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The impact of vitamin D in type 1 diabetes in pediatric patients

Adriana Pana[1], Irina-Elena Muntean[1], Ana Maria Pitea[2,3]

[1]"Algocalm" Polyclinic, Targu Mures, Romania
[2]"George Emil Palade" University of Medicine, Pharmacy, Sciences and Technology of Targu Mures, Romania
[3]Pediatric Department of County Emergency Clinical Hospital, Targu Mures, Romania

ABSTRACT

Background and objectives. Type 1 diabetes is a chronic disease, whose incidence is increasing worldwide. Patients with chronic illnesses are more likely to have a deficiency in vitamin D. The aim was to evaluate the impact of vitamin D on biochemical parameters in type 1 diabetes in patients under 18 years of age.

Materials and methods. We performed a prospective observational study in 2023, on a sample of 121 type 1 diabetic patients aged between 5 and 18 years, who had previously undergone vitamin D screening before the study's start date. This time was called the initial time (T0). During the consultation, patients who agreed to participate in the study received a voucher for vitamin D screening, referred to as the final time (Tf). The period between T0 and Tf was 3 months.

Results. At the initial time, 88 (72.73%) of patients had vitamin D deficiency, while at the final time, 11 (9.09%) had deficiency ($p<0.05$). Vitamin D levels were 18.69 ± 4.14 ng/mL at T0 compared to 31.28 ± 7.60 ng/mL at Tf ($p<0.05$). Additionally, at the initial time, 72.73% of patients presented with hypocalcemia, and 66.94% of them with hypophosphatemia, whereas at the final time, hypocalcemia was noticed in 19.01% ($p<0.05$), and hypophosphatemia in 25.62% ($p<0.0001$). Correlation between T0 and Tf vitamin D levels shows an $r = 0.5764$ ($p<0.0001$, 95% CI = 0.4392 - 0.6873).

Conclusions. The study reveals a direct proportional relationship between imbalances in biochemical parameters and vitamin D deficiency, and indicates that vitamin D supplementation significantly contributed to the improvement of biochemical parameters.

Keywords: pediatric patient, screening, type 1 diabetes, vitamin D

Abbreviations (in alphabetical order):

DKA	– diabetic ketoacidosis
DS	– deviation from standard
HbA1c	– glycated hemoglobin
T1D	– type 1 diabetes
Tf	– the final time
T0	– the initial time

INTRODUCTION

Type 1 diabetes (T1D) is a relatively common chronic disease that affects pancreatic β cells. Its incidence is increasing worldwide and causes substantial lifelong morbidity, affecting patients during childhood and throughout their adult lives [1,2]. Type 1 diabetes primarily affects children and young people, but it can occur at any age. Most cases develop before the age of 30, with a peak incidence among school-aged children and adolescents. T1D accounts for approximately 5-10% of all diabetes cases. According to data from the International Diabetes Federation, in 2022, approximately 8.75 million people with diabetes had type 1 diabetes, with 1.52 million of them being under the age of 20. Notably, half of the world's countries, including some highly populated nations, lack data for children and adolescents, so the rates have been extrapolated from neighboring coun-

Corresponding authors:
Adriana Pana
E-mail: adriana.pana@algocalm.ro

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tries, with varying accuracy depending on genetic and environmental factors [3,4]. The most recent research studying the incidence of T1D in children under 14 years of age, conducted in 2018 in Romania, revealed that the Transylvania region had the highest incidence, with 7.9 children per 100,000 inhabitants per year [5].

Currently, there are no known therapies that can be used to prevent type 1 diabetes, but there is evidence that low vitamin D levels may play a role in predisposition to this disease. Animal studies [6,7] and observational studies [8-12] have shown that reduced serum 25-hydroxyvitamin D levels are associated with an increased risk of type 1 diabetes. Additionally, it has been demonstrated that vitamin D could prevent cytokine-induced apoptosis of human pancreatic islets [13].

The relation between vitamin D and T1D may be mediated by the effects of vitamin D on the immune system. There is evidence that the active form of vitamin D, 1,25-dihydroxyvitamin D, is an immune modulator, reducing immune system activation, and that vitamin D also has non-immunological effects on the pancreas and, therefore, may directly influence β cell function [14-16]. The most recent observational evidence comes from a nested case-control study in the Trial to Reduce IDDM in the Genetically at Risk cohort, which showed a protective role of higher levels of 25-hydroxyvitamin D [17].

The peak period for bone mass formation can only be reached with sufficient calcium and vitamin D intake. In its absence, the risk of osteoporosis later in life reaches 60%. The role of vitamin D is not limited to bone health, as vitamin D receptors are found in numerous cells, including immune cells (T and B), osteoblasts, pancreatic β cells, and mononuclear cells, as well as in organs such as the heart, brain, reproductive system, and intestines [18].

The interaction between transcription factors, 1,25-hydroxyvitamin D2, and vitamin D receptors modulates gene expression, influencing numerous physiological functions and including antitumor, immune, and anti-inflammatory effects [19,20].

Vitamin D, also known as the anti-rickets vitamin, is a predictor of nutritional status in children and adolescents and significantly contributes to maintaining a strong and healthy immune system by modulating it and reducing inflammation. The effectiveness of vitamin D has been demonstrated in the primary prevention of T1D [1-17].

The harmonious development of children and adolescents is one of the important goals of a nation. In type 1 diabetes, the discovery of other associated risk factors, quantification, and monitoring of these risk factors, must be an important objective to reduce the occurrence of comorbidities and biochemical imbalances. Thus, we aimed to investigate the prevalence of vitamin D deficiency and the impact of vitamin D on biochemical parameters in T1D in patients under 18 years of age.

MATERIALS AND METHODS

We performed a prospective observational study between regarding the influence of vitamin D levels on the growth and harmonious development of pediatric patients, with the primary classification criterion being the presence of type 1 diabetes. The study was approved by the Ethics Committee of the "George Emil Palade" University of Medicine, Pharmacy, Science, and Technology of Targu Mures (Approval number: 2065/09.02.2023). The sample size consisted of 121 children, aged between 5 and 18 years (not fulfilled, until the date of completion study).

The inclusion criteria for the study were as follows: patients with T1D under 18 years old, registered between January 31 and June 1, 2023, who had undergone vitamin D screening before January 31, 2023, and whose parents/guardians agreed to follow the vitamin D supplementation recommendations.

The exclusion criteria included: patients with T1D under 18 years old registered between January 31 and June 1, 2023, who had not undergone vitamin D screening before January 31, or whose parents/guardians did not agree to follow the vitamin D supplementation recommendations; patients aged ≥18 years, and patients with conditions other than type 1 diabetes.

The data collection was longitudinal, with data collected at predefined intervals. Regarding the data collection method, secondary data were gathered from available medical documents, observation sheets, electronic databases, medical records, consultation registers, and laboratory reports.

The research began with a review of bibliographic materials, and after receiving ethics approval, informed consent was obtained from the parents or guardians of the patients, along with agreement to participate in the study through the signing of an information form. The informed consent and information forms were administered during medical consultations, and those who agreed received a voucher for vitamin D screening. Samples were collected at the clinic, and analyses were performed at collaborating laboratories. Patients who mentioned that they had access to free screening as part of the "National Screening Program" did not receive vouchers. Voucher funding was covered by the researchers' own resources. All patients included in the study submitted their results electronically. This point was designated as the final time (Tf). The initial time (T0) was represented by the date before January 31, 2023, when vitamin D screening was performed at the recommendation of the diabetes specialist. Samples

were collected at the clinic, and analyses were performed at the same laboratories. Based on the results, the diabetes specialist prescribed vitamin D supplementation. The period between T0 and Tf was 3 months.

To evaluate changes in biochemical parameters after vitamin D supplementation in type 1 diabetic patients under 18 years old, vitamin D levels were classified as follows:

- **major deficiency:** levels below 12 ng/ml;
- **deficiency:** levels between 12 and 20 ng/ml;
- **insufficiency:** levels between 21 and 29 ng/ml;
- **normality:** levels between 30 and 100 ng/ml.

The variables tracked included patient age, gender, and living environment. For the clinical and biochemical evaluation of nutritional status, the following parameters were calculated and categorized: weight-for-height, height-for-age, total serum proteins, serum albumin, calcium, phosphorus, magnesium, erythrocyte count, platelet count, leukocyte count, lymphocyte count, eosinophil count, hemoglobin level, glycated, and comorbidities.

Statistical analysis

In the descriptive analysis, indicators of central tendency and dispersion were monitored: mean, median, minimum, maximum, mode, standard deviation, and coefficient of variation for quantitative variables. Dispersion was checked with a significance threshold of $\alpha=0.05$ and a confidence interval of 95%. The coefficient of variation was calculated using the formula, coefficient of variation = (standard deviation × 100)/mean. For a coefficient of variation ≥30%, the validity test, specifically Grubbs' test, was applied to eliminate outliers, followed by the Kolmogorov-Smirnov test to check normality according to the steps mentioned for a coefficient of variation <30%. For group comparisons, for coefficient of variation <30%, if both paired variables passed the normality test, the paired T-test was applied, or the F-test or T-test for unequal variances was used for unpaired variables. If one or both paired variables did not pass the normality test, the Wilcoxon test was applied, and for unpaired variables, the Mann-Whitney test was used. The Spearman test was used to calculate correlations.

The database was created and processed using Microsoft Excel and GraphPad software.

RESULTS

Our study shows that the majority of the patients were male 56.20% (n = 68), and came from rural areas, specifically 54.55% of them (n = 66). The mean age was 12 (5 - 18) years. Among 121 patients, 68 of them (56.20%) had comorbidities. Atopic dermatitis, was the main comorbidity, with the proportion of 12%. Regarding nutritional status, for both the weight-for-height indicator and the height-for-age indicator, it was observed that the deviation from the standard -1 predominated, affecting 40.50% of patients (n = 49) and 58.68% of patients (n = 71), respectively (Table 1).

TABLE 1. Baseline characteristics of the patients (Total n=121)

Characteristics		n (%)
Gender		
	Male	68 (56.20%)
	Female	53 (43.80%)
Residence		
	Rural	66 (54.55%)
	Urban	55 (45.45%)
Age		
	Median age (range)	12 (5-18)
Comorbidity		
	Yes	68 (56.20%)
	No	53 (43.80%)
Comorbidity description		
	Atopic dermatitis	12 (9.92%)
	Other allergies	11 (9.09%)
	Hypothyroidism	10 (8.26%)
	Gluten intolerance	9 (7.44%)
	Autoimmune thyroiditis	8 (6.61%)
	Episodes of DKA*	7 (5.79%)
	Celiac disease	5 (4.13%)
	Vitiligo	4 (3.31%)
	Epilepsy	2 (1.65%)
Nutritional status		
weight-for-height		
	DS-1**	49 (40.50%)
	DS-2	21 (17.36%)
	DS-3	10 (8.26%)
	Normality	41 (33.88%)
height-for-age		
	DS-1	71 (58.68%)
	DS-1	35 (28.93%)
	DS+1	6 (4.96%)
	DS+2	9 (7.44%)

**DKA = Diabetic ketoacidosis; **DS = deviation from standard*

TABLE 2. Distribution of vitamin D levels at T0 and Tf

Variables	n (%)
Vitamin D at T0	
Deficiency	84 (69.42%)
Insufficiency	33 (27.27%)
Major deficiency	4 (3.31%)
Vitamin D at Tf	
Normality	79 (65.29%)
Insufficiency	31 (26.62%)
Deficiency	11 (9.09%)

Note: T0 = the initial time; Tf = the final time

The Table 2 shows that the distribution of vitamin D levels at initial time T0, respectively: 27.27% (n = 33) of patients had vitamin D insufficiency, 69.42% (n = 84) of patients had vitamin D deficiency, and 3.31% (n = 4) of patients had major vitamin D deficiency. Moreover, at final time Tf, 65.29% (n = 79) of patients

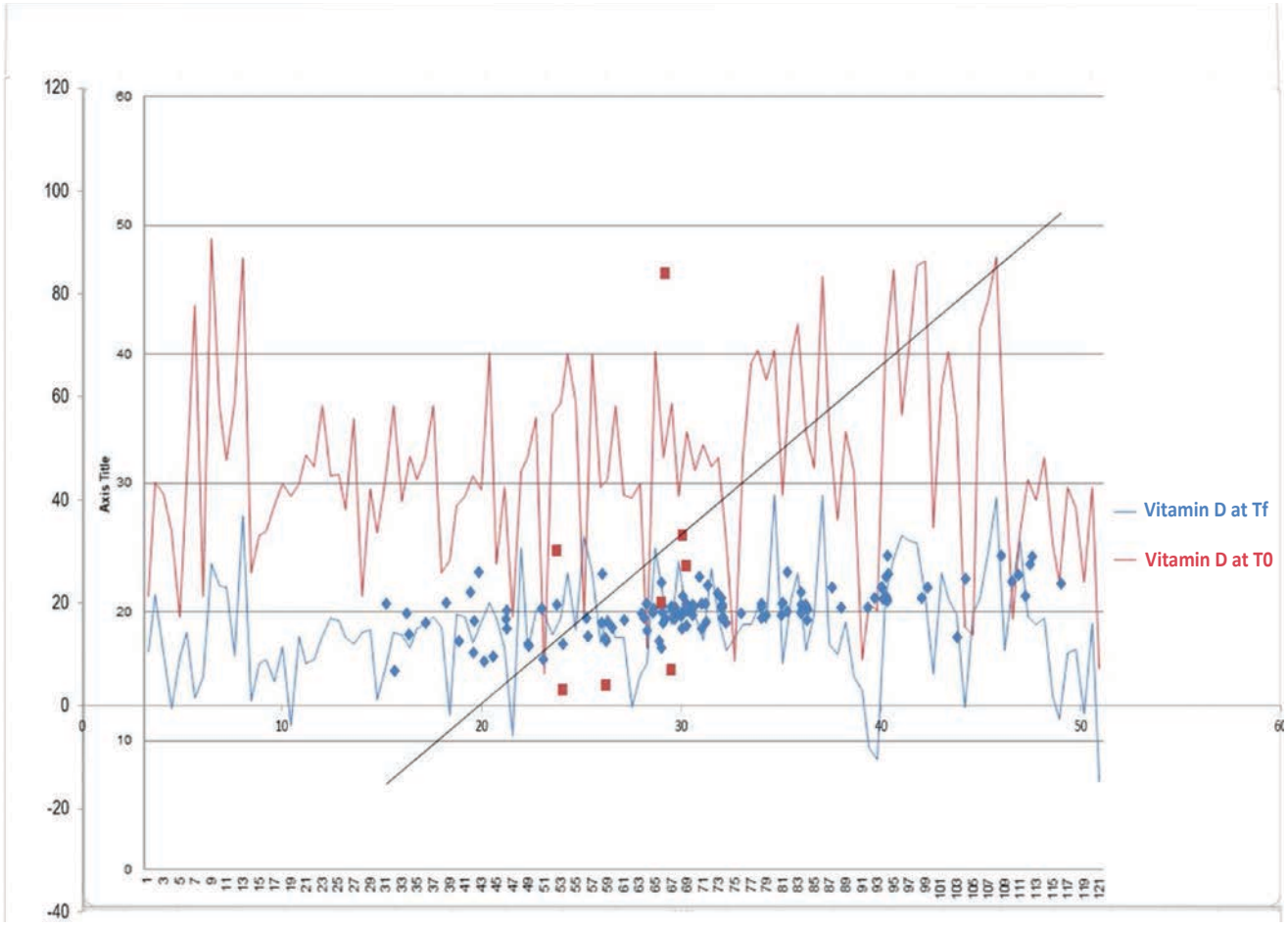

FIGURE 1. Correlation between the vitamin D levels at initial time T0 and final time Tf
**Spearman Test, significant if p <0.05*

had a normal vitamin D level, 25.62% (n = 31) of patients had vitamin D insufficiency, and 9.09% (n = 11) of patients had vitamin D deficiency.

Additionally, at initial time, 88 patients had vitamin D deficiency, while at final time, 11 of them had vitamin D deficiency, being the statistically significant differences between the medians of the variables revealed by applying the Wilcoxon test (p <0.05).

The mean vitamin D level at the initial time T0 was 18.69 ng/mL with a range of 6.84 - 29.10 ng/mL, while the mean vitamin D level at the final time Tf was 31.28 ng/mL with a range of 15.23 - 49 ng/mL. The application of the Spearman Test reveals a statistically significant moderate correlation between the vitamin D level at T0 and Tf. The correlation between the vitamin D levels at the initial time T0 and the final time Tf shows a statistically significant moderate correlation, an r = 0.5764 (p <0.0001, 95% CI = 0.4392 - 0.6873) (Figure 1).

At initial time, the main deviations from normal biochemical parameter values were observed as follows: 72.73% (n = 88) of patients had hypocalcemia, hypomagnesemia was observed in 69.42% (n = 84) of them, while 66.94% (n = 81) of subjects presented with hypophosphatemia. Moreover, 48.76% (n = 59) of patients had lower abnormal values of glycated hemoglobin and 11.57% (n = 14) of them had higher abnormal values of glycated hemoglobin, instead leukopenia was presented in 44.63% (n = 54) of patients and leukocytosis in 17.36% (n = 21) of them.

TABLE 3. The distribution of patients based on various biochemical parameters at initial time and final time

Variables	n (%) at T0	n (%) at Tf	p
Hypocalcemia	88 (72.73%)	23 (19.01%)	0.0413*
Hypophosphatemia	81 (66.94%)	31 (25.62%)	<0.0001**
Hypomagnesemia	84 (69.42%)	26 (21.49%)	0,0394*
DS of HbA1c	73 (60.33%)	21 (17.35%)	<0.0001*
Thrombocytopenia	35 (28.93%)	16 (13.22%)	<0.0001**
Hypoalbumin	31 (25.62%)	13 (10.64%)	0.3371*
DS of Proteins	31 (25.62%)	15 (12.40%)	0.0725*
DS of Leukocytes	75 (61.99%)	46 (38.01%)	0.0433**
DS of Eosinophils	49 (40.50%)	28 (23.15%)	0.0037*

** Wilcoxon Test; **T student Test; DS = deviation from standard; HbA1c = glycated*

In the study, it was found that there were statistically significant differences in the level of hypocalcemia (p = 0.0413), hypomagnesemia (p =0.0394), hypophosphatemia (p <0.0001), thrombocytopenia (p <0.0001), also in the deviations of leukocyte values (p

= 0.043), and of eosinophils values (p = 0.0037). In addition, statistically significant differences were observed among subjects with abnormal values of glycated hemoglobin (p <0.0001) (Table 3).

DISCUSSION

The study evaluated the impact of vitamin D on biochemical parameters in type 1 diabetes in patients under 18 years of age, and revealed that the most patients were from rural areas, were male, and had an average age of 12 years. A large proportion of the patients had a vitamin D deficiency. Significant levels of vitamin D deficiency have also been observed in studies conducted in Finland and Sweden by Adorini, and Littorin, et al. in patients with type 1 diabetes [8,10].

The majority of these patients had associated conditions, with atopic dermatitis, various allergies, and hypothyroidism being the most common. Additionally, a study conducted in 2005 observed the role of vitamin D in the development of conditions associated with type 1 diabetes [7].

In a cohort study on children, vitamin D supplementation was associated with a reduced risk of T1D compared to those who did not receive supplements [8].

Most of the subjects had weight-for-height deviations, with DS -1 being predominant, while all patients had height-for-age deviations, with DS -1 being predominant [7,8,10].

At the initial time, the vitamin D level defined as deficiency was predominant, while at the final time, the vitamin D level defined as normal was predominant. No patient had a major vitamin D deficiency at the final time. Significant differences were observed in biochemical parameters between the two time points, showing improvements towards reference values for serum calcium, phosphorus, magnesium, erythrocyte count, platelet count, leukocyte count, eosinophil count, and glycated hemoglobin level. In 2004, Giulietti, et al., in a study conducted on mice by the research team in Belgium, also showed significant changes in biochemical parameters like calcium, leukocytes, and lymphocytes following vitamin D supplementation [6].

A highly significant correlation was found between vitamin D levels at the two time points. Both the 2020 nested case-control study within the Trial to Reduce IDDM in the Genetically at Risk cohort and the 2004 study also report significant correlations in vitamin D levels after supplementation [6,17].

In our study, patient selection was based on prior vitamin D screening, which not only ensured the inclusion of individuals who had baseline data on their vitamin D status, but also underscored the clinical relevance and specificity of the data collected. Vitamin D deficiency is particularly significant in diabetes management, and this selection criterion allowed us to precisely measure the effects of supplementation. In Romania, vitamin D screening is not covered by healthcare insurance and requires out-of-pocket payment, making it a challenge for widespread implementation. As a result, the number of participants in our study was realistically aligned with the resources available and the clinical context of the population studied. Despite this limitation, the study was able to include patients from multiple counties across Romania, thereby achieving a representative sample that reflects regional differences.

The prospective observational design of our study inherently precluded the inclusion of a control group. In this design, we followed patients longitudinally to observe changes over time in response to the intervention, in this case, vitamin D supplementation. Patients were recruited based on their previous vitamin D screening, before the study's start date, which was performed alongside standard biochemical assessments relevant to diabetes management. These baseline assessments allowed us to monitor changes in vitamin D levels and their associated impact on key metabolic parameters after supplementation. The patients demonstrated adherence to vitamin D supplementation as prescribed by their treating diabetologist, which was a crucial aspect of the study as compliance directly influences the outcomes. After three months of supplementation, the same cohort of patients underwent repeat vitamin D screening and similar biochemical analyses to those performed at baseline. By comparing results within the same group of patients at two distinct time points - prior to supplementation and following supplementation - we were able to assess the direct impact of vitamin D on both vitamin D levels and the associated biochemical parameters.

Our findings are consistent with those of other observational and preclinical studies that have explored the role of vitamin D in glucose metabolism and immune modulation, particularly in patients with type 1 diabetes. The study confirms that vitamin D supplementation is effective in raising serum vitamin D levels and improving related biochemical markers, thus supporting its potential role in managing diabetes-related complications. Although the study period might be considered relatively short for evaluating long-term outcomes, the three-month follow-up was adequate for detecting significant changes in both vitamin D levels and specific biochemical parameters. These changes are known to occur relatively quickly in response to vitamin D supplementation, as supported by other studies in the field. The results of our study align with existing literature that demonstrates the efficacy of vitamin D supplementation in patients with type 1 diabetes,

further validating the observed effects within our sample [6,8,17].

While seasonal variations in vitamin D levels due to changes in sun exposure were not explicitly addressed in our study design, the monitoring period was kept consistent across all participants, minimizing the influence of seasonal fluctuations. This approach helped ensure that changes in vitamin D levels were primarily attributed to supplementation rather than external factors like sunlight exposure. Moreover, vitamin D supplementation was individually adjusted for each patient based on their specific needs, which further mitigated any potential impact of seasonal changes on serum vitamin D levels. This personalized approach allowed us to maintain stable and adequate levels of vitamin D across the patients, despite varying environmental factors [6,16].

Though detailed data on dietary habits and lifestyle factors were not systematically collected, the focus of our study was on adherence to vitamin D supplementation, which we monitored closely throughout the study period. Adherence to supplementation was essential in evaluating its effectiveness, and this was tracked through patient reports and follow-up consultations. Diet and lifestyle factors, such as physical activity and overall nutrient intake, are recognized as factors that can impact vitamin D metabolism and overall health outcomes [8,18,19]. In future study, we aim to to include more extensive data on these variables to better control for factors that may influence the response to supplementation, and to have a more holistic understanding of how they may interact with vitamin D supplementation.

Furthermore, extended research and implementing vitamin D screening as part of routine tests covered by the National Health Insurance Fund for pediatric patients with T1D could represent an important step in preventing and managing comorbidities and complications associated with type 1 diabetes.

Limitations

Our study has several limitations. The main limitations are the small sample size and the fact that the study was conducted after the COVID-19 pandemic (a period characterized by movement restrictions and limited exposure), as well as partly during months with limited sun exposure. Additionally, the absence of data on dietary patterns in different geographical regions from early life and later on, as well as the absence of evidence regarding the evolution of diabetes incidence in adolescents and young adults are further limitations. The lack of studies providing data on vitamin D levels in the general population, particularly in pediatric patients with type 1 diabetes, represents another significant limitation.

CONCLUSIONS

Vitamin D deficiency remains high in a significant proportion of pediatric patients with type 1 diabetes, affecting 7 out of 10 patients, and should be considered a risk factor for various pathologies. The study reveals a directly proportional relationship between imbalances in biochemical parameters and vitamin D deficiency and indicates that vitamin D supplementation significantly contributed to the improvement of biochemical parameters. Given the deleterious impact of chronic vitamin D deficiency, these findings highlight the importance of monitoring vitamin D levels in type 1 diabetic pediatric patients. Further research is needed.

Authors' contributions:
AP (concept, design, materials, sources, data processing, interpretation and analysis, planning, literature research, manuscript editing, evaluation, and critical review); IEM (concept, design, planning, literature research, interpretation and analysis); AMP (concept, evaluation, analysis and interpretation, guidance, and critical review).

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