Residência RP Pediátrica
Publicação Oficial da Sociedade Brasileira de Pediatria
ISSN-Online: 2236-6814

Submitted on: 01/06/2020
Approved on: 01/07/2020

ORIGINAL ARTICLE

Lipid profile of children and adolescents with type 1 diabetes mellitus

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Keywords:
diabetes mellitus, type 1, hypercholesterolemia, hydroxymethylglutaryl-coa reductase inhibitors, cholesterol, dyslipidemias, child.

Abstract

Introduction: Cardiovascular diseases are the main cause of death in patients with type 1 diabetes mellitus (T1DM) and atherosclerotic process begins in childhood. **Objective:** To evaluate lipid profile of patients with T1DM accompanied at the pediatric endocrinology (UEP), Hospital de Clínicas, Federal University of Paraná (HC-UFPR), the prevalence of dyslipidemia and its correlation with glycemic control, duration of T1DM, family history of dyslipidemia and nutritional profile status. **Methods:** Data of diagnostic information, comorbidities, birth weight, sex, family history of diabetes, dyslipidemia and heart diseases were reviewed. Anthropometric measurements, glycemic control, blood pressure (BP), lipid profile, and pharmacological treatment for dyslipidemia were obtained in four moments: after three months of diagnosis (t1), two (t2), five (t3), and ten (t4) years of illness. **Results:** 228 patients (122 girls), mean age at diagnosis of 7.3 years, were included. In t3 and t4 there was a significant increase in BP elevation. Prevalence of dyslipidemia was 31.7% in t1, 33.7% in t2; 37.4% in t3; and in 63.6% in t4. There was a significant increase in total cholesterol and LDL-cholesterol level over time (p<0.001) and a significant increase in triglycerides levels only in t4 (p=0.002). **Conclusion:** Changes in lipid profile in children and adolescents with T1DM are prevalent, but they are undertreated, and the greater age, the greater probability of developing dyslipidemia. Thus, screening for dyslipidemia should be done and pharmacological treatment should be encouraged as recommended.

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DOI: 10.25060/residpediatr-2022.v12n2-322

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INTRODUCTION

Type 1 diabetes mellitus (T1DM) is the most prevalent chronic endocrine disease in children and adolescents. Incidence in Brazil has been estimated at 10.4 per 100,000 population. Individuals with the disease are at increased risk of cardiovascular events and are ten times more likely of dying of heart disease or any other cause than the general population[1,2]. Children with T1DM rarely suffer with cardiovascular events (acute myocardial infarction, cerebrovascular disease), although atherosclerosis usually begins to develop slowly and gradually during childhood and persists into adulthood. Children with T1DM may present subclinical cardiovascular alterations, such as increases in carotid intima-media thickness[3,4].

Dyslipidemia is an important element in atherosclerosis. Although reported prevalence in children and adolescents varies, some studies have indicated that 50% of the individuals with dyslipidemia experience lipid profile alterations[5]. In addition to being an important factor in the establishment of macrovascular disease and cardiovascular risk, dyslipidemia also affects microvascular disease., Dyslipidemia is a predictor of poorer outcomes In patients with T1DM and a history of kidney disease[6]. Development of proliferative diabetic retinopathy (PDR) may also be correlated with hypercholesterolemia[7].

Many lipid profile anomalies have been described in children with T1DM[5]. The main findings were high levels of total (TC) and low-density lipoprotein cholesterol (LDL-C) and low levels of high-density lipoprotein cholesterol (HDL-C)[3,5]. However, a study conducted in Brazil comparing the lipid profiles of children with and without T1DM did not find significant differences between groups[8].

Inadequate glycemic control has been associated with increased prevalence of hypercholesterolemia in children and adolescents with T1DM. Patients with a high body mass index (BMI) also presented lipid anomalies more frequently. Metabolic syndrome is becoming a more prevalent finding in children, a trend also observed in children and adolescents with T1DM[3].

Screening for dyslipidemia must be performed soon after the diagnosis of T1DM (when diabetes is stabilized) in every child aged 10 years and older. If normal results are found (Table 1), screening tests must be repeated every five years. In individuals with a family history of hypercholesterolemia, early cardiovascular disease (CVD), or an unknown family history, screening tests must be initiated at the age of two years. If LDL-C is above 130 mg/dL, lifestyle changes must be introduced. If these interventions fail to decrease LDL-C to levels below 130 mg/dL and if the patient present one or more risk factors for CVD, statins must be started in patients aged 10 years and older[7]. According to the National Heart, Lung, and Blood Institute (NHLBI), statins must be initiated if LDL-C is above 190 mg/dL or if it is in the 160-189 mg/dL range for patients with a positive family history of disease or with one or more high risk factors; diabetes mellitus is a high risk factor for CVD[9].

Table 1. Serum lipid, lipoprotein, and apolipoproteína levels rated as acceptable, borderline-high, or high for children and adolescents (NHLBI, 2011).

Levels	Acceptable	Borderline-high	High
TC (mg/dL)	<170	170-199	≥200
LDL-C (mg/dL)	<110	110-129	≥130
HDL-C (mg/dL)	≥45	40-44	<40
TG (mg/dL)			
0-9 years	<75	75-99	≥100
10-19 years	<90	90-129	≥130

Note: TC, total cholesterol; LDL-C, low density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglycerides. Ref. - National Heart, Lung, and Blood Institute (NHLBI)[9]. Expert panel on integrated guidelines for cardiovascular health and risk reduction in children and adolescents: summary report. *Pediatrics*. 2011;128 Suppl 5:S213-256.

Despite these recommendations, the SEARCH study found a discrepancy between patients who should have been prescribed drug therapy versus patients who were actually prescribed medication, suggesting that dyslipidemia in children and adolescents aged 10+ years has not been properly investigated or treated[5], even though statins can be used safely by individuals in this age group[3,10].

This study aimed to evaluate the lipid profiles, the prevalence of dyslipidemia and its correlation with glycemic control, time with T1DM, family history of dyslipidemia, the nutritional profile of patients with T1DM seen at the Pediatric Endocrinology Unit (PEU) of the Hospital de Clínicas of the Federal University of Paraná (HC-UFPR), and review the dyslipidemia therapy prescribed to them.

MATERIAL AND METHODS

A group of children and adolescents seen at the pediatric diabetes outpatient clinic was included in this retrospective observational study. The patients were selected from the list of individuals registered with the outpatient clinic. Only individuals diagnosed with T1DM between 2004 and 2014 and who had taken multiple doses of insulin analogs or human insulin were included. Patients without a lipid profile were excluded. Data points were collected from patient medical charts at four different times during follow-up: three months after the diagnosis of T1DM (t1); and at two (t2), five (t3), and ten (t4) years of disease. The following patient data were collected: age, weight, height, BMI, sexual maturity, blood pressure (BP), hemoglobin A1c (HbA1c), TC, HDL-C, LDL-C, and triglycerides (TG). Since this is a retrospective study, some data were not available. Patients were also investigated for family history of types 1 and 2 diabetes mellitus, dyslipidemia, systemic hypertension, and acute myocardial infarction.

Data about the birth of the subjects were also collected. Patients were categorized as appropriate for gestational age (AGA), small for gestational age (SGA), or large for gestational

age (LGA) based on weight and/or length at birth in accordance with sex and gestational age within ranges of 2 SD and -2 SD, ≤-2 SD and ≥2 SD, respectively[11]. The BMI was calculated from the formula weight/height2 (kg/m^2) and expressed in standard deviations (SD) using data from AnthroPlus® and the World Health Organization (WHO)[12] as a reference. Patients were rated according to the WHO criteria as low-weight, normal weight, overweight, or obese[13]. BP was deemed altered if recorded levels were above the 90th percentile as per the simplified table proposed by Kaelber and Pickett[14]. Start of puberty was defined based on physical examination: Tanner M2 stage or greater for girls[15] and testicular volume equal to or greater than 4 mL in boys[16].

Serum lipid and lipoprotein levels were deemed acceptable, borderline-high, or high based on the reference values of the NHLBI[9] (Table 1). Glycemic control was rated as good for patients with HbA1c<7.5%[17].

Data were expressed as mean values ± SD, unless otherwise indicated. Categorical variables were expressed as absolute or relative frequencies. The differences in the mean values calculated for the variables were tested using parametric or non-parametric tests depending on the distribution pattern of each variable. Chi-squared and Fisher's exact test were used in the analysis of categorical variables. A multivariate linear regression model was fitted to assess the independent effect of each co-variable. Probability curves were developed to estimate the chances of occurrence of dyslipidemia. A p-value <0.05 was deemed significant. The data were analyzed with software package Statistica® (v 10.0-Statsoft).

The Research Ethics Committee at HC-UFPR approved this study.

RESULTS

A total of 239 patients were enrolled in the study. The medical charts of 11 patients did not contain records of lipid profile and were thus excluded. In the end, the study included 228 patients (122 females). The mean age at diagnosis was 7.3 years. Seventy-three patients (32.0%) had findings associated with other conditions, with hypothyroidism (n=28), asthma (n=11), and celiac disease (n=10) accounting for most of them. Most patients were rated as AGA at birth, with only ten rated as SGA and five as LGA. Sixty-six patients (28.9%) had a family history of dyslipidemia, 125 (54.8%) of systemic hypertension, 35 (15.6%) of T1DM, 106 (46.5%) of type 2 diabetes mellitus, and 46 (20.2%) of acute myocardial infarction.

Table 2 contains the information about BMI, glycemic control, and blood pressure at different time points. No significant variation in the number of overweight or obese patients was observed with time. Glycemic control worsened and the prevalence of high blood pressure increased significantly during follow-up.

There was no change in HDL-C levels, a significant increase in TC and LDL-C levels during follow-up, and an increase in TG levels on t4 (Table 3). Although this increase brought mean values to borderline levels, they cannot be considered as altered.

Low HDL-C was the most prevalent type of dyslipidemia on t1 (20.5%). Prevalence of this lipid alteration did not vary substantially with time. From t2 onwards, higher levels were observed in TC, LDL-C, and TG levels (Table 4).

SGA patients did not have a higher prevalence of dyslipidemia when compared to AGA or LGA individuals (p=0.76). Hypothyroidism did not increase the risk of developing dyslipidemia on t4 when patients with and without this comorbidity were compared (p=1.0). Overweight and obese patients did not have a higher prevalence of dyslipidemia on t4 when compared to low and normal weight patients (p=0.42). However, when the logistic regression model considered the different lipid profile alterations on t3, overweight was associated with a two and three times greater chance of having an elevated TC and LDL-C level, respectively. This difference in the data may be explained by the smaller number of patients analyzed on t4. The logistic regression model was applied only on t3, due to the lower number of patients in the other time intervals.

Variables tied to family history of dyslipidemia, T1DM, type 2 diabetes mellitus, acute myocardial infarction, and high blood pressure did not significantly affect the prevalence of dyslipidemia on t4. However, logistic regression analysis performed on t3 found that family history of dyslipidemia was associated with a three times greater chance of having elevated TC and LDL-C levels. In logistic regression analysis, time with T1DM was deemed a risk factor for increased TC and LDL-C levels on t3.

Presence of dyslipidemia was not correlated with glycemic control. Few patients (36 on t1, 23 on t2, and 8 on t3) had good glycemic control during the study, and on t4 no patient met the HbA1c target (<7.5%). Only on t4 older age was correlated with greater chances of developing dyslipidemia (p<0.01), as seen in Figure 1.

No patients were on drug therapy for dyslipidemia on t1 and t2, but three individuals aged less than ten years had LDL-C levels above 130 mg/dL on t1 and 14 on t2, which would make them eligible for treatment with statins. On t3, five patients with an average age of 14.7 years were on simvastatin. On t4, eight patients with an average age of 16.6 years were on the drug. All patients on simvastatin were on puberty. Thirteen patients on t3 and nine on t4 met the indications to use statins as recommended by the ISPAD and the NHLBI, but were not prescribed medication.

DISCUSSION

Few longitudinal studies have looked into the lipid profiles of children and adolescents with T1DM, and the literature lacks data on the temporal behavior of lipid profiles of young people with T1DM. Reh *et al*.[18] published a longitudinal study in which they followed young people with T1DM for three years

Table 2. Patient characteristics, nutritional profile, metabolic profile, and blood pressure levels at different times.

	Time 1 (t1)	Time 2 (t2)	Time 3 (t3)	Time 4 (t4)	*p*
n (%)	127 (100)	196 (100)	140 (100)	44 (100)	
Time since diagnosis (mean)	0.85	2.3	5.3	10.1	
Mean age (years)	8.2	9.8	11.6	14.9	
Pre-pubescent/pubescent (n)	90 / 37	111 / 85	69 / 71	7 / 33	
Overweight and obese, *n* (%)	43 (24.2)	47 (23.7)	43 (30.7)	13 (29.6)	0.4
Mean HbA1c (%)	8.8	9.7	10.0	10.9	
Good glycemic control*, *n* (%)	36 (28.4)	23 (11.7)	8 (5.7)	0 (0)	0.001
SBP>90th percentile, *n* (%)	2 (1.5)	9 (4.5)	17 (12.1)	7 (15.9)	<0.001
DBP>90th percentile, *n* (%)	3 (2.3)	9 (4.5)	9 (6.4)	5 (11.4)	0.01

Nota: HbA1c, hemoglobin A1C; SBP, systolic blood pressure; DBP, diastolic blood pressure.*HbA1c < 7.5%.

Table 3. Lipid profile values (mean ± SD) at four different times.

	Time 1 (t1)	Time 2 (t2)	Time 3 (t3)	Time 4 (t4)	*p*
TC (mg/dL)	160.2±40.5	169.0±31.5	172.3± 49.8	195.6 ±40.4	<0.001
LDL-C (mg/dL)	93.8 ±22.7	101.2±25.4	102.1±34.2	118.3±31.4	<0.001
HDL-C (mg/dL)	51.4±13.3	53.1±12.6	51.6±11.5	52.4±13.2	0.96
TG (mg/dL)	64.6±27.3	72.9±41.6	86.8±76.2	126.8±93.6	0.001

Note: Note: TC, total cholesterol; LDL-C, low density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglycerides.

Table 4. Prevalence of lipid profile alterations at different times.

	Time 1 (t1)	Time 2 (t2)	Time 3 (t3)	Time 4 (t4)
CT ≥200 mg/dL*, *n* (%)	11 (8.7)	34 (17.3)	24 (17.3)	20 (45.5)
LDL-c ≥130 mg/dL*, *n* (%)	7 (5.5)	31 (15.9)	24 (17.3)	16 (36.4)
HDL-c <40 mg/dL*, *n* (%)	26 (20.5)	28 (14.4)	20 (14.5)	8 (18.2)
High TG*, *n* (%)	11 (8.7)	16 (8.2)	16 (11.4)	16 (36.4)

Note: *Patients aged 0-9 years. TG ≥ 100 mg/dL Patients aged 10-19 years. TG ≥ 130 mg/dL (NHLBI, 2011)[9]. Note: TC, total cholesterol; LDL-C, low density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglycerides.

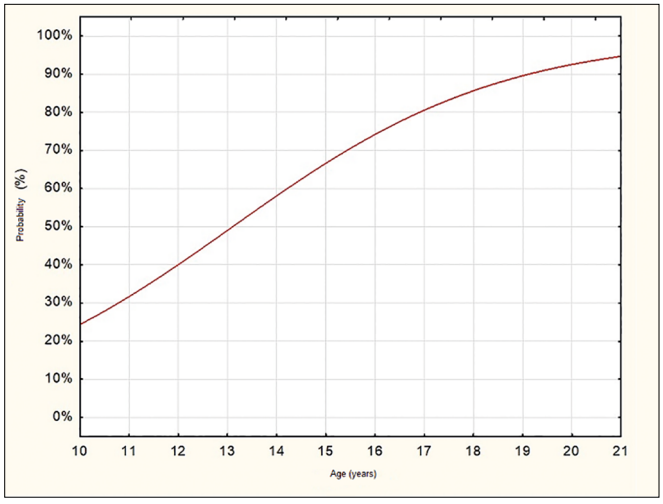

Figure 1. Probability of developing dyslipidemia after 10 years of type 1 diabetes mellitus versus age.

and found that LDL-C levels tended to increase with time, as also seen in our study[18,19].

In our study, the prevalence of dyslipidemia increased significantly ten years after the diagnosis of T1DM (t4), from 37.1% at five years (t3) to 63.6% at ten years of disease (t4). In addition to T1DM, puberal development may also produce changes in lipid profiles, as described in the literature[20,21].

The prevalence of dyslipidemia varied considerably in the different studies conducted with pediatric patients with T1DM. Bulut *et al.* reported a prevalence of 26.2% for dyslipidemia in a population with disease for an average of 5.6 years[22]. Homma *et al*. described a prevalence of dyslipidemia in Brazil of 72.5% in patients with the disease for an average of 10.6 years[23]. These discrepancies may be ascribed to differences in population profiles, including eating habits and lifestyle.

Other authors have reported increases in TC and LDL-C as the most prevalent types of dyslipidemia[19,23], as also found in our study. The prevalence of high TC, LDL-C, and TG levels

increased with time with the disease, and prevalence was higher in individuals with T1DM for ten years (t4). Shah *et al*. described similar findings, with 19% of the patients developing dyslipidemia via the non-HDL-C component[19]. In the same study, only 5% of the patients had low HDL-C levels[19], as also found in our study.

Hypothyroidism may interfere with lipid profiles. However, patients given levothyroxine with adequate levels of thyroid-stimulating hormone (TSH) are probably free from such interference, which might explain the lack of a correlation between the two in our study. Screening for hypothyroidism is performed routinely in individuals with T1DM and treatment is performed whenever necessary.

Most patients in our study had a normal weight in every time period of the analysis, and prevalence of overweight and obesity remained constant throughout the study. However, overweight children had two to three times greater chances of having high TC or LDL-C levels. Reh *et al.* found a significant association between BMI and lipid profile alterations. The authors noted that weight management in young people with T1DM might protect them against dyslipidemia[18]. Homma *et al.* also described an association between excess weight and dyslipidemia in children and adolescents,[23] while Kershnar *et al*. showed the same correlation however using a ratio between the waist circumference and height to analyze nutritional profiles[5].

Family history of dyslipidemia was associated with greater risk of having high TC and LDL-C levels after five years with T1DM. A significant association between the lipid profiles of parents and their children has been described, suggesting the existence of a genetic link between the two in patients with T1DM[24]. However, Bulut *et al.* were unable to find a correlation between dyslipidemia and a family history of diabetes or dyslipidemia.[22] Reh *et al*. found a correlation between family history of cerebrovascular disease and higher levels of LDL-C, but were unable to find that same association with acute myocardial infarction[18].

Although many authors have postulated that inadequate glycemic control negatively affects the lipid profile[18,25], this was not analyzed in our study, since few patients were deemed as having good glycemic control.

Risk of dyslipidemia was greater in older children or adolescents with T1DM for longer periods of time. This finding is in agreement with the SEARCH study, which showed that patients developing dyslipidemia by the non-HDL-C component throughout the study were older than the ones who presented normal lipid levels. In the same study, time with disease was also a risk factor for dyslipidemia progression[5].

Although 35 patients aged 10+ years met the ISPAD criteria, not all were prescribed drug therapy for hypercholesterolemia, as also reported by Bjornstad *et al.*[26] and Schwab *et al*.[27]. Canas *et al.* published a randomized double-blind trial about atorvastatin for children with T1DM and showed the medication was safe and effective at reducing LDL-C levels in this population without altering glycemic control during a follow-up period of six months[28]. However, in the same study the authors commented that they still lacked data about the long-term impact this therapy might have in decreasing deaths for cardiovascular events[28]. Although substantial evidence exists on the benefits of statins in adults and on its safety in children, data on the long-term benefits of this drug class are still lacking.

We may conclude that lipid profile alterations in children and adolescents with T1DM become more frequent as age and time with the disease increase. Diagnosis and drug therapy for dyslipidemia in children and adolescents must not be neglected, particularly for populations at greater risk. This retrospective study presented limitations such as failure to describe the lipid profiles of children before puberty and the fact that most patients with T1DM did not present proper levels of glycemic control.

Conflict of interest

The authors have no conflict of interest to declare.

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