of acute and/or chronic complications (1). Although onset frequently occurs in childhood (between the ages of 4 to 6) and in early puberty (10 to 14 years), it can develop at any age (2).

Type 1 diabetes accounts for 5-10 % of all diagnosed cases of diabetes and 90% of diabetes in children and adolescents (2). In Asia, the incidence of type 1 diabetes was 15 per 100 000 population, and the prevalence was 6.9 per 10 000. Globally, the incidence of type 1 diabetes was 15 per 100 000 population and the prevalence of type 1 diabetes was 9.5 per 10 000 people (3). The peak age for being diagnosed with type 1 diabetes is around 13 to 14 years (4). Most individuals are lean but some may be at a higher weight (5).

Vitamin D deficiency is a major public health problem worldwide in all age groups, even in those residing in countries with low latitude, where it was generally assumed that UV radiation was adequate enough to prevent this deficiency, and in industrialized countries, where vitamin D fortification had been implemented for years (6). Previously published scientific literatures documented the high prevalence of serum vitamin D deficiency in American (25%), Canadian (36%), and South Asian populations (61%), addressing different age groups [7,8,9].

Vitamin D is a powerful nutritional factor contributing to beta-cell autoimmunity and the development of type 1 diabetes. Vitamin D supplementation especially in the early stages of life (vitamin D supplementation during infancy had a 78% risk reduction in developing type 1 diabetes) reduce the risk of development of type 1 diabetes (10). Recent studies also reported a relationship between low vitamin D levels and several other autoimmune diseases like rheumatoid arthritis, polymyalgia rheumatica, and psoriasis. Vitamin D can play an important role in the pathogenesis of diabetes and glycemic control by inhibiting inflammatory and autoimmune responses, promoting insulin synthesis, secretion and enhancing insulin sensitivity (11). Vitamin D deficiency is common among type 1 diabetic patients (90%) as in the general population (60%) (12). Since vitamin D levels are affected by sun exposure, the fact that multiple studies showed that type 1 diabetes was more commonly diagnosed in winter and at high altitude which would support an association between vitamin D deficiency and type 1 diabetes (13).

Vitamin D is a class of fat-soluble steroid hormones. It has an established role in calcium homeostasis and bone health. Many of the body's organs and tissues have receptors for vitamin D, which suggest important roles beyond bone health, and scientists are actively investigating other possible functions. Laboratory studies shows that vitamin D can reduce cancer cell growth, help control infections, regulate immune function, reduce inflammation and ischemic heart disease risks (14). Vitamin D has two main forms, D2 is a plant source (ergocalciferol) and D3 which is animal source (cholecalciferol). Vitamin D3 more effective than vitamin D2 in increasing levels of vitamin D in the blood (15).

Vitamin D obtained from sun exposure (vitamin D3), foods, and supplements is biologically inert and must undergo two hydroxylations in the body for activation. The first hydroxylation occurs in the liver and the second hydroxylation occurs primarily in the kidney and forms the physiologically active 1,25-dihydroxyvitamin D [1,25(OH)2D], also known as "calcitriol". Serum concentration of 25(OH)D is currently the main indicator of vitamin D status (16). The Endocrine Society recommends a preferred range of ≥30 to 60 ng/mL which is the best level for optimal bone health and parathyroid hormone level.To maintain this level, the Endocrine Society recommends an intake at least 400 International Units (IU) daily for infants less than one year, at least 600 IU for children and adolescents from 1 to 18 years, and at least 600 IU for all adults and for those older than 70 years require at least 800IU/day of vitamin D. The Endocrine Society define insufficiency as 21 to 29 ng/mL and deficiency as less than 20 ng/mL (17). Vitamin D found in fish liver oil, fatty fish, mushrooms, dairy products, fortified cereals, egg yolks, beef liver, and also can be taken as a vitamin D supplements (14).

Patients and methods:

It is a cross sectional study for 6 months between 1st of October 2022 to 30th of March 2023, where one hundred thirty-two patients with type 1 diabetes who attended The Specialized Center for Endocrinology and Diabetes in Baghdad Government-Iraq, there ages between 2-18 years were investigated for fasting blood glucose (FBG), Hemoglobin A1c (HbA1c), vitamin D and serum Calcium (S. Ca). Growth parameters of the patients (height, weight and body mass index (BMI)) were assessed according to Centers for Disease Control and Prevention (CDC) growth charts' (18)

All these patients were divided into three groups according to Endocrine Society definitions of vitamin D levels (17)**:**

- vitamin D deficiency: Serum 25-Hydroxyvitamin D (25-OH D) equal or less than 20ng/ml (<50 nmol/l).
- vitamin D insufficiency: Serum 25-OH D 21-29ng/ml (52.5- 75 nmol/l)
- Vitamin D adequacy: Serum 25-OH D level ≥ 30ng/ml (>75 nmol/l)

Statistical Methods:

Data were entered into 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 ± 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.

Results:

Table (1) shows ages and sex of the diabetic patients whose enrolled in this study, where 57.6% of the patients were older than 10 years and 59.8% of the diabetic patients were females. Type 1 diabetes was more in those older than 10years (P-value=0.000) with no sex predominance (P-value= 0.879).

Table 1: Sex and age of the patients with type 1 diabetes

Age	Female No.	Female %	Male No.	Male %	Total No.	Total %
2-5yrs	9	11.3	5	9.4	14	10.6
>5-10yrs	24	30.4	18	33.9	42	31.8
>10-18	46	58.3	30	56.7	76	57.6
total	79	59.8	53	40.2	132	

Table (2) shows means BMI for the diabetic patients according to their age and sex with higher BMI in those older than 10 years (P-value=0.000) but still within normal limit according to CDC growth charts and higher BMI in the male patients (p-value=0.000).

Table2: Mean Body Mass Index± Standard Deviation (BMI±SD kg/M^2) values of Diabetic patients with ages and sex

Age	Female Mean BMI±SD kg/M^2	Male Mean BMI±SD kg/M^2
2-5yrs	15.4±2.1	16.7±1.8
>5-10yrs	17.6±2.6	20.2±2.9
>10-18	18.8±2.3	21.8±3.7

Table (3) shows that means HbA1c± Standard Deviation were higher in those older than 10 years (14.8±3.9 in females and 12.7±2.2 in males with P value=0.000) and higher HbA1c in females than males (P-value=0.000).

Table3: Mean HbA1c± Standard Deviation values of Diabetic patients and their ages

Age	Female Mean HbA1c±SD	Male Mean HbA1c±SD
2-5yrs	8.2±1.5	9.3±1.2
>5-10yrs	11.1±2.4	9.8±3.1
>10-18	14.8±3.9	12.7±2.2

Figure 1 shows that 71.1% of the diabetic patients were vitamin D deficit and 22 % with vitamin D insufficiency, and 6.9% with normal vitamin D levels. Of those with vitamin deficiency, 42.4% were females and 28.7% were males with no significant relation between sex and vitamin D deficiency (P-value=0.907).

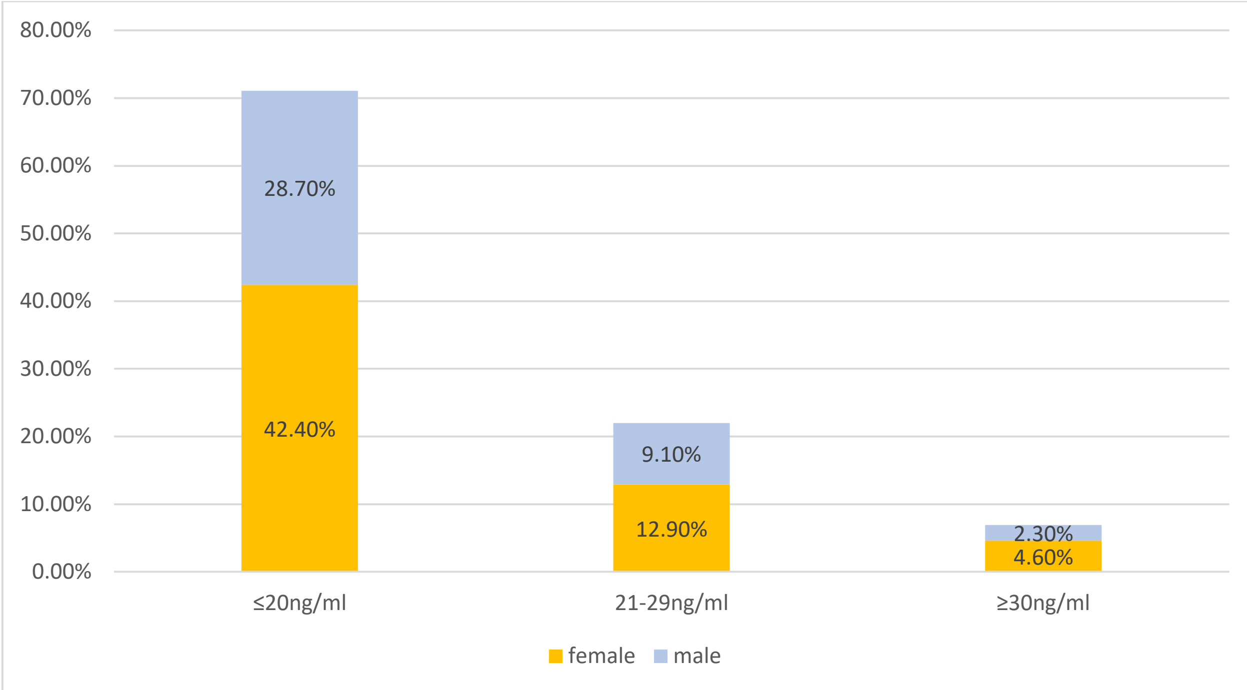

Figure (1): Percentages of the diabetic patients with vitamin D deficiency and insufficiency

Table (4) shows that vitamin D deficiency was high in all the age groups with no age predominance (P-value=0.630).

Table4: levels of vitamin D ng/ml and the ages of the Diabetic patients

Age	2-5yrs No.	%	>5-10yrs No.	%	>10-18 No.	%
≤20ng/ml	9	64.3	30	71.4	55	72.4
21-29ng/ml	5	35.7	9	21.4	15	19.7
≥30ng/ml	0	0	3	7.2	6	7.9
Total	14		42		76	

Figure (2) shows that 35.6% of the diabetic patients had hypocalcemia (serum calcium<8.5mg/dl) , all of them with vitamin D deficiency (100%) and 64.4% have normal serum calcium (serum calcium≥8.5-10.5mg/dl) , of those with normal serum calcium, 55.3% were vitamin D deficit and 34.1% were vitamin D insufficient (table5).

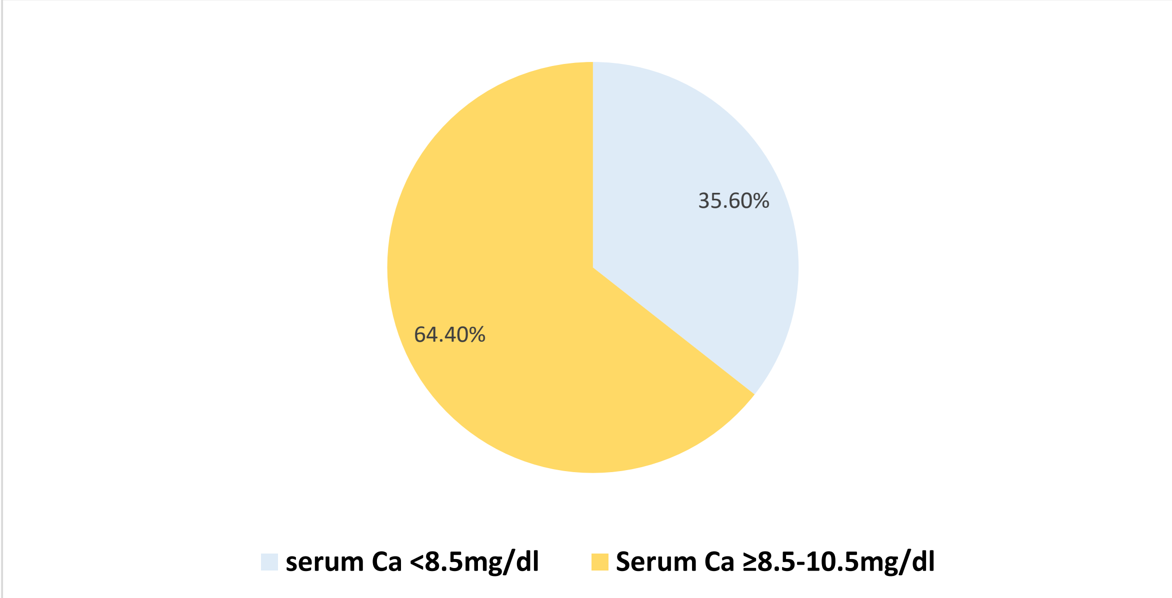

Figure (2): Diabetic patients with hypocalcemia and those with normal serum calcium (mg/dl)

Table5: Type 1 diabetic patients with normal serum calcium (mg/dl) and their vitamin D levels

Serum Ca level	**≤20ng/ml**	**%**	**21-29ng/ml**	**%**	**≥30ng/ml**	**%**
≥8.5-10.5mg/dl	47	55.3	29	34.1	9	10.6

Table (6) shows that levels of HbA1c in those with vitamin D deficiency and insufficiency were higher than those with normal vitamin D levels but with no significant differences (p-value=0.943).

Table 6: levels of vitamin D ng/ml with mean HbA1c±SD

Vit. D level	**Mean HbA1c±SD**
≤20ng/ml	13.3±1.2
21-29ng/ml	12.2±1.9
≥30ng/ml	9.4±1.1

Discussion:

Table (1) shows that type 1 diabetes was common in those older than 10years (57.6% of the diabetic patients were older than 10 and P-value=0.000) with no sex predominance (P-value=0.879). Many studies shows that no firm data on gender differences in type 1 diabetes mellitus, although males appear to be more frequently affected by the disease and this may vary in different populations (19,20) and highest incidence among those 10-14 years old which is due to sex hormones, increase in appetite with puberty and rapid growth during this period all will increases insulin requirement (20).

Body mass indexes were higher in those older than 10 and in male patients (P-value=0.000) as seen in table 2 but still within normal range according to CDC BMI charts. The risk factors of weight gain include using high doses of exogenous insulin, intensified insulin therapy, fear of hypoglycemia and related decrease in physical activity, and psychological factors, such as emotional eating and binge eating (21). Paul Fellinger's study shows that patients with T1DM had significantly higher BMI values than general population; however, prevalence of overweight and obesity was not significantly different. Obesity was not a cause of T1DM but it might increase diabetic complications, especially cardiovascular disease (22). Traditionally, people with type 1 diabetes have tended to be underweight. This is because insulin and blood glucose management technologies were less advanced, and as a result, more glucose – and therefore calories – pass out of the body through the urine and also restrictive diet regimens will lead to their weights on the average or sometimes underweight (23).

HbA1c as shown in table3 were higher in those older than 10years and in female patients, so risk of poor glycemic control increase with increasing the age and in female more than male patients. Gudrun Wagner et al study also shows that adolescent girls with longer diabetes duration show the highest HbA1c (24). Medivizor in 2015 posted that 75% of patients aged 2-4 years achieved the recommended HbA1c target, between 6-13 years of age, the percentage of patients achieving the target decreased to 50%, between 13-18 years, only 25% achieved the recommended target (25). In Bulgaria, Margarita Archinkova, et al found that maintaining optimal glycemic control was shown to be most difficult in teenagers, which is most likely connected with the specifics of this age, low motivation, hormones, psychological lability and issues with parents and school. Small children under 6 years achieved good glycemic control easier due to families' devotion to diabetes control, which gives hopes for maintaining this good glycemic control in the following years (26).

Figure 1and table 4 shows that 71.1% of the diabetic patients were vitamin D deficit and 22% were vitamin D insufficient with no significant relations to the sex or the age. These results were comparable to the results of Mauri Carakushansky et al's study, where they found that the prevalence of vitamin D deficiency in children with type 1 Diabetes Mellitus were 64% with no significant associations of vitamin D deficiency based on sex or age (27). Also in Bahrain, Hasan

Isa and Mohamed Almaliki's study shows that no gender preferences in vitamin D deficiency and insufficiency in healthy children between 6 and 15 years of age (28). Our data shows that vitamin D insufficiency and/or deficiency is significantly high in type 1 diabetic patients but does not seems to be more prevalent than general pediatric population as evident by study done in Mosul where vitamin D deficiency was found in 59.7% of children, vitamin D insufficiency was evident in 33.8% of children, whereas only 6.3 % of children had vitamin D sufficiency (29).Also in southern Iran, 81·3 % of the healthy children were vitamin D deficient with no significant difference in vitamin D concentration between boys and girls(30). Factors such indoor lifestyle, physical inactivity, avoidance of exposure to sunlight, environmental pollution and the scarce dietary sources of vitamin D should be considered in relation to the high levels of vitamin D deficiency (28). The high incidence of vitamin D insufficiency documented in our study and many other studies in the near areas demonstrates that residing in areas with easy access to sunlight does not guarantee protection against the development of vitamin D deficiency or insufficiency. Also, one of the plausible mechanisms of vitamin D deficiency in diabetics is decreased vit D binding proteins; this has been initially demonstrated in diabetic rats. Later on, in humans, it has been founded that the urinary loss of vitamin D binding protein (VDBP) is secondary to diminished function or availability of megalin or low-density lipoprotein-related protein 2 (LRP2), correlated with proteinuria (31).

Figure2 and table 5, shows that 35.6% of the diabetic patients were hypocalcemic and all of them were vitamin D deficit, 64.4% were normocalcemic and only 10.6% of them had normal level of vitamin D. Kurt A. study shows that 25-50% of vitamin D deficit patients were normocalcemic by the effect of parathyroid hormones (32). Because of vitamin D deficiency can be risk factor for developing type 1 diabetes, increase insulin resistance and increase insulin need which may lead to poor glycemic control, so even in normocalcemic patients, vitamin D assessment preferred to be sent (32).

Mean HbA1c in our study was high among those with vitamin deficit, insufficient and those with normal vitamin D levels as seen in table6. These results were comparable to many studies that founded that vitamin D level had no relation to HbA1c (33,34). Other studies founded that vitamin D deficiency associated with poor glycemic control and HbA1C improves with vitamin D3 supplementation, these results needed further evaluation regarding doses of vitamin D and the duration of treatment (35).

CONCLUSIONS

The prevalence of vitamin D deficiency and insufficiency among T1 D children was very high and there were no sex or age predominance. Poor diabetic control was seen in all age groups mainly in females and in those older than 10years with no significant relation with the serum levels of vitamin D. So, screening for vitamin D in diabetic patients recommended which that may improve the glycemic control and also for other beneficial effects of vitamin D on the general health.

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