Assessment of Vitamin D Levels among Children and Adolescents with Diabetes Mellitus

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Received:1.9.2024 **Accepted:28.11.2024**

Abstract

Background: Vitamin D plays a crucial role in the pathogenesis of diabetes mellitus (DM) in children. Researches suggest that its deficiency is associated with an increased risk of developing Type 1 diabetes mellitus (T1DM) and Type 2 diabetes mellitus (T2DM) in children. Vitamin D helps in the regulation of insulin secretion and sensitivity, and its deficiency may contribute to improper diabetes control and increased diabetes complications in children and adolescents.

Aims: The present study was conducted to investigate the relationship between serum vitamin D levels and parameters of controls in children and adolescents with diabetes.

Methods: A cross-sectional study was conducted at Basrah Maternity and Children Hospital and Faiha Specialized Diabetes, Endocrine, and Metabolism Center. All the new and old cases who attended the study centers with DM (TIDM or T2DM) or complications of DM were included, the study period was from March 2023 to March 2024, in Basrah governorate, the southern part of Iraq. The demographic and clinical data were gathered using an organized questionnaire and medical records. HbA1c, RBS, and 25 OH cholecalciferol levels were measured. After data collection, SPSS version 26 was used for statistical analysis.

Results: The vitamin D levels among the 107 children and adolescents with type one and type two diabetes who enrolled in the study were: 62 (57.9%) had a deficiency, 25 (23.4%) had insufficiency, and 20 (18.7%) had sufficient levels. In comparison to the sufficient and insufficient group, the vitamin D deficiency group's participants were significantly older (p =0.038), and lived in rural regions 65 (60.7%). Additionally, the vitamin D deficient group had higher mean values of random blood sugar (RBS) 227.41±25.31 mg/dL and glycosylated hemoglobin (HbA1c) 7.72±0.47 % values; however, these differences did not achieve statistical significance. A negative correlation was found between the number of hospital admissions in the last year (r= -0.177), the number of diabetic keto-acidosis (DKA) in the last year (r= 0.154), the number of hypoglycemia episodes (r= -0.120), and BMI (r= -0.252) with the serum vitamin D levels. Additionally, a negative correlation was found between HbA1c values (r= -0.131) and RBS values (r= -0.260) with the serum vitamin D levels

Conclusion: This study found no significant association between serum vitamin D levels and poor diabetes control. However, the deficient group showed higher rates of poor clinical and laboratory indices.

Keywords: Children and adolescents, Diabetes mellitus, Vitamin D, Basrah.

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Introduction

Diabetes mellitus (DM) is a group of complicated multifactorial metabolic illnesses. Hyperglycemia caused by abnormalities in insulin action and/or secretion is the major characteristic of DM (1). In addition to its role in calcium and phosphorus metabolism, vitamin D also plays an immunomodulatory function by interacting with the nuclear vitamin D receptor (VDR) to control the expression of transcription factors (2). By inhibiting inflammatory and autoimmune responses,

promoting insulin synthesis and secretion, improving insulin sensitivity, and increasing vitamin D-related gene polymorphisms, vitamin D can play a significant role in the pathogenesis of diabetes and glycemic control (2, 3).

T1DM control can be affected by vitamin D deficiency, particularly in children with newly diagnosed Type 1 diabetes mellitus (T1DM). Low vitamin D levels are closely linked to ketoacidosis (4). Even in patients with T1DM who have been diagnosed for several months, vitamin D deficiencies are still a cause for concern (5).

Glycosylated hemoglobin (HbA1c) can also be better maintained in children with T1DM by simply controlling their vitamin D intake without altering their insulin dosage, according to studies (6), Another perspective is that children with T1DM may experience poor blood glucose control due to vitamin D insufficiency, According to research from Saudi Arabia, children with T1DM who are vitamin D deficient are more prone to experience hypoglycemia and metabolic disorders (7).

The potential significance of vitamin D supplementation as an additional medication to promote insulin sensitivity and glycemic control offers new avenues for improving diabetic patients' health and disease management (3). In a double-blind randomized controlled research by Treiber et al., Cholecalciferol supplementation after the onset of T1DM has been shown to enhance the suppressive capacity of regulatory T cells, this highlights vitamin D's potential role in immunomodulating the progression of T1D. The findings suggest that cholecalciferol could be considered as part of combination therapies for managing T1D (8). This shows that people with T1DM who have insufficient or deficient vitamin D levels should receive vitamin D treatment. to alter the progression of T1DM (9). The present study investigated the relationship between serum vitamin D levels and parameters of controls in children and adolescents with diabetes.

Patients and Methods

A cross-sectional study was held at Basra Maternity and Children Hospital and Faiha Specialized Diabetes, Endocrine, and Metabolism Center. The study period was from March 2023 to March 2024, in Basra governorate, the southern part of Iraq. The target study population was children and adolescents who attended the inpatient wards and the outpatient clinic with DM.

All the new and old cases who attended the study centres with DM (TIDM or T2DM) or complications of DM were included in the study. While the exclusion criteria were:

- Patients more than 18 years old
- Patients with acute illnesses
- medication interfering with vitamin D metabolism
- Rickets
- Parathyroid disease
- Celiac disease
- Inflammatory bowel disease or malabsorption syndrome
- Nephropathy
- Liver impairments

Written informed consent from the patient's parent, as well as Basrah Health directorate approval, was obtained before data collection.

Each patient underwent a clinical evaluation including, a full medical assessment, regarding the patient’s history of previous hospital admissions due to DKA or other DM complications, the patient’s treatment history, school attendance, insulin type, regimen and dosage, compliance with the treatment, and any comorbidities.

Full clinical examination including weight, height, and calculation of BMI had been done for all patients who enrolled in this study. Height was measured by the Harpenden stadiometer and weight by using an electronic scale. BMI was calculated as the BMI-for-age percentile based on CDC growth charts for children and teens (10).

All patients included in this study were evaluated for serum vitamin 25 OH cholecalciferol levels, random blood sugar (RBS), and HbA1c levels.

On Mindray CL-1000i immunoassay analyzers, the electrochemiluminescence binding assay is intended for the quantitative detection of total 25-hydroxyvitamin D in human blood and plasma, based on the competition principle. The process was fully automated from the sample loading until the showing of the results.

The COBAS INTEGRA 400 plus was used for HbA1c and RBS estimation. For HbA1c, Glycated hemoglobin at the ß-chain N-terminus which has antibody-recognizable regions identical to that of HbA1c determined by assay method.

For RBS, Hexokinase (HK) is a catalytic enzyme that catalyzes the phosphorylation of glucose by ATP to produce glucose6phosphate and ADP. A second enzyme, glucose6phosphate dehydrogenase (G6PDH), is employed to monitor the process by catalyzing the oxidation of glucose6phosphate by NADP + to generate NADPH. The amount of NADPH generated is directly proportional to the amount of glucose present.

107 children and adolescents were included. The patients were divided into 3 groups based on their 25 (OH) vitamin D levels, and cut-off values were used depending on previously published local and international studies (11-14). Vitamin D sufficient group (25 (OH) vitamin D >30 ng/mL) (n=20), vitamin D insufficient group (25 (OH) vitamin D 20-30 ng/ mL) (n=25), and vitamin D deficient group (25 (OH) vitamin D <20 ng/mL) (n=62).

International Business Machines- Statistical Package for the Social Sciences (IBM-SPSS) statistics version 25 used for data analysis. Categorical data were presented as numbers and percentages. The chi-square test (X2) was used to assess group differences. Continuous data was expressed as Mean ± SD and the differences between the groups were assessed by one-way ANOVA test. P-values lower than 0.05 were considered statistically significant.

Results

The demographic characteristics of the studied population are illustrated in **Table (1).** A total of 107 children and adolescents with diabetes mellitus were included in the study.

In concern to age, the mean values for the age among the studied groups were (7.55 ± 0.87 years) for the normal vitamin D group, (7.08 ± ٠.61year) for insufficient, and (9.02 ± 0.44 years) for the deficient group. There was a statistically significant difference regarding the age among the studied group (P value=0.038).
Regarding sex distribution, 40 (37.4%) were males and 67 (62.6%) were females.
When the residency of patients was evaluated, it was found that 65 (60.7%) of those patients were living in rural while 42 (39.3%) were living in urban areas.
In concern to weight, the mean values for the weight among the studied groups were (24.30 ± 2.31 kg) for the normal vitamin D group, (22.04 ± 2.03 kg) for insufficient, and (28.12 ± 1.60 kg) for the deficient group.
Regarding the patient's height, the mean values for height among diabetic children and adolescents were (118.05 ± 5.33 cm) for the normal vitamin D group, (114.12 ± 3.60 cm) for insufficient, and (122.21± 2.42 cm) for the deficient group.
When the patients BMI was evaluated, most of them 73 (68.2%) were underweight and the remaining 34 (31.8%) had normal BMI levels. No overweight patients were observed in this study.

Table 1 Demographical Data Among the Studied Patients

Variables		Diabetics with normal vitamin D levels (20)	Diabetics with vitamin D insufficiency (25)	Diabetics with vitamin D deficiency (62)	P value
Age (years) (Mean ±SD)		7.55 ± 0.87	7.08 ± 0.61*	9.02 ± ٠.44*	0.038 *
Sex (N)(%)	Male (40) (37.4%)	6 (30%)	11 (44%)	23 (37.1 %)	0.626
	Female (67) (62.6%)	14 (70%)	14 (56%)	39 (62.9 %)	
Address (N) (%)	Rural (65) (60.7%)	11 (55%)	19 (76%)	35 (56.5%)	0.202
	Urban (42) (39.3%)	9 (45%)	6 (24%)	27 (43.5%)	
Height in Cm (Mean ±SD)		118.05 ± 5.33	114.12 ± 3.60	122.21± 2.42	0.216
Weight in Kg (Mean ±SD)		24.30 ± 2.31	22.04 ± 2.03	28.12 ± 1.60	0.075
Body mass index (BMI) (Mean ±SD)	Normal (34)(31.8%)	6 (30%)	5 (20%)	23 (37.1%)	0.296
	Underweight (73) (68.2%)	14 (70%)	20 (80%)	39 (62.9%)	

*A significant difference between the groups at the 0.05 level

SD: standard deviation, N: number of cases, BMI: body mass index

Figure 1 shows the vitamin D status among the enrolled patients, most of them had inadequate levels of vitamin D. Deficiency was observed in 62 (57.9%), insufficiency in 25 (23.4%), and normal levels in 20 (18.7%).

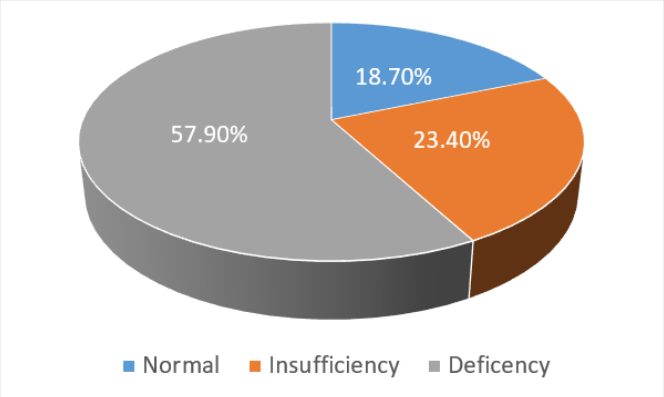

Figure 1: Vitamin D Status Among the Studied Children and Adolescents with Diabetes

Different clinical parameters of diabetes control are shown in **Table 2**. Concerning the number of hospital admissions and Diabetic ketoacidosis (DKA) episodes in the last year, 38 (68.3%) from the deficient group and 16 (64%) from the insufficient group had one or more hospital admissions in the last year mostly due to DKA, in comparison to 10 (50%) of patients with normal vitamin D group had a history of hospital admission or DKA. Frequent hospital admissions (three or more) was reported among the deficient groupin higher rates 8 (61.5 %) in comparison to 4 (30.76 %) and 1 (7.69 %) for insufficient and normal vitamin D levels groups respectively.

Diabetics with inadequate vitamin D levels showed significantly higher rates (p=0.034) of frequent hypoglycemia episodes (three or more) 18 (29%) for the deficient group, and 9 (36%) for the insufficient group, compared to individuals with normal levels (10%).

Regarding the history of absence from school, it was observed in 25 (48.1%) from the deficient, 11 (57.9%) from the insufficient, and 7 (50%) from normal vitamin D level groups, without significant differences.

Table 2 Clinical parameters of the studied patients

Variables		Diabetics with normal vitamin D levels (20)	Diabetics with vitamin D insufficiency (25)	Diabetics with vitamin D deficiency (62)	P value *
Number of hospital admission / last year	No admission (43) (40.2%)	10 (50%)	9 (36%)	24 (31.7%)	0.90
	One (30) (28%)	6 (30%)	7 (28%)	17 (27.4%)	
	Two (21) (19.6%)	3 (15%)	5 (20%)	13 (21%)	
	Three or more (13) (12.1%)	1 (5%)	4 (16%)	8 (12.9%)	
Number of DKA / last year	Zero (45) (42.1%)	10 (50%)	9 (36%)	26 (41.9%)	0.702
	One (36) (33.6%)	5 (25%)	12 (48%)	19 (30.6%)	
	Two (19) (17.8%)	4 (20%)	3 (12%)	12 (19.4%)	
	Three or more (7) (6.5%)	1 (5%)	1 (4%)	5 (8.1%)	
Hypoglycemia episodes / last year	Zero	9 (45%)	9 (36%)	36 (58.1%)	0.034
	One	7 (35%)	4 (16%)	7 (11.3%)	
	Two	2 (10%)	3 (12%)	1 (1.6%)	
	Three	2 (10%)	2 (8%)	7 (11.3%)	
	More than three	0	7 (28%)	11 (17.7%)	
History of not attending school	Yes (43) (50.6%)	7 (50%)	11 (57.9%)	25 (48.1%)	0.636
	No (42) (49.4%)	7 (50%)	8 (42.1%)	27 (51.9%)	

***One-way ANOVA test**

DKA: diabetic ketoacidosis

In concern to HbA1c %, the mean values among the studied groups were (7.15%) for the normal vitamin D group, 7.36 ± .58%) for insufficient, and (7.72 ± 0.47) for the deficient group which was higher than the other two groups (**Table 3**.)

When the patients were divided into three groups according to the low (<7%), medium (7-9%), and high (>9%) HbA1c readings, a comparable number of patients with normal, deficient, or insufficient vitamin D levels where located in every group (**Figure 2)**.

Regarding the patient's RBS levels, higher levels were observed in the deficient group (227.41 ± 25.31mg/dL) and insufficient group (176.38 ± 37.7 mg/dL) than the normal vitamin D group (140.74 ± 24.94 mg/dL) (**Table 3**).

Table 3 Laboratory Parameters of the Studied Patients

Variables	Diabetics with normal vitamin D levels	Diabetics with vitamin D insufficiency	Diabetics with vitamin D deficiency	P value*
HbA1c % (Mean ±SD)	7.15 ± 0.42	7.36 ± 0.58	7.72 ± 0.47	0.793
RBS in mg/dL (Mean ±SD)	140.74 ± 24.94	176.38 ± 37.7	227.41 ± 25.31	0.170

***One-way ANOVA test**

HbA1c: glycosylated haemoglobin, RBS: random blood sugar

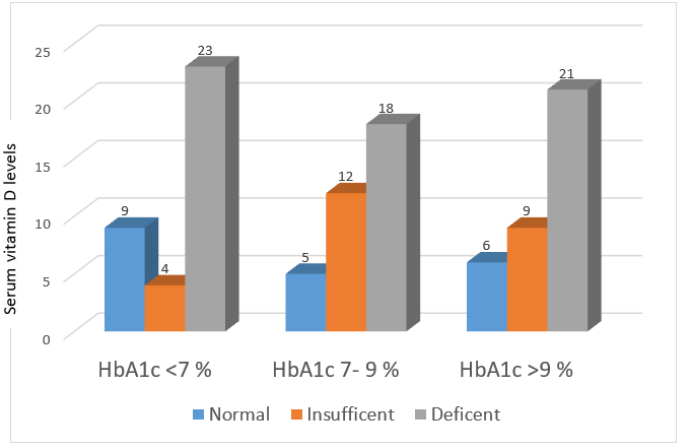

Figure 2 Vitamin D levels among different HbA1c groups

A negative correlation was found between age (r= -0.250), number of hospital admissions in the last year (r= -0.177), number of DKA in the last year (r= -0.154), number of hypoglycemia episodes (r= -0.120), and BMI (r= -0.252) with the serum vitamin D levels. as shown in **(Table 4)**. The negative correlation was significant (p <0.05) regarding the age and BMI.

During the evaluation of the correlation between the laboratory parameters of diabetes control (HbA1c and RBS), A negative correlation was found between HbA1c values (r= --0.131) and RBS values (r= -0.260) with the serum vitamin D levels. as shown in **(Table 4)** and **(Figure 3).** This finding indicates that when those parameters increase, serum vitamin D decreases.

Table 4 Pearson Correlation Between Serum Vitamin D Levels and Different Clinical and Laboratory Parameters in the Studied Population

		Age	No. of hospital admission	No. of DKA	No. of hypoglycemia	BMI kg/m^2	RBS	HbA1c
Vitamin D serum levels (ng/mL)	R-value	-0.250**	-0.177	-0.154	-0.120	-0.252**	-0.260	-0.131
	Significance	0.009	0.068	0.114	0.219	0.009	0.053	0.178

** Correlation is significant at the 0.01 level (2-tailed).

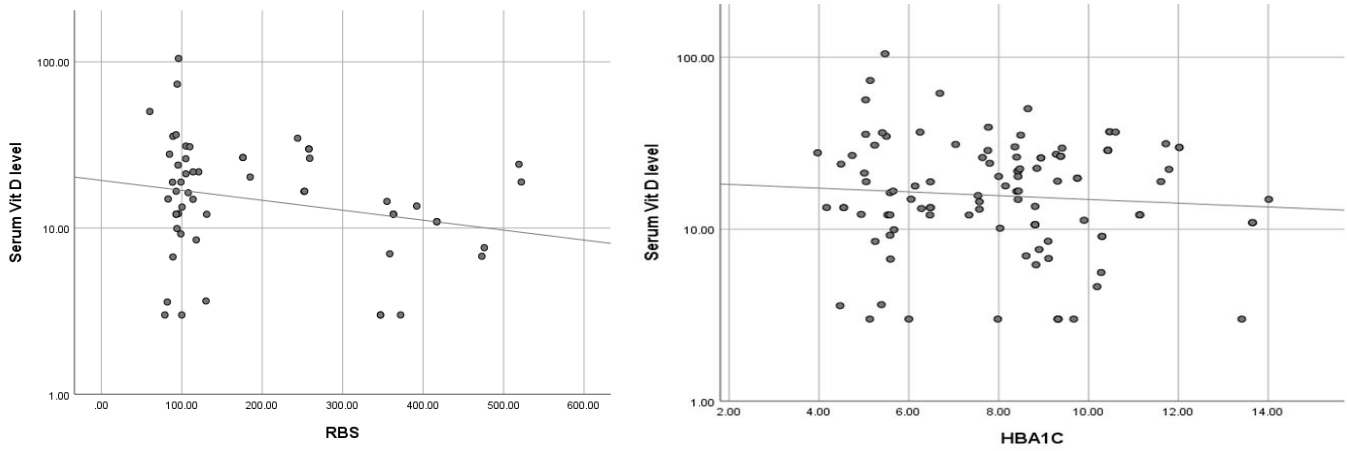

Figure 3: Correlation between serum vitamin D levels with RBS and HbA1c%

HbA1c: glycosylated haemoglobin, RBS: random blood sugar HbA1c: glycosylated haemoglobin, RBS: random blood sugar

4. Discussion

Vitamin D has traditionally been linked to calcium metabolism, bone development, and the maintenance of mineral homeostasis. However, Several researches are currently being conducted to clarify the association between vitamin D and DM (15, 16).

The present study showed that the mean age of the vitamin D-deficient group (9.02 ± ٠.44 years) was significantly higher than the insufficient (7.08 ± 0.61 years) and normal (7.55 ± 0.87 years) vitamin D groups. The negative relationship between vitamin D levels and age was also confirmed by the person correlation test (-0.250). This finding was consistent with previous studies from Iran (17, 18). The results can be explained by the links between a lack of vitamin D and DM duration that were found in several previous studies, by Janner et al. (19) and Vojtkov et al. (20).

The current study showed that females have a higher percentage of vitamin D deficiency than males but without a significant relationship, consistent with prior findings by Al-Agha et al. in Saudi Arabia (21) and Jafari et al in Iran (17). This could be due to Middle east girls usually covering most of their bodies for cultural and religious reasons. Additionally, females may require more vitamin D for bone growth during their rapid pubertal development (22).

Patients with higher BMI had higher rates of vitamin D deficiency and insufficiency than the normal vitamin D group, furthermore, the correlation test between serum vitamin D level and BMI showed a significant negative relationship (p=0.009). The most widely recognized physio-pathological explanation is that vitamin D, being fat-soluble, is over-absorbed by adipose tissue which causes a reduction in its serum levels (23).

Regarding vitamin D levels in relation to clinical parameters of glycemic control in the current study, children and adolescents from the deficient or insufficient groups usually had higher rates of hospital admissions, DKA, hypoglycemia episodes, and absence from school for 6 years and above children. However, this is not present in all domains, the association was statistically not significant for some of the parameters. Most of the hospital admissions are usually due to DKA episodes, in turn, these episodes affect the attendance to the school.

Soliman and colleagues did a study regarding the assessment of vitamin D status in Egyptian children with T1DM, they included 43 children with poor glycemic control and 10 children with good glycemic control. Their work concluded that children with poor DM control exhibited significantly lower serum vitamin D levels (16.9 ± 3.7 ng/ml) compared to the good DM control group (28.6 ± 6.5 ng/ml), additionally, they stated that vitamin D helps diabetics to manage their blood sugar levels and prevent complications (24). A recent study by He et al. on the association between serum vitamin D levels and ketosis episodes in patients with DM found that low Vitamin D levels are linked to ketosis in DM patients, adequate serum vitamin D levels may be a protective factor for the development of ketosis in these patients (25).

This study found a negative correlation (-0.260) between the RBS levels and the serum vitamin D levels. This is similar to recent studies by Johnson et al. (26), and Juliaty et al. (27) who discovered that children with Vitamin D insufficiency had higher fasting plasma glucose levels. Therefore, it can be concluded that vitamin D deficiency may contribute to elevated blood sugar levels in children.

The present study showed that there is a negative correlation (-0.131) between serum vitamin D levels and the HbA1c values. However, the distribution of normal deficient and insufficient vitamin D cases was comparable between the low (<7%), medium (7-9%), and high (>9%) HbA1c readings (Figure 3). This may indicate that the diabetic state per say is a reason for low vitamin D levels and is not secondary to any hyperglycemic or insulin-resistant state. Similar to this study's results, Zabeen et al. found that higher values of HbA1c were observed in all three groups (deficient, insufficient, and normal vitamin D groups) indicating that vitamin D alone may not significantly improve glycemic control in patients with diabetes (28). Ordooei et al. and Savastio S et al. found that vitamin D consumption reduces fasting blood sugar and HbA1c levels in children and adolescents with diabetes (6, 16). However, additional research by Hafez et al. found no statistically significant decrease in HbA1c values after 3 months of vitamin D intake in children and adolescents with diabetes (29). Till now, the role of sufficient vitamin D in the pathogenesis and development of DM is crucial, However, its role in DM control is still mysterious.

In conclusion, this study found no statistically significant association between serum vitamin D levels with poor clinical and laboratory diabetes control parameters. However, higher rates of poor clinical and laboratory indices were found mostly in the deficient group.

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تقييم مستويات فيتامين د بين الأطفال والمراهقين المصابين بداء السكري

الخلفية: يلعب فيتامين د دورًا حاسمًا في التسبب في داء السكري (DM) لدى الأطفال. تشير الأبحاث إلى أن نقصه يرتبط بزيادة خطر الإصابة بمرض السكري من النوع الأول (T1DM) والنوع الثاني (T2DM) لدى الأطفال. يساعد فيتامين د في تنظيم إفراز الأنسولين وحساسيته، وقد يساهم نقصه في سوء السيطرة على السكري وزيادة مضاعفاته لدى الأطفال والمراهقين.

الأهداف: تم إجراء هذه الدراسة للتحقق من العلاقة بين مستويات فيتامين د في الدم ومعايير التحكم لدى الأطفال والمراهقين المصابين بالسكري.

الطرق: أُجريت دراسة مقطعية في مستشفى البصرة للولادة والأطفال ومركز الفيض التخصصي للسكري والغدد الصماء والأيض. شملت الدراسة جميع الحالات الجديدة والقديمة التي راجعت مراكز الدراسة المصابة بالسكري (T1DM أو T2DM) أو مضاعفات السكري، خلال الفترة من مارس ٢٠٢٣ إلى مارس ٢٠٢٤ في محافظة البصرة جنوب العراق. تم جمع البيانات الديموغرافية والسريرية باستخدام استبيان منظم وسجلات طبية. تم قياس مستويات HbA1c، وسكر الدم العشوائي (RBS)، ومستويات ٢٥ هيدروكسي كوليكالسيفيرول. تم تحليل البيانات باستخدام برنامج SPSS الإصدار ٢٦.

النتائج: كانت مستويات فيتامين د لدى ١٠٧ أطفال ومراهقين مصابين بالسكري من النوع الأول والنوع الثاني المشمولين في الدراسة كما يلي: ٦٢ (٥٧,٩٪) لديهم نقص، ٢٥ (٢٣,٤٪) لديهم قصور، و٢٠ (١٨,٧٪) لديهم مستويات كافية. مقارنة بمجموعتي المستويات الكافية والقصور، كان المشاركون في مجموعة نقص فيتامين د أكبر سنًا بشكل ملحوظ (p=0.038) ويعيشون في المناطق الريفية ٦٥ (٦٠,٧٪). بالإضافة إلى ذلك، أظهرت مجموعة نقص فيتامين د متوسطات أعلى لمستويات سكر الدم العشوائي (٢٢٧,٤١±٢٥,٣١ ملغم/ديسيلتر) والهيموغلوبين السكري (٧,٧٢±٠,٤٧٪)، ومع ذلك، لم تكن هذه الفروق ذات دلالة إحصائية. وُجدت علاقة عكسية بين عدد مرات الدخول إلى المستشفى خلال العام الماضي (r= -0.177)، وعدد حالات الحماض الكيتوني السكري (r= 0.154) (DKA)، وعدد نوبات نقص السكر في الدم (r= -0.120)، ومؤشر كتلة الجسم (r= -0.252) (BMI) مع مستويات فيتامين د في الدم. كما وُجدت علاقة عكسية بين قيم HbA1c (r= -0.131) ومستويات سكر الدم العشوائي (r= -0.260) مع مستويات فيتامين د في الدم.

الاستنتاج: لم تجد هذه الدراسة ارتباطًا كبيرًا بين مستويات فيتامين د في الدم وضعف التحكم بالسكري. ومع ذلك، أظهرت مجموعة نقص فيتامين د معدلات ضعف أعلى من المؤشرات السريرية والمخبرية.

الكلمات المفتاحية: الأطفال والمراهقون، داء السكري، فيتامين د، البصرة.