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[Luis Felipe Pimenta](#) , [Eduardo Federighi Baisi Chagas](#) ^{*} , Jesselina Francisco dos Santos Haber ,
Thais Menegucci , [Karina Quesada](#) ^{*} , Pedro Zutin , Tereza Lais Menegucci Zutin , [Adriano Cressoni Araújo](#) ,
[Cláudia Rucco Penteado Detregiachi](#) , Elizandra Lopes , [Lucas Fornari Laurindo](#) , [Sandra M. Barbalho](#) ^{*} ,
[Elen Landgraf Guiguer](#)

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Article

Vitamin D Levels on Glycemic Control, Lipid Profile, and Apolipoprotein in Children and Adolescents with Type 1 Diabetes Mellitus

Luis Felipe S. Pimenta ^{1,†}, Eduardo Federighi Baisi Chagas ^{1,2,3,†},
Jesselina Francisco dos Santos Haber ^{3,4,†}, Thais Menegucci ¹, Karina Quesada ^{4,5},
Pedro Henrique Menegucci Zutin ⁶, Tereza Laís Menegucci Zutin ⁴, Adriano Cressoni Araújo ^{1,4},
Cláudia Rucco Penteado Detregiachi ^{1,4}, Elizandra Aparecida de Oliveira Lopes ⁴,
Lucas Fornari Laurindo ^{4,7,8}, Sandra M. Barbalho ^{1,4,5,*} and Elen Landgraf Guiguer ^{1,4,5}

- ¹ Postgraduate Program in Structural and Functional Interactions in Rehabilitation, School of Medicine, Universidade de Marília (UNIMAR), Marília 17525-902, São Paulo, Brazil
 - ² Postgraduate Program of Health and Aging, School of Medicine, Faculdade de Medicina de Marília (FAMEMA), Marília 17519-030, São Paulo, Brazil
 - ³ Interdisciplinary Center on Diabetes (CENID), School of Medicine, Universidade de Marília (UNIMAR), Marília 17525-902, São Paulo, Brazil
 - ⁴ Department of Biochemistry and Pharmacology, School of Medicine, Universidade de Marília (UNIMAR), Marília 17525-902, São Paulo, Brazil
 - ⁵ Department of Biochemistry and Nutrition, School of Food and Technology of Marília (FATEC), Marília 17500-000, São Paulo, Brazil
 - ⁶ Hospital de Base de Bauru, Bauru 17800-000, São Paulo, Brazil
 - ⁷ Department of Biochemistry and Pharmacology, School of Medicine, Faculdade de Medicina de Marília (FAMEMA), Marília 17519-030, São Paulo, Brazil
 - ⁸ Department of Administration, Associate Degree in Hospital Management, Universidade de Marília (UNIMAR), Marília 17525-902, São Paulo, Brazil
- * Correspondence: smbarbalho@gmail.com
- † These authors contributed equally to the build of this study.

Abstract: Background/Objectives: Type 1 Diabetes Mellitus (T1DM) is the reduction or non-production of insulin. As T1DM increases cardiovascular risk, in addition to glycemic control, the monitoring of other risk factors, such as lipid profile, has gained attention. Vitamin D deficiency has been associated with the pathophysiology of T1DM, metabolic syndrome, and cardiovascular diseases. This study investigated the relationship between vitamin D, glycemic control, and lipid profiles in children and adolescents with T1DM. **Methods:** This observational study consisted of 81 patients with T1DM. Laboratory test data were collected to determine the lipid profile. Glycated hemoglobin (HbA1c) and fasting glucose levels assessed glycemic control. **Results:** A significant association was observed between serum vitamin D levels and a pubertal stage and a moderate negative correlation between vitamin D, age, and HbA1c. There is a negative correlation between vitamin D levels and age, as well as with HbA1c, and a positive correlation of HbA1c with glucose, total cholesterol, triglycerides, Low-density lipoprotein (LDL-c), non-HDL cholesterol (non-HDL cholesterol), apolipoprotein B (apoB), and the apolipoprotein B/apolipoprotein A ratio. Finally, the study indicated that vitamin D levels, insulin administration method, and total cholesterol, when considered together, explained approximately 43.6% of the observed variation in HbA1c, highlighting the complex interdependence of these factors in regulating glycemia. **Conclusions:** Our results show that Vitamin D levels are associated with glycemic control and other biochemical parameters and its control can bring benefits to the patient with T1DM.

Keywords: type 1 diabetes Mellitus; vitamin D; lipid profile; apolipoprotein; Children; adolescents

1. Introduction

Type 1 Diabetes Mellitus (T1DM) is a chronic endocrine-metabolic disease caused by insulin deficiency due to immune-mediated destruction of pancreatic β cells, resulting in hyperglycemia [1] stemming from alterations in insulin production and/or secretion [2,3]. With a prevalence of 1,211,900 (0-19 years old), T1DM is the second most prevalent chronic disease in the pediatric age group [4] and its incidence increases each year, affecting more families and the economy [5,6].

In a population dependent on caregiver assistance, managing T1DM during childhood demands constant support from family and professionals [7]. Therefore, health education involving both the family, and the child is essential for effective treatment and proper glycemic control, encompassing not only aspects directly related to medication therapy but also nutritional considerations [8].

Studies have shown a significant relationship between vitamin D deficiency and metabolic disorders such as obesity and T1DM [9]. Various tissues, including pancreatic β cells crucial for glucose regulation, possess vitamin D receptors, suggesting a possible link between vitamin D and glucose and lipid metabolism [10]. In addition to playing a crucial role in insulin secretion and insulin receptor regulation [3], vitamin D exerts anti-inflammatory effects through receptors on immune system cells [11,12]. In fact, several studies demonstrate that vitamin D, through modulation of intracellular calcium levels, can improve insulin secretion and resistance. Additionally, the effect on the immune system can decrease the secretion of pro-inflammatory cytokines and associated with the reduction of oxidative stress, decrease the destruction of pancreatic beta cells [11].

Although defined as a vitamin, vitamin D acts as a prohormone with a significant role in bone metabolism, calcium, and phosphorus homeostasis, as well as cellular functions in the body [10–13]. Synthesized through cutaneous synthesis (80% cholecalciferol) and diet (20%), vitamin D needs metabolic conversion in the liver to calcidiol (25-hydroxyvitamin D) and further in the kidney to form the active calcitriol (1,25-dihydroxyvitamin D) [14–16].

To prevent vitamin D deficiency, guidelines recommend prophylactic supplementation for all children and adolescents with 400 IU/day (under 6 months), 400-600 IU/day (under 1 year), and 600 IU/day (under 3 years) [17].

However, even with adequate prophylaxis, it is estimated that up to 20.9% of the pediatric population may have reduced levels [18,19].

Due to the growing cases of T1DM and the critical role of Vitamin D on metabolic parameters, this study aimed to investigate the relationship of vitamin D intake and levels and glycemic parameters, lipid profile and apolipoprotein levels in children and adolescents with this type of diabetes.

2. Materials and Methods

2.1. Study Design and Population

This is an observational, primary, cross-sectional, and analytical study. Medical records of children and adolescents seen at the Interdisciplinary Center for Diabetes (CENID) of the Specialties Medical Outpatient Clinic (AME) at the Associação Beneficente Hospital Unimar (ABHU) of the University of Marília (UNIMAR) were evaluated.

The study included medical records of patients diagnosed with T1DM, aged between 4 and 19 years of both sexes, and referred by the Municipal Health Department of Marília to CENID at AME UNIMAR. Patients with Autism Spectrum Disorder, physical disabilities, or paralysis of upper and/or lower limbs were excluded from the study.

Patient data were obtained from a database compiled from medical records of patients seen between January 2019 and December 2020, after obtaining authorization from the patients and their legal guardians through the signing of an Assent Form (TA) and an Informed Consent Form (TCLE). The study is part of project previously approved by the Ethics and Research Committee of UNIMAR (protocol number 3.606.397/2019).

The sample size was calculated using G*Power software, version 3.1.9.2 (Franz Faul, University of Kiel, Germany), to estimate the correlation between vitamin D and HbA1c in children and

adolescents with T1DM. Considering a medium effect size (0.30) [20] a Type I error rate (α) of 5%, and a study power of 80%, a sample of 81 patients was estimated.

2.2. Study Variables

The stage of sexual maturation was classified using the Tanner scale [21]. Body composition was assessed using the body mass index z-score (BMI-z) and categorized as underweight, normal weight, overweight, and obese according to the World Health Organization recommendations [22].

Laboratory test data were collected to determine the lipid profile: apolipoproteins A-I and B (ApoA-I and ApoB), total cholesterol (TC), LDL cholesterol (LDL), HDL cholesterol (HDL-c), triglycerides (TG), and non-HDL cholesterol (calculated by the Friedewald equation $TC - (TG/5) - HDLc$ [23]). Lipid profile results were considered altered when: $TC \geq 170$ mg/dL; $LDL-c \geq 110$ mg/dL; $HDL-c \leq 45$ mg/dL; $non-HDL-c \geq 120$ mg/dL; $TG \geq 75$ mg/dL (0 to 9 years) and ≥ 90 mg/dL (10 to 19 years); $ApoA-I < 120$ mg/dL; and $ApoB \geq 90$ mg/dL [24].

Glycemic control was assessed by HbA1c and fasting glucose levels. However, due to the population's profile, HbA1c values were also categorized as less than 7%, between 7 and 8%, and greater than 8% [25]. Fasting glucose values were collected, using the values suggested by the Brazilian Diabetes Society [24] as a reference. Vitamin D intake was estimated through information on dietary intake obtained using a habitual intake recall based on weekly dietary routine [26] and serum levels (25-hydroxyvitamin D) were assessed through laboratory tests, categorized into two levels: <30 ng/mL (insufficient level) and >30 ng/mL (normal level).

2.3. Statistical Methods and Data Analysis

Quantitative variables were described using mean and standard deviation (SD). Qualitative variables were described using absolute and relative frequency distributions. Normality distribution was verified using the Shapiro-Wilk test with Lilliefors correction. The student's t-test for independent samples or the non-parametric Mann-Whitney test was used to analyze mean differences between two independent groups. Levene's test assessed variance homogeneity. For comparison of means among three or more independent groups, the one-way ANOVA test or the non-parametric Kruskal-Wallis test was applied. The correlation between quantitative variables was analyzed using Pearson's correlation or the non-parametric Spearman test. The association between dependent and independent qualitative variables was assessed using the chi-square test or Fisher's exact test. Multiple variable relationships were explored through regression analysis. All analyses were conducted using SPSS software version 19.0 for Windows, adopting a significance level of 5%.

3. Results

As demonstrated in Table 1, out of the 81 patients in the study, 59.3% were men, and 40.7% were women. The majority of the sample had a BMI classified as normal weight (64.2%), presented with HbA1c above 8% (54.3%), and were in pubertal and post-pubertal stages (34.6% and 39.5%, respectively).

No significant difference was found in the distribution of gender and nutritional status by BMI-z among categories of serum vitamin D levels. However, a higher proportion of subjects with HbA1c $>8\%$ was observed for those with serum vitamin D levels <30 ng/mL, as well as in the pubertal pubescent stage (Table 1).

Table 1. Association of absolute frequency (N) and relative (%) distribution of qualitative sample variables regarding the categorization of serum vitamin D levels.

Variables	Categories	Vitamin D		Total	P-value
		<30 ng/mL (n=16)	≥ 30 ng/mL (n=65)		
Gender	Men N (%)	9 (56.3%)	39 (60,0%)	48 (59.3%)	0.784
	Women N (%)	7 (43.8%)	26 (40,0%)	33 (40.7%)	
HbA1c class	< 7%	2 (12.5%)	18 (27,7%)	20 (24.7%)	0.038*
	7 a 8%	1 (6.3%)	16 (24,6%)	17 (21.0%)	
	> 8%	13 (81.3%)	31 (47,7%)	44 (54.3%)	
Pubertal stage	Prepubertal	2 (12.5%)	19 (29,2%)	21 (25.9%)	0.009**
	Pubertal	11 (68.8%)	17(26,2%)	28 (34.6%)	
	Postpubertal	3 (18.8%)	29 (44,6%)	32 (39.5%)	
BMI-z class	Underweight	3 (18.8%)	6 (9.2%)	9 (11.1%)	0.392
	Healthy	8 (50%)	44 (67.7%)	52 (64.2%)	
	Overweight	5 (31.3%)	13 (20.0%)	18 (22.2%)	
	Obesity	0 (0%)	2 (3.1%)	2 (2.5%)	

*, **indicates a significant association by the Chi-square test for p-value ≤ 0,050; HbA1c (glycated hemoglobin); BMI-z (score z BMI).

No significant differences were observed for age, diagnosis time, glucose levels, lipid profile, Apo A-I, Apo B, BMI-z, and percentage of fat. Analyzing HbA1c values and serum vitamin D levels, a statistically significant difference was observed between groups with serum vitamin D levels <30 ng/mL and >30 ng/mL (Table 2).

Table 2. Comparison of the mean and standard deviation (SD) of the sample's quantitative variables in relation to the categorization of serum vitamin D levels.

Variables	Vitamin D				p-value
	<30 ng/mL (n=16)		≥ 30 ng/mL (n=65)		
	Mean	SD	Mean	SD	
Age (years)	12.38	2.03	12.66	3.87	0.684
Diagnosis time (years)	3.88	1.82	4.43	3.21	0.508
Glycemia (mg/dL)	196.50	71.38	173.68	68.39	0.239
Total Cholesterol (mg/dL)	173.49	35.03	163.25	33.46	0.280
Triglycerides (mg/dL)	89.71	57.05	80.79	51.66	0.546
LDL-c (mg/dL)	92.30	30.28	88.65	26.86	0.637
HDL-c (mg/dL)	55.72	10.00	54.91	10.89	0.789
Non-HDL-c	117.78	40.81	108.34	32.76	0.329
HbA1c (%)	10.38	2.69	8.12	1.93	0.0001*
Apo A-I	151.27	12.82	148.44	18.97	0.575

Apo B	79.08	20.29	76.74	18.31	0.655
Ratio Apo B / ApoA-I	0.53	0.15	0.52	0.12	0.767
Fat percentage	21.19	6.45	21.86	7.94	0.754
BMI-z	0.25	1.22	0.26	1.25	0.975

* indicate significant differences between means by the independent Student t test for p-value ≤ 0.050; LDL-c (LDL cholesterol); HDL-c (HDL cholesterol); Not HDL-c (not HDL cholesterol); HbA1c (glycated hemoglobin); Apo A-I (Apolipoprotein A I); Apo B (Apolipoprotein B); BMI-z (BMI z score).

As observed in Table 3, age and HbA1c showed a significant negative correlation with serum vitamin D levels. The increase in age and HbA1c is related to a reduction in serum vitamin D levels, with a moderate correlation calculated through the Pearson correlation coefficient. Considering that HbA1c showed a significant correlation with serum vitamin D levels, the correlation between HbA1c and other study variables was also evaluated. It was found that an increase in total cholesterol, triglycerides, LDL-c, non-HDL-c, Apo B, and the ApoB/Apo A-I ratio is related to an increase in HbA1c values.

Table 3. Correlation between serum vitamin D levels (ng/mL) and the quantitative variables.

Variables	Vitamin D (ng/mL)		HbA1c (%)	
	r	p-value	r	p-value
Vitamin D (µg)	0.030	0.788		
HbA1c (%)	-0.377	0.0005*		
Age (years)	-0.257	0.020*	0.102	0.366
BMI-z	0.042	0.708	-0.031	0.783
Fat percentage	-0.133	0.236	0.202	0.071
Glycaemia (mg/dL)	0.049	0.661	0.684	<0.0001*
Total cholesterol (mg/dL)	-0.076	0.499	0.410	0.0001*
Triglycerides (mg/dL)	-0.019	0.864	0.256	0.020*
LDL-c (mg/dL)	-0.109	0.332	0.429	<0.0001*
HDL-c (mg/dL)	-0.043	0.704	-0.063	0.577
Non-HDL-c	-0.062	0.585	0.422	<0.0001*
Apo A-I	-0.080	0.479	0.103	0.358
Apo B	-0.082	0.464	0.401	<0.0001*
Coefficient Apo B / Apo A-I	-0.064	0.570	0.359	0.001*

* indicates significant correlation (p≤ 0.05) using the Pearson correlation test. r: Pearson correlation coefficient; LDL-c (LDL cholesterol); HDL-c (HDL cholesterol); non-HDL-c (non-HDL cholesterol); HbA1c (glycated hemoglobin); ApoA-I (Apolipoprotein A I); ApoB (Apolipoprotein B); BMI-z (BMI z score).

A multiple linear regression model was constructed to analyze the variables that, together with serum vitamin D levels, could contribute to HbA1c variation. In addition to the variables that showed a significant correlation with HbA1c, variables such as age, diagnosis time, insulin administration

method, and pubertal stage were included in the initial model (Table 4). In the initial model (Model 1), a significant model effect and a coefficient of determination (r²) indicating that changes in independent variables explain 47.5% of HbA1c variation were verified. However, many of the independent variables included in the initial model did not show a significant effect (age, diagnosis time, pubertal stage, total cholesterol, triglycerides, LDL-c, non-HDL-c, ApoB, ApoB/ApoA-I ratio) (Table 4).

In the final model (Model 2), after excluding non-significant independent variables by the Backward method, a significant model effect and an r² demonstrating that changes in independent variables explain 43.6% of HbA1c variation were observed. In the final model, a significant effect of serum vitamin D levels, insulin administration methods, and total cholesterol levels was verified. Regression coefficient (B) analysis indicates that a decrease in serum vitamin D levels, an increase in total cholesterol, and the use of the pen as an insulin administration method contribute to an increase in HbA1c and, therefore, worsen glycemic control (Table 4).

Table 4. Multiple linear regression analysis for the effect of serum vitamin D level and covariates on HbA1c.

Variables		CI95%		P-value	Model	
Dependent	Independent	B	LI	LS	p-value	r ²
HbA1c (model 1)	(Constant)	3.176	-3.011	9.363	0.309	<0.001† 0.475
	Vitamin D (ng/mL)	-0.107	-0.155	-0.059	<0.001*	
	Age (years)	0.067	-0.250	0.383	0.675	
	Diagnosis time (years)	-0.051	-0.244	0.142	0.600	
	Insulin administration methods	1.773	0.700	2.847	0.002*	
	Pubertal stage	-0.431	-1.724	0.862	0.508	
	Total cholesterol (mg/dL)	0.046	-0.029	0.121	0.223	
	Triglycerides (mg/dL)	0.010	-0.001	0.021	0.068	
	LDL-c (mg/dL)	0.024	-0.019	0.066	0.278	
	Non-HDL-c	-0.038	-0.110	0.033	0.288	
	Apo B	-0.041	-0.148	0.065	0.443	
HbA1c (model 2)	Apo B/Apo A-I ratio	6.437	-6.575	19.448	0.327	<0.001† 0.436
	(Constant)	4.845	2.015	7.675	0.001*	
	Vitamin D (ng/mL)	-0.109	-0.153	-0.065	<0.001*	
	Insulin administration methods	1.991	1.107	2.875	<0.001*	
	Total cholesterol (mg/dL)	0.026	0.014	0.037	<0.001*	

B: Regression coefficient; 95% CI: 95% confidence interval; LI: Lower limit; LS: Upper limit; r²: Model determination coefficient; *indicates significant effect of the independent variable; † indicates significant effect of the model; LDL-c (LDL cholesterol); Not HDL-c (non-HDL cholesterol); HbA1c (glycated hemoglobin); Apo A-I (Apolipoprotein A I); Apo B (Apolipoprotein B).

4. Discussion

Vitamin D, in addition to its known role in bone health, has been increasingly associated with carbohydrate and lipid metabolism [45]. Despite this, the impact of vitamin D levels in patients with Diabetes is still controversial [46].

The insufficiency and deficiency of vitamin D are common issues in the pediatric age group worldwide. In Brazil, despite the majority of the population residing in regions with adequate sunlight exposure, hypovitaminosis D is a frequent problem affecting children and adolescents [27,28]. According to the American Society of Endocrine Medicine, vitamin D levels between 20ng/mL and 29ng/mL are considered low, while deficiency is considered with levels below 20ng/mL [47]. In the population evaluated, only 3 patients had vitamin D levels below 20ng/mL. For this reason, it was decided to categorize the patients into two groups: vitamin D levels above and below 30ng/mL.

Among the results, as presented in Table 1, although the highest prevalence of vitamin D insufficiency occurred in males, there were no significant differences between genders, consistent with the findings of Zabeen [29]. On the contrary, a systematic review demonstrated a higher prevalence of vitamin D deficiency in girls (77.5%) compared to boys (66.1%), with statistical significance ($p = 0.01$) [30,31].

Although no statistically significant difference was found between the nutritional status by BMI-z and the categories of serum vitamin D levels (Table 1), the severity of obesity may be associated with 25(OH)D levels, considering that studies have demonstrated a strong correlation between overweight, insulin sensitivity, and hypovitaminosis D [31,32]. The presence of obesity and overweight was observed in 20 patients, 5 in the group with vitamin D levels <30ng/mL and 15 in the group with vitamin D >30ng/mL (Table 1). In this sense, it is known that body fat can interfere with vitamin D levels, but the percentage of body fat did not show a significant difference between the groups (Table 2).

It is also noteworthy to emphasize the role of HbA1c in long-term glycemic control, and there is a significant negative correlation between HbA1c levels and serum concentrations of 25 OHD (Table 2), indicating a potential influence of vitamin D on glycemic control in patients with diabetes. This finding is consistent with results from other studies, such as the one conducted by Svoren et al. in the USA [33], which identified vitamin D deficiency as a factor associated with poor glycemic control [10].

Vitamin D plays a crucial role in glucose regulation, impacting insulin production and glycemic control. A study involving 79 adolescents associated vitamin D deficiency with elevated levels of glucose and HbA1c [34]. Notably, fasting blood glucose values in Table 3 did not significantly correlate with vitamin D levels, unlike HbA1c. This may be explained by fasting blood glucose measuring glucose after an overnight period, while HbA1c reflects the average of the last 2-3 months. In some cases, fasting blood glucose may not show significant changes, but HbA1c can indicate poor glycemic control over time [29].

A systematic review aiming to assess vitamin D deficiency as a potential cause of type 1 diabetes (T1DM) development in children and adolescents aged zero to 15 years found that the majority of the reviewed studies demonstrated a statistically significant correlation between low serum levels of 25(OH) and T1DM. Children diagnosed with T1DM generally exhibited lower vitamin D levels compared to the control group [35].

This discovery is consistent with the hypothesis that vitamin D deficiency may play a role in the development of T1DM at a young age. However, it is important to note that two studies did not find a statistically significant association, emphasizing the complexity of this relationship and the need for further research to fully clarify the role of vitamin D in the etiology of T1DM [28].

Furthermore, the results suggest that the frequent occurrence of vitamin D deficiency in patients with T1DM may be attributed to physiological and environmental changes associated with the disease itself. For instance, the presence of the vitamin D receptor in immune cells suggests a potential role of vitamin D in modulating the immune response, which could influence the development of T1DM [35].

Studies investigating vitamin D supplementation in children with T1DM have shown promising results, indicating that vitamin D supplementation may improve glycemic control and beta cell function in T1DM patients [36,37].

The findings presented in Table 4, revealing a significant inverse association between vitamin D levels and HbA1c in patients with diabetes, are supported by additional studies [37] also identified a reverse association between HbA1c and 25 (OH)D, noting that vitamin D supplementation contributed to improving glycemic control, reflected in the reduction of HbA1c levels [11–40].

Ghavam et al. [41] endorse these results by demonstrating a linear inverse relationship between 25(OH)D and HbA1c, as well as with fasting blood glucose. The inverse correlation between vitamin D and HbA1c, as observed in this study, is consistent with the findings of Salih et al. [42], who showed significantly lower levels of 25 (OH)D in patients with poor glycemic control.

Regarding blood lipids, there is a notable positive correlation between vitamin D levels and total cholesterol, HDL-c, non-HDL-c, and Apo A-I, as well as a negative correlation with triglycerides, LDL-c, Apo B, and the Apo B/Apo A-I ratio (Table 3). These associations may indicate a potential role of vitamin D in lipid regulation, supporting the findings of the studies conducted by Argano et al [43].

The findings from Table 3 are also consistent with a study conducted in Bangladesh involving 422 patients, with 198 males and 224 females. The age range of the patients was 10 to 18 years, and the frequency of dyslipidemia was 64%, with a higher prevalence during the pubertal age (84%). Glycemic control between the two compared groups and HbA1c were significantly higher in the dyslipidemic group ($p = 0.001$). Fasting blood glucose levels were also significantly higher in the dyslipidemic group ($p < 0.0001$) [29].

These findings corroborate with the elevation of total cholesterol, triglycerides, LDL-c, non-HDL-c, ApoB, and the Apo B/Apo A-I ratio in response to increased HbA1c values found in the present study (Table 3), which may be associated with a higher prevalence of dyslipidemia in patients with poor glycemic control [29].

A systematic review carried out by Nascimento et al [44] had inconclusive results on the effect of supplementation with high doses of vitamin D on glycemic parameters. On the other hand, several studies have shown that vitamin D can modulate the immune system, which may interfere with T1DM. In this sense, our results demonstrate that in the population evaluated, composed of children and adolescents, low levels of vitamin D are associated with worse glycemic control. All of this, associated with its insufficiency in the Brazilian population, reinforces that ensuring adequate levels of vitamin D may be important to minimize complications as well as improve the quality of life of patients with T1DM.

5. Conclusions

In the children and adolescents evaluated, there is a significant association between low levels of vitamin D and puberty. Furthermore, low levels of the vitamin have shown a negative correlation with HbA1c, being associated with HbA1c above 8%. There is also a positive correlation of HbA1c with glycemia, total cholesterol, triglycerides, LDL-c, non-HDL-c, Apo B and the Apo B/Apo A-I ratio. Finally, the level of vitamin D, the method of insulin administration and total cholesterol together explain 43.6% of the variation in HbA1c observed. Even though the number of patients evaluated is not high, in the population evaluated, low levels of vitamin D were associated with worse glycemia control, as seen by the increase in HbA1c levels, highlighting the importance of vitamin D in the control of T1DM in children and adolescents.

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