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Predictive factors of non-HDL cholesterol in children and adolescents with type 1 diabetes mellitius: A cross-sectional study

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ABSTRACT

Aims: To assess predictors of non-HDL cholesterol in children and adolescents with T1DM.
Methods: A cross-sectional study of 120 children and adolescents aged 7–16 with T1DM, but without any other chronic morbidities, at a referral outpatient clinic for the treatment of diabetes in Rio de Janeiro, Brazil. Socio-demographic, anthropometric, dietary, and clinical factors were assessed, which included measurements of serum lipids and glycated hemoglobin (HbA1c). Food intake was assessed by 24-h dietary recall. Multiple linear regression was adopted in the analysis.
Results: The mean age of of the subjects was 11.74 ± 2.88 years, 53.3% were female, and the mean duration of T1DM was 6.68 ± 3.33 years. The mean energy intake from carbohydrates, proteins, and lipids was 51.98% (±9.20), 21.43% (±6.13), and 26.57% (±9.98), respectively. The energy intake from processed and ultra-processed foods represented 40.79% of total energy intake. The predictors of non-HDL cholesterol were: HbA1c (%) ($p = 0.000$, $\beta = 8.5$, CI: 4.8–12.1), duration of T1DM ($p = 0.000$, $\beta = 2.8$, CI: 1.3–4.3), and sex ($p = 0.032$, $\beta = 10.1$, CI: 0.9–19.4).
Conclusion: Glycemic control was the major modifiable predictor of non-HDL cholesterol concentrations, a significant indicator of cardiovascular risk.

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1. Introduction

Cardiovascular diseases (CVD) are the main cause of morbidity and mortality in patients with type 1 diabetes mellitus (T1DM). Alterations in the lipid profile, as isolated increases in LDL-c and triglycerides and reduced HDL cholesterol (HDL-c), are strongly related to the increased risk of CVD and have been a common finding in children and adolescents with T1DM [1,2]. Isolated increases in LDL-c and triglycerides and reduced HDL-c may be associated with increased cardiovascular risk. However, non-HDL cholesterol is starting to be considered as just as good a predictor of future cardiovascular events as LDL-c, total cholesterol, or HDL-c alone, in both children and adults with DM. It has therefore become a good variable for identifying, even in childhood, which individuals are at greater or lesser risk of cardiovascular complications in young adult life [3].

Alterations in the lipid profile of children and adolescents with DM1 may be influenced by sociodemographic, clinical, anthropometric and dietary factors. Among the sociodemographic variables studied the older age and the female sex have been associated with a higher prevalence of dyslipidemia [4–5].

Poor glycemic control, characterized by high concentrations of glycated hemoglobin (HbA1c) is one of the main clinical factors related to lipid changes and consequent increased risk of macro and microvascular complications [6]. A case-control study in the United States showed that young people with T1DM had lipid profile abnormalities that were directly influenced by poor glycemic control, with the presence of smaller, more dense, pro-atherogenic LDL-cholesterol (LDL-c) particles. Those with good glycemic control had similar or less atherogenic lipid concentrations than those who did not have diabetes [7]. In addition to glycemic control, the longer duration of the disease may also be related to the increase in lipid concentrations [8].

Anthropometric factors related to lipid changes include: BMI and excess of visceral adiposity. However, other anthropometric measures such as percentage of body fat (%) and waist-to-height ratio may be better related to lipid abnormalities [9–11].

Diet is an important component for promoting a desirable lipid profile and adequate glycemic control, especially in individuals with T1DM. A balanced intake of macronutrients, especially lipids and carbohydrates, is of great importance in nutritional therapy [12–13].

Recent studies point to a relationship between the consumption of processed and ultraprocessed foods and cardiometabolic outcomes, including negative effects on the lipid profile [14–15]. However, no information was found in the scientific literature on the effects of the consumption of these foods on the control of T1DM and on non-HDL cholesterol concentrations.

Sociodemographic factors, anthropometric factors, variables related to disease control and diet may influence concentrationsof non-HDL cholesterol, an important indicator of cardiovascular risk. The objective of this study is to evaluate thepredictive factors of non-HDLcholesterol in children and adolescents with T1DM.

2. Materials and methods

This is an observational, cross-sectional study, which is part of the project entitled "Diet Quality and its Association with Nutritional Status and Metabolic Control of Children and Adolescents with Type 1 Diabetes Mellitus."

Data collection was carried out from May 2016 to December 2016 at the diabetes outpatient clinic of a pediatric hospital in Rio de Janeiro. The outpatient clinic attends approximately 200 patients a month and is a reference for the treatment of T1DM in children and adolescents in the state of Rio de Janeiro, Brazil. The care team is multiprofessional and consultations are integrated, performed by doctors, nutritionists, psychologists, social workers, and nurses.

The study population consisted of school-age children and adolescents. The eligibility criteria were: age between 7 and 16 years; diagnosis of T1DM at least 1 year previously; absence of other autoimmune diseases, sickle cell anemia, kidney disease and genetic syndromes; and non-use steroids and use of an insulin pump.

The dependent variable was non-HDL cholesterol (mg/dL). The independent variables were: mean hemoglobin concentration (HbA1c %, HbA1c mmol/mol) measured over the previous 6 months, socio-demographic variables (age, sex, income, place of residence, sanitation), anthropometric variables (z-score of BMI/age), clinical variables (duration of T1DM, insulin dose, type of dietary planning-carbohydrate counting method or traditional method), and the food intake variables (% of macronutrients, lipid-carbohydrate ratio, % of energy from each food processing category).

Socio-demographic and outpatient follow-up data were collected on specific formsfrom medical records. Information on household income per capita, place of residence, and sanitation conditions was collected in an interview with the child/adolescent's parent/guardian.

Food consumption was assessed by one 24-h dietary recall (24HR), which was taken in a separate room reserved for this purpose. The team of researchers had received training in order to avoid biases in administering surveys, such as inadequate filling out of information, influence of the interviewer, and influence of the place of administration [16].

The Five-Step Multiple-Pass Method was used when administering the 24HR. This method helps the interviewee to recall the foods consumed by means of five steps: uninterrupted listing of foods and beverages consumed; questions about foods that are often forgotten; time and place at which food was consumed; detailed description of quantities and other characteristics of the food cited; and final review of the information provided to make sure that no food intake is omitted [17].

During the 24HR, the food products consumed were described by their brand, dietary specifications (full-fat, low-fat, low-sugar, zero sugar), and other characteristics. The home measures were converted into units of mass and volume by means of the Table for Evaluation of Food Consumption in Domestic Measures [18] and their energy content and centesimal composition were calculated using the Brazilian Food Composition Table [19].

The foods reported were classified according to the degree of processing, as described in the NOVA classification. Group 1 consisted of unprocessed or minimally processed foods: fruits, vegetables, tubers, rice, legumes, dried fruit, fruit juices without added sugar, spices in general, fresh or frozen meat, eggs, vegetables, coffee, water, and culinary preparations with one or more fresh or minimally processed ingredients. Group 3 consisted of processed foods, and Group 4 consisted of ultraprocessed foods, including soft drinks, snack foods, candies and sweets in general, biscuits, cakes and cake mixes, chocolate drinks, flavored fruit beverages, nuggets, sausages, hamburgers, instant noodles, and other processed products made from five or more ingredients. The foods from Group 2 (processed culinary ingredients like salt, sugar, molasses, honey, oils, and fats) were not included in the analysis because of the inaccuracy of the quantities reported [20].

Daily total energy intake was quantified and the percentage contribution of each of the three food processing categories to total energy intake was calculated. The macronutrients (carbohydrates, proteins, lipids) were also quantified and their percentage contribution to total energy intake was calculated, as was the lipid-to-carbohydrate ratio.

World Health Organization growth reference for school-aged children and adolescents [21] was used to classification of BMI/age. The biochemical analyses were carried out in the clinical analysis laboratory of Instituto de Puericultura e Pediatria Martagão Gesteira (IPPMG), a teaching hospital linked to the Federal University of Rio de Janeiro. To determine the percentage of glycated hemoglobin (HbA1c %, HbA1cmmol/mol), the endpoint test was used in VITROS® 5600, 4600, 5.1, and FS (Ortho Clinical Diagnostics). For the analysis of serum lipid concentrations, the colorimetric test was performed using VITROS® 5600, 5.1 FS, 950, 250/350. The LDL-c fraction was estimated by Friedewald's formula. Non-HDL cholesterol was calculated by subtracting HDL-c from total cholesterol.

Non-HDL cholesterol and other lipid parameters were evaluated according to the *Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents* report, which sets the following reference values for children and adolescents with T1DM: non-HDL cholesterol < 120 mg/dL, total cholesterol < 170 mg/dL, LDL-c $\leq$ 100 mg/dL, HDL-c > 45 mg/dL, and triglycerides < 90 mg/dL [22] .

The sample consisted of 120 participants. For the sample size calculation it was considered that to detect a difference of 0.2 mmol/L HDL cholesterol, considering standard deviation of 0.3, alpha error of 5%, and test power of 80%, the sample size should be at least 111 children and adolescents [23].

The original study was planned respecting the ethical considerations set forth in resolution 466/2012, and approved by the Research Ethics Committee of IPPMG/UFRJ, registered under CAAE 52560216.8.0000.5264. Participants and study researchers signed informed assent forms and informed consent forms, respectively.

2.1. *Statistical analysis*

A descriptive analysis of the sample was performed, with the categorical variables being the frequencies and the continuous variables being the means and standard deviations. Bivariate linear regression was used to test the independent variables related to the outcome, with $p < 0.20$. Based on the results of this analysis, a multiple regression model was developed using non-HDL cholesterol as the dependent variable and the variables that demonstrated a significant association in the initial analysis ($p < 0.20$) as independent variables. In the final model, all associations with $p < 0.05$ were considered significant, and the β coefficients and their respective 95% confidence intervals were estimated. Data were entered and analyzed using SPSS software, version 21.0.

3. Results

The total sample was made up of 120 children and adolescents. Their sociodemographic, anthropometric, and outpatient follow-up characteristics are given in Table 1. Their mean age was 11.47 (7–16) years, and 53.3% (n = 64) were female. Most were adolescents (71.7%, n = 86), and most lived in Greater Rio de Janeiro (93.3, n = 112). Most of the parents/guardians reported having incomplete high school education (65.3%, n = 77). The *per capita*household income was R$ 667.54 (146.67–1760.00), and 98.3% (n = 118) of the participants reported having adequate sanitation conditions.

Regarding the anthropometric characteristics, 31.7% (n = 38) of the participants were overweight, and the z-score for BMI/age was 0.65 (1.72–2.9). As for the data monitored at outpatient consultations, the time since diagnosis was 6.68 (1,08–15,16) years, the mean insulin dose was 1.05 (0.23–3.0) kg/day, and mean HbA1c was8.13%(65 mmol/mol). Dietary planning based on carbohydrate counting was followed by 80% (n = 96) of the sample, while 20% (n = 24) used the traditional method (Table 1).

The mean values for each lipid parameter are presented in Table 2. High concentrations of total cholesterol, non-HDL-c, LDL-c and triglycerideswere observed in 44.2% (n = 53), 30% (n = 36), 35.8% (n = 43), and 21% (n = 25) of the subjects, respectively. About 12.5% (n = 15) had inadequate HDL- c values.

The characterization of the participants' food consumption is presented in Table 3. The average total energy intake reported by the participants was 1756.38 kcal (±518.38). Mean energy intake from ultraprocessed foods and processed foods was 24.2% ± 17.9 (425.59 ± 380.15 kcal) and 16.5% ± 13.8 (285.12 ± 261.01 kcal), respectively. Together, these two categories accounted for 40.79% of total energy intake. The mean lipid/carbohydrate ratio was 0.57 (±0.43).

The independent variables that were related to non-HDL cholesterol in the linear bivariate regression ($p < 0.20$) were: sex (p = 0.086), household income per capita (p = 0.151), age (p = 0.143), duration of T1DM (p = 0.002), mean HbA1c (p = 0.000), and type of dietary planning (p = 0.142).

The other variables tested were: age group (p = 0.922), school attendance (p = 0.805), BMI/age (p = 0.985), insulin dose (p = 0.500), percentage of total energy intake from lipids

Table 1 – Sociodemographic, anthropometric, and clinical variables of children and adolescents with T1DM attended at a pediatric hospital in Rio de Janeiro, Brazil, 2016 (n = 120).

Continuous variables	Mean (SD)
Age, in years (n = 120)	11.47 (2.88)
Household income per capita (R$) (n = 120)	667.54 (364.83)
BMI/age (z-score) (n = 120)	0.65 (0.89)
Duration of T1DM (years) (n = 119)	6.68 (3.33)
HbA1c(%) (n = 120)	8.13%(1.25)
HbA1c (mmol/mol) (n = 120)	65 mmol/mol(9.0)
Insulin dose per kg of weight per day (n = 120)	1.05 (0.45)
Categorical variables	**n (%)**
Sex (n = 120)	
Female	64 (53.3)
Male	56 (46.7)
Age group (n = 120)	
School-age	34 (28.3)
Adolescents	86 (71.7)
Place of residence (n = 120)	
Greater Rio	112 (93.3)
Other regions and states	8 (6.7)
Sanitation conditions (n = 120)	
Adequate	118 (98.3)
Inadequate	2 (1.7)
Schooling of parent/guardian (n = 118)	
Incomplete elementary school	17 (14.4)
Incomplete high school	77 (65.3)
Incomplete higher education	24 (20.3)
Nutritional status according to BMI/age (n = 120)	
Underweight	2 (1.7)
Normal weight	80 (66.7)
Overweight	27 (22.5)
Obese	11 (9.2)
Dietary method (n = 120)	
Carbohydrate Counting	96 (80)
Traditional Method (by cups)	24 (20)

T1DM: type 1 diabetes mellitus; BMI: body mass index; HbA1c: glycated hemoglobin.

Table 2 – Lipid profile of children and adolescents with T1DM attended at a pediatric hospital in Rio de Janeiro, Brazil, 2016 (n = 120).

	Mean (SD)	n (%)
Total cholesterol (mg/dL) (n = 120)	107.4 (32.65)	
Adequate	–	67 (55.8)
Inadequate	–	53 (44.2)
Non-HDL cholesterol (mg/dL) (n = 120)	109.7 (29.62)	
Adequate	–	84 (70)
Inadequate	–	36 (30)
LDL cholesterol (mg/dL) (n = 120)	93.9 (23.93)	
Adequate	–	77 (64.2)
Inadequate	–	43 (35.8)
HDL cholesterol (mg/dL) (n = 120)	60.6 (16.03)	
Adequate	–	105 (87.5)
Inadequate	–	15 (12.5)
Triglycerides (mg/dL) (n = 119)	77.4 (47.58)	
Adequate	–	95 (79)
Inadequate	–	25 (21)

SD: standard deviation; non-HDL: non-high-density lipoprotein; LDL: low-density lipoprotein; HDL: high-density lipoprotein.

Table 3 – Food consumption variables of children and adolescents with T1DM attended at a pediatric hospital in Rio de Janeiro, Brazil, 2016 (n = 120).

	Mean (DP)
Total daily energy intake	1756.38 kcal (±518.38)
Proteins (% energy)	21.43% (±6.13)
Carbohydrates (% energy)	51.98% (±9.20)
Lipids (% energy)	26.57% (±9.98)
Lipid/carbohydrate ratio (g)	0.57 (±0.43)
Energy from unprocessed foods (kcal)	1044.86 (±472.01)
Energy from unprocessed/minimally processed foods (%)	58.22 (±18.94)
Energy from processed foods (kcal)	285.12 (±261.01)
Energy from processed foods (%)	16.53 (±13.78)
Energy from ultraprocessed foods (kcal)	425.59 (±380.15)
Energy from ultraprocessed foods (%)	24.26 (±17.88)

SD: standard deviation.

Table 4 – Multiple linear regression model of the variables associated with the non-HDL cholesterol outcome of children and adolescents with T1DM seen at a pediatric hospital in Rio de Janeiro, Brazil, 2016 (n = 120).

Variables	Gross Effects			Effects adjusted[a]		
	β	95% CI	p	β	95% CI	p
Mean HbA1c (%, mmol/mol)	9.2	(5.0–13.4)	0.000	8.5	(4.8–12.1)	0.000
Duration of T1DM (years)	2.5	(1.0–4.1)	0.002	2. 8	(1.3–0.3)	0.000
Female sex	9.3	(−1.3 to 19.9)	0.086	10.1	(0.9–9.4)	0.032

CI: confidence interval; HbA1c: glycated hemoglobin; T1DM: type 1 diabetes mellitus.
[a] Controlled variables in the model: age, household income per capita, and z-score of BMI-to-age ratio.

($p = 0.976$), percentage of total energy intake from carbohydrates ($p = 0.759$), energy from unprocessed and minimally processed foods ($p = 0.860$), energy from processed foods ($p = 0.302$), energy from ultraprocessed foods ($p = 0.480$), energy from processed and ultraprocessed foods ($p = 0.879$), and lipid/carbohydrate ratio ($p = 0.483$).

Table 4 shows the best multiple regression model for non-HDL cholesterol adjusted for household income per capita, age, and BMI/age (z-score). Although $p > 0.20$, the variables age and BMI/age were enrolled in the final model due to biological plausibility. It was found that for each 1% (increase in HbA1c, non-HDL cholesterol increased by 8.5 mg/dL ($\beta = 8.5$, $p = 0.000$, CI:4.8–12.1), and for every 1 year duration of T1DM, non-HDL cholesterol increased by 2.8 mg/dL ($\beta = 2.8$, $p = 0.000$ CI: 1.3–4.3). Sex was also significantly associated with the outcome ($\beta = 10.1$, $p = 0.032$, CI: 0.9–19.4), with the female sex presenting higher concentrations of non-HDL cholesterol.

4. Discussion

Mean HbA1c (%, mmol/mol), the duration of T1DM, and female sex were predictors of non-HDL cholesterol concentrations, an important indicator of cardiovascular risk, regardless of income, age, and nutritional status [24].

Non-HDL cholesterol is considered to be a better predictor of risk for cardiovascular diseases than LDL, since its measure encompasses all the lipoproteins containing Apo B includingLDL-c [25]. The Pediatric NCEP Panel recommends the maintenance of non-HDL cholesterol at <120 mg/dL as a treatment goal for children and adolescents with diabetes [22].

The predictive value of HbA1c on the concentrations of non-HDL cholesterol observed in this study is well described in the scientific literature [3,26,27]. A cross-sectional study that used data of SEARCH for Diabetes in Youth Study, showed that for each 1% increase in HbA1c there was a 7.6 mg/dL increase ($p < 0.001$; CI: 6.6–8.6) in non-HDL cholesterol, which is similar to the findings of the present study [28].

In our series, no relation was observed between the concentrations of non-HDL cholesterol and the nutritional status. This finding is in disagreement with some studies that observed increasing values of non-HDL cholesterol with increased BMI, given the relationship of overweight with worsening of the lipid profile [26,29,30]. However, a cohort study showed that effect of BMI was only associated with changes in HDL-c and TG concentrations, which may explain the absence of a relationship between this indicator and non-HDL cholesterol concentrations [31].

In the present study we found a positive association between the duration of T1DM and higher concentrations of non-HDL cholesterol. Several longitudinal studies have confirmed this relationship, insofar as longer exposure to the disease contributes to worsening of lipid parameters [27,32].

In our study, female sex was significantly associated with non-HDL cholesterol concentrations ($p = 0.032$). Evidence indicates that girls present a higher percentage of total cholesterol and elevated LDL-c. It is not clear whythe female sex is associated with lipid alterations. One possible hypothesis is related to the higher prevalence of overweight and poorer glycemic control observed among girls than boys [33–34].

Dyslipidemia has been a common finding among children and adolescents with T1DM. A cross-sectional study evaluating the lipid profile of 239 children and adolescents with T1DM found high concentrations of total cholesterol, LDL-c, and triglyceridesin 56.7%, 44%, and 11.8% of the sample, respectively. Inadequate concentrations of HDL-c were observed in 21.7% of the subjects studied. These results are similar to the ones found in the present study [35].

Diet is one of the pillars of CVD prevention. A cross-sectional, multicenter study showed that patients who reported a better adherence to diet presented lower HbA1c, with values closer to the glycemic target and lower concentrations of triglycerides and LDL-c [36]. Therefore, HbA1c represents an important predictive factor for diet-modifiable cardiovascular diseases.

Research with children and adolescents without diabetes has shown very similar results to the ones found in our study as regards the contribution of processed and ultraprocessed foods to overall energy intake. A longitudinal study of 345 Brazilian children found that the percentage of energy they obtained from such foods was approximately 49% at school age [15]. In contrast, a cross-sectional study of 784 Brazilian adolescents found that ultraprocessed foods alone accounted for 49.23% of total daily energy intake, twice the percentage observed in this cohort [37].

Regarding macronutrients, there was no association between the percentage of carbohydrates, lipids, lipid/carbohydrate ratioand non-HDL cholesterol concentrations. In contrast to this result, a cross-sectional study that evaluated the effect of diet composition showed that non-HDL cholesterol concentrations were positively associated with lipid intake and negatively associated with carbohydrate intake. After adjusting for other variables, the lipid/carbohydrate ratio was more strongly associated with non-HDL cholesterol concentrations [11]. The difference between our data and this American study may probably due to the lower carbohydrate consumption by the patients in the American study, since the macronutrient consumption of our sample met the recommendation. Thus, the American authors concluded that children and adolescents with T1D may restrict their consumption of carbohydrates, which may have adverse effects on BMI and the lipid profile, particularly if there is a compensatory increased fat intake.

For a long time, dietary recommendations designed to maintain a desirable lipid profile concentrated on the percentage of dietary lipids. However, a large longitudinal study has found that carbohydrates are the nutrients that are most strongly associated with cardiovascular risk. It should be noted that these results were found in a population of adults with excessive carbohydrate consumption (60–70% of total energy intake) [38]. While in this cohort, the mean percentage values were adequate for all macronutrients, probably because the study population receives routine nutritional counseling.

The limitations of this study include: the absence of body composition measurements related to visceral adiposity, such as waist circumference and percentage of body fat (%), due to their association with cardiovascular risk, and assessments of physical activity levels, because of their influence on the lipid profile. As for the analysis of food consumption, the use of a single 24HR was also a limiting factor because it may not reflect regular consumption habits.

The strengths of this study include the evaluation of the influence of sociodemographic, clinical, anthropometric and dietary factors on non-HDL cholesterol and the evaluating food consumption using NOVA food groups.

The findings highlight the importance of adequate glycemic control as the main modifiable predictor, reinforcing the strategic role of nutritional therapy in the treatment of children and adolescents with T1DM. The maintenance of glycated hemoglobin concentrations within the recommended dose may contribute to the reduction of cardiovascular risk in this population.

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Declaration of Competing Interest

The authors declare no conflict of interest in relation to the publication of this article.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diabres.2019.06.005.

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