Short Communication

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Non-HDL-cholesterol and C-reactive protein in children and adolescents with type 1 diabetes

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Abstract

Background: To what extent high sensitivity C-reactive protein (hsCRP) is associated with known cardiovascular risk factors in children with type 1 diabetes (T1D) has not been fully explored.
Methods: Forty-two T1D children (age: 12+/−1 years) without hypertension, retinopathy, hypothyroidism, albuminuria or other endocrine diseases and 20 controls were studied. Out of the 42 T1D patients studied 57% were prepubertal or early pubertal (Tanner I/II), 38% were pubertal (Tanner III/IV) and 5% post-pubertal (Tanner V).
Results: Children with T1D showed higher hsCRP than controls [0.51 (0.31–1.71 vs. 0.20 (0.20–0.90) mg/L, $p < 0.05$]. However, hsCRP levels were not different in subgroup analysis [hemoglobin A_{1c} (HbA_{1c}) > 7.5% or disease duration > 3 years] within the group of children with T1D. Conversely, non-high density lipoprotein (HDL)-cholesterol was different in the subgroup analysis. Moreover non-HDL-cholesterol was correlated with age ($r = 0.37$, $p < 0.01$), disease duration ($r = 0.36$, $p < 0.01$) and fasting glucose ($r = 0.55$, $p < 0.0001$).
Conclusions: Non-HDL-cholesterol might be more useful than hsCRP to evaluate future cardiovascular risk in children with T1D.

Keywords: adolescents; children; C-reactive protein; diabetes; non-HDL-cholesterol.

Introduction

Several reports indicate that type 1 diabetes (T1D) prevalence is rising at an overall rate of 3%–4% per year. Moreover, T1D incidence is expected to double in children aged 0–5 years [1]. Such an increase implies a larger number of patients at risk for several comorbidities, including, cardiovascular disease (CVD). In this regard, novel biomarkers of CVD may contribute to the early identification of patients that will benefit from a prompt initiation of the pharmacological treatment for CVD risk factors. Such an argument is highlighted, in the case of glycemic control, by the demonstration of the so-called "metabolic memory" [2].

Numerous reports indicate that patients with T1D can show signs of atherosclerosis, such as endothelial dysfunction, presence of carotid plaques and elevated calcium artery score, as early as the onset of puberty [3]. In these studies, the variables associated with subclinical atherosclerosis were age, disease duration, blood pressure, waist circumference and low density lipoprotein-cholesterol (LDL-C) [3]. Recently, high sensitivity C-reactive protein (hsCRP) was also shown to be associated with subclinical atherosclerosis in children with T1D [2]. However, to what extent hsCRP is associated with known-CVD risk factors in children and adolescents with T1D has not been fully explored.

On the other side, non-high density lipoprotein (HDL)-C, has been recently recommended for screening of dyslipidemia in children at age 9–11 and again at age 17–21 in the Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents [4]. Such a recommendation was based on the growing body of evidence showing that non-HDL-C may predict persistent dyslipidemia, atherosclerosis and the incidence of cardiovascular events in children and adolescents as well as in adults [5]. Moreover, non-HDL-C measurement can be measured accurately in the non-fasting state and, therefore, is a practical approach for the screening of dyslipidemia in children and adolescents [4]. Our aim was to study the relationship of hsCRP and non-HDL-C with variables known to be associated with subclinical atherosclerosis in children and adolescents with T1D.

Subjects and methods

Forty-two children and adolescents diagnosed with T1D attending the Endocrinology Department, of Tucumán Pediatric

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Hospital, Tucumán, Argentina were included. Patients were treated with Neutral Protamine Hagedorn (NPH) and regular insulin, and none had hypertension, retinopathy, malabsorption, hypothyroidism or other endocrine diseases, chronic renal diseases or elevated albumin to creatinine ratio (>30 mg/g; DCA 2000, Siemens, Munich, Germany). T1D children were compared with a group of 20 healthy individuals with comparable age, body mass index (BMI) and sex distribution. All patients underwent an interview in which the study was explained and the patients and their parents gave informed consent to participate. Then, a complete clinical evaluation consigning duration of disease, hypertension, a cardiovascular exam and Tanner stage was performed. Blood samples were obtained in the morning, after a 12-h fast and analyzed in the laboratories of Professional Practice Chair of the Faculty of Biochemistry, University of Tucuman. T1D patients under treatment for hypertension or with statins were excluded. Fasting plasma glucose (FPG) and lipid profile were determined by standardized methods (Wiener Lab, Rosario, Argentina) and glycated hemoglobin A_{1c} (HbA_{1c}) in a point-of-care analyzer (DCA 2000, Siemens, Munich, Germany). HsCRP was determined by chemiluminiscence (Immulite 2000, Siemens, Munich, Germany). Data distribution was tested by the Shapiro-Wilk test and results were expressed as mean ± standard deviation (SD) or median (Q1–Q3), according to normal or skewed distribution, respectively. Spearman's coefficient ($p < 0.05$) was used to investigate the correlations. Differences were tested by the Student's t-test or Mann-Whitney U-test, according to data distribution. Multiple linear regression was used to evaluate which variables were significantly associated with non-HDL-C. Non-HDL-C was log transformed to achieve normal distribution prior to this analysis. The study protocol was approved by the review board of the Tucumán Pediatric Hospital.

Results

Out of the 42 patients with T1D studied 57% were prepubertal or early pubertal (Tanner I/II), 38% were pubertal (Tanner III/IV) and 5% post-pubertal (Tanner V). Table 1 shows the clinical characteristics and biochemical parameters of T1D patients and controls. Significant differences were found in FPG, HbA_{1c} and hsCRP between patients and controls.

When patients with T1D were grouped according to the duration of disease (≤ 3 or > 3 years), we observed that those with a disease duration > 3 years (n = 20) had higher values of total cholesterol, LDL-C and non-HDL-C, while hsCRP levels were similar (Table 2).

When patients were divided according to the glycemic status (HbA_{1c} < or ≥ 7.5%; n = 7 vs. n = 35), no significant differences were found between the two groups except from HbA_{1c} and FPG (Table 3).

Non-HDL-C was correlated with age ($r = 0.37$; $p = 0.01$), disease duration ($r = 0.36$; $p = 0.01$) and FPG ($r = 0.55$; $p = 0.0001$). Age and FPG were the only two non-lipid variables which were independently associated with non-HDL-C in a multivariate analysis ($r^2 = 0.43$). On the other hand, hsCRP did not show any significant correlation with the clinical and biochemical parameters evaluated. Tanner stage was only significantly correlated with HDL-C levels ($r = -0.33$; $p < 0.05$).

Discussion

In children and adolescents with T1D and no signs of micro or macrovascular complications, non-HDL-C showed better correlation with disease duration and glycemic status than hsCRP. Importantly, these variables were consistently associated with subclinical atherosclerosis in children with T1D [2, 3, 6]. Therefore, non-HDL-C would be more informative than hsCRP when evaluating the risk of future cardiovascular complications in children and adolescents with T1D. In fact, it was shown that hsCRP levels do not track between stages of life like lipid variables do [6].

Table 1: Clinical and biochemical characteristic of type 1 diabetes patients and control subjects.

	T1D patients (n = 42)	Controls (n = 20)	p-Value
Gender, F/M	23/19	10/10	NS
Age, years	12 (11–13)	12 (10–15)	NS
BMI, kg/m²	19 (16–21)	18 (18–21)	NS
FPG, mmol/L	12.2 (6.1–15.9)	4.4 (3.7–4.5)	< 0.001
HbA_{1c}, %	10.3 (9.6–13.2)	5.9 (5.8–6.1)	< 0.001
hsCRP, mg/L	0.51 (0.30–1.71)	0.20 (0.20–0.90)	0.020
Triglycerides, mmol/L	0.75 (0.68–1.12)	0.98 (0.89–1.13)	NS
Total cholesterol, mmol/L	4.3 (3.6–4.9)	4.4 (3.4–4.7)	NS
HDL-C, mmol/L	1.09 (0.96–1.32)	1.03 (0.88–1.22)	NS
LDL-C, mmol/L	2.7 (2.0–3.3)	2.6 (1.9–3.4)	NS
Non-HDL-C, mmol/L	3.02 (2.38–3.88)	3.05 (2.22–3.77)	NS

T1D, type 1 diabetes; BMI, body mass index; FPG, fasting plasma glucose; HbA_{1c}, glycated hemoglobin A_{1c}; hsCRP, high sensitivity C reactive protein; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol. Data are presented as median (interquartile range).

Table 2: Clinical and biochemical characteristic of type 1 diabetes patients classified by the median value of disease duration (3 years).

	Disease duration <3 years (n=22)	Disease duration >3 years (n=20)	p-Value
Gender, F/M	12/10	11/9	NS
Age, years	12 (11–13)	13 (11–14)	0.046
BMI, kg/m^2	18 (16–20)	18 (17–21)	NS
FPG, mmol/L	9.8 (6.0–14.4)	12.3 (7.4–18.9)	NS
HbA_{1c}, %	10.2 (7.7–12.6)	11.2 (9.7–13.8)	NS
hsCRP, mg/L	0.40 (0.20–1.00)	0.90 (0.30–2.79)	NS
Triglycerides, mmol/L	0.87 (0.62–1.13)	0.89 (0.72–1.01)	NS
Total cholesterol, mmol/L	3.8 (3.4–4.4)	4.4 (4.0–5.4)	0.014
HDL-C, mmol/L	1.01 (0.93–1.29)	1.14 (0.96–1.37)	NS
LDL-C, mmol/L	2.3 (2.0–2.9)	3.1 (2.8–3.5)	0.017
Non-HDL-C, mmol/L	2.59 (2.30–3.41)	3.50 (2.97–4.24)	0.022

BMI, body mass index; FPG, fasting plasma glucose; HbA_{1c}, glycated hemoglobin A_{1c}; hsCRP, high sensitivity C reactive protein; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol. Data are presented as median (interquartile range).

Table 3: Clinical and biochemical characteristic of type 1 diabetes patients classified according to the glycemic status.

	HbA_{1c} <7.5% (n=7)	HbA_{1c} >7.5% (n=35)	p-Value
Gender, F/M	4/3	19/16	NS
Age, years	11 (9–13)	12 (11–14)	NS
BMI, kg/m^2	18 (16–20)	19 (17–21)	NS
FPG, mmol/L	5.5 (4.5–6.6)	12.7 (9.6–17.8)	<0.001
HbA_{1c}, %	7.1 (6.8–7.3)	11.1 (10.0–14.1)	<0.001
hsCRP, mg/L	0.70 (0.43–2.20)	0.34 (0.21–1.75)	NS
Triglycerides, mmol/L	0.85 (0.60–1.06)	0.89 (0.72–1.01)	NS
Total cholesterol, mmol/L	3.8 (2.7–5.0)	4.3 (3.6–4.9)	NS
HDL-C, mmol/L	1.01 (0.91–1.16)	1.14 (0.96–1.37)	NS
LDL-C, mmol/L	2.3 (1.5–3.7)	2.8 (2.1–3.3)	NS
Non-HDL-C, mmol/L	2.59 (2.30–3.41)	3.13 (2.46–3.88)	NS

BMI, body mass index; FPG, fasting plasma glucose; HbA_{1c}, glycated hemoglobin A_{1c}; hsCRP, high sensitivity C reactive protein; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol. Data are presented as median (interquartile range).

The cross-sectional nature of our study did not allow us to make correlations with HbA_{1c} values over a long time-lapse. Thus, the HbA_{1c} value used in the present study was only representative of the glycemic control over the last 2–3 months. Nonetheless, the correlations exhibited by non-HDL-C could not be a mere consequence of worse metabolic control. Indeed, the DCCT/EDIC study has recently shown that differences in circulating lipoproteins between intensive and conventional treatment groups were qualitative rather than quantitative [7]. In this regard, the ability of non-HDL-C to identify children and adolescents with T1D and high cardiovascular risk may not be completely explained by long-term exposure to hyperglycemia.

In children and adolescents with T1D only one study showed a significant association between hsCRP and subclinical atherosclerosis [3]. The present results are in agreement with those of Schwab et al. [8] in which they did not find a correlation between the carotid intima-media thickness (a subclinical atherosclerosis marker) and inflammatory markers in children with T1D. Most likely these results show that although chronic inflammation contributes to atherosclerosis development in patients with T1D, hsCRP levels might not be reliable to follow the atherosclerotic process during childhood/adolescence. This situation resembles that of T1D onset in which in spite of the known-role of inflammatory mechanisms in T1D, an increase of hsCRP levels was not observed previous to the diagnosis of diabetes [9]. For sure, future studies will help to clarify the relationship between inflammatory markers and CVD in children and adolescents with T1D.

Recent guidelines suggest that a lipid profile should be performed on prepubertal children with T1D (>2 years old) at the time of diagnosis if the family history for CVD

is positive or unknown. If family history is known and negative, screening should begin at puberty. When some borderline or high values were observed, the study should be repeated (after 2-weeks but within a 3-month period) and if confirmed, medical nutrition therapy and tight glucose control are recommended. If LDL values remain high during yearly lipid profile evaluations, then lipid-lowering therapy is recommended [4, 10]. In this context, the measurement of hsCRP would not change the clinical management of children and adolescents with T1D for CVD risk reduction.

In conclusion, non-HDL-C could more useful than hsCRP for the identification of children and adolescents with T1D and increased cardiovascular risk.

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