**Comparison of Carotid Intima-Media Thickness in Mexican Children with Hyperlipidemia vs. Controls**

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**Abstract**

Premature cardiovascular disease is related to childhood hyperlipidemia. The carotid intima-media thickness (cIMT) is used as a surrogate marker of arteriosclerosis. In hyperlipidemic children, this parameter is found to increase.

**Objectives:** To compare cIMT in children with and without hyperlipidemia, to correlate cIMT with other variables (age, serum lipids, C reactive protein, and blood pressure) and to describe cIMT percentiles in Mexican children.

**Methods**

This was an observational, analytic, prospective, cross-sectional, single-blind study conducted in children, aged 2 to 17 years, that were attended at the National Institute of Pediatrics, where cIMT of hyperlipidemic children (≥ 5.17 mmol/L total plasma cholesterol) was compared with that of normal children (≤ 4.4 mmol/L). cIMT and other relevant variables were assessed. Sample size was calculated at 81 patients per group, considering predicted cIMT values.

**Results:** Hyperlipidemic children had higher median cIMT than paired controls (0.5 mm and 0.45 mm, respectively, p<0.001). In multivariate analysis, adjusted for confounders, hypercholesterolemia (β coefficient 0.036, CI 95% 0.016-0.055, p = 0.0004), age (β coefficient 0.004, CI 95% 0.001-0.006, p=0.003), and diastolic blood pressure (β coefficient 0.001, CI 95% 0.000004-0.002, p=0.051) were significantly correlated to cIMT.

**Conclusions:** Regardless of the cause of hyperlipidemia, it was found that cIMT increased in children with hyperlipidemia and that the variables associated with this increase are hypercholesterolemia, age, and diastolic blood pressure.

**ABBREVIATIONS**

BMI: Body Mass Index; cIMT: Carotid Intima-Media Thickness; CRP: C Reactive Protein; DBP: Diastolic Blood Pressure; GE: General Electric Medical; HDL: High-Density Lipoproteins; LDL: Low-Density Lipoprotein; SBP: Systolic Blood Pressure

**INTRODUCTION**

Arteriosclerotic process begins in early childhood, and its closely related to hypercholesterolemia and/or hypertension [1]. The first two preclinical stages in the development of arteriosclerosis are endothelial dysfunction and the thickening of the intima and media arterial muscles. Since the 90’s, noninvasive techniques for vascular evaluation have permitted the assessment of both, endothelial function and blood vessel structure [2], which are the vital parameters used in the diagnosis of preclinical arteriosclerosis. In children, the most commonly used method is the measurement of carotid intima-media thickness (cIMT) [3]. In this study, we compared the cIMT in children with and without hyperlipidemia, and analyzed the variables related to the cIMT.

**MATERIALS AND METHODS**

An observational, comparative, prospective, cross-sectional, single-blind study was carried out in children with hyperlipidemia that were managed as outpatients in Nephrology or Endocrinology department between 2007 and 2009 at a tertiary care hospital and a major medical center for children in Mexico City. Inclusion criteria were children aged 2 - 17, hyperlipidemia (serum cholesterol levels ≥ 5.17 mmol/L) and a paired group of healthy controls (cholesterol level ≤ 4.4 mmol/L and free of arteriosclerosis risk factors), while the exclusion criteria were hypothyroidism, hypertension, diabetes, kidney failure stages III to V, and those that suffered infections within 15 days prior to the onset of the study. Based on Tonstad [4] publication, the sample size was calculated considering carotid thickness as dependent variable and serum cholesterol levels as independent variable, with α-error of .05, power of 80% and applying the formula used in comparing the means of two samples with Gaussian distribution, we have:

\[ n = \frac{(s_1^2 + s_2^2) \left(Z_{1-α/2} + Z_{1-β}\right)^2}{d^2}, \quad n = \frac{((0.049^2 + 0.513^2) (1.96 + 0.84)^2)}{(0.494 - 0.472)^2} = 81 \text{ patients per group.} \]
Demographic, clinical and laboratory measurements were collected exactly on the day or close to the day carotid ultrasound was performed. The cIMT was measured by an associate investigator who was unaware of the clinical status of the children. The measurement of the intima and muscular layers of both sides of the common carotid arteries was performed using Logic 9 equipment General Electric Medical (GE) with a 12-14 MHz multifrequency transducer running Linux. Patients were laid on a supine position, with lateral deviation of the neck and head extension to facilitate access on each side. Measurements of the far and near walls of the two common carotids, performed directly in the patients, at 1 cm from the carotid bulb were done using the GE equipment and the average of the four measurements were recorded. The cIMT was defined as the distance from the leading edge of the first echogenic line to the second echogenic line drawn from the upper layer of the tunic adventitia. The measuring technique was standardized using healthy patient two months prior to the onset of study measurements.

**Statistical analysis**

To compare cases and controls for the studied variables, Mann-Whitney U test was used for numerical values and Pearson χ² test for categorical variables. To relate cIMT with the studied variables, Spearman correlation test was performed for numerical variables and Mann-Whitney U or Kruscal-Wallis tests for categorical ones. Based on the results, multiple linear regressions were performed to establish a cIMT prediction model by introducing into the model all those variables with a significance lower than 0.1. Finally, cIMT percentiles were established for cases and controls.

The study was approved by the Research and Ethics committees of the National Institute of Pediatrics. At least, one of the parents gave consent for the inclusion of their child in the study.

**RESULTS AND DISCUSSION**

**Results**

Eighty-three cases and 83 controls were included. Almost two-third of the cases were associated with a nephropathy comprising of proteinuria in 24, renal failure in 22 and kidney transplant in 7; primary hypercholesterolemia were registered in 24 cases and other diseases in 6 cases. For the controls 29 were healthy and 7; primary hypercholesterolemia were registered in 24 cases and other diseases however, none of the controls had any risk factor for arteriosclerosis. Table 1 summarizes the anthropometric, biochemical and other characteristics of the study patients. The median and the range were expressed as numeric variables and the frequencies and percentages as categorical variables. In hypercholesterolemic children as compared with the controls, the cIMT, systolic and diastolic blood pressures as well as creatinine and glucose serum levels were higher while serum albumin levels were lower. Also in this group, C-reactive protein (CRP) and proteinuria were quite elevated and hypertension was present in 35 of the cases with hyperlipidemia (hypertension was an exclusion criterion for controls). The increase in the levels of serum cholesterol and LDL were in accordance with the inclusion criterion.

With regard to carotid thickness, Table 2 depicts the relation between this and the categorical variables. It could be seen that in addition with the cases of hyperlipidemia, the carotid thickness is greater when there is arterial hypertension and CRP elevation. There were no significant differences between the different causes of hyperlipidemia and neither with the gender nor nutritional status, even when only obesity was considered in the later.

Table 3 shows the spearman rho correlation index between the numerical variables and carotid thickness. It can be observed that although the correlation is not very considerable, it is significant when we consider the anthropometric variables like age, weight, height and body mass index (BMI) and with hypelipidemic duration, blood pressure, serum lipid levels with the exception of HDL, creatinine, glucose and proteinuria.

In multivariate analysis, adjusted for confounders, only hypercholesterolemia (B coefficient 0.036, CI 95% 0.016-0.055, p = 0.0004), age (B coefficient 0.004, CI 95% 0.001-0.006, p=0.003), and diastolic blood pressure (B coefficient 0.001, CI 95% 0.000004-0.002, p=0.051) were significantly correlated to cIMT. The model is highly significant and these variables can predict the cIMT by the following equation, with a correlation coefficient of 0.495: \( \text{cIMT} = 0.361 + (\text{hypercholesterolemia} \times 0.036) + (\text{age in years} \times 0.004) + (\text{diastolic blood pressure} \times 0.001) \).

**Abbreviations:**

BMI: Body Mass Index; Cimt: Carotid Intima-Media Thickness; CRP: C Reactive Protein; DBP: Diastolic Blood Pressure; HDL: High-Density Lipoproteins; LDL: Low-Density Lipoprotein; SBP: Systolic Blood Pressure

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**Table 1: Clinical and laboratory characteristics of the studied patients.**

<table>
<thead>
<tr>
<th>Variables</th>
<th>cases</th>
<th>p-value**</th>
<th>controls</th>
<th>p-value**</th>
</tr>
</thead>
<tbody>
<tr>
<td>females</td>
<td>47/57%</td>
<td>47/57%</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>age (years)</td>
<td>10 (2-17)</td>
<td>11 (2-17)</td>
<td>0.121</td>
<td>---</td>
</tr>
<tr>
<td>weight (kg)</td>
<td>33.4 (9.8-95)</td>
<td>37.0 (10.8-91.5)</td>
<td>0.149</td>
<td>---</td>
</tr>
<tr>
<td>height (m)</td>
<td>1.3 (0.83-1.81)</td>
<td>1.35 (0.86-1.74)</td>
<td>0.496</td>
<td>---</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>17.9 (12-31)</td>
<td>18.8 (12.7-39.3)</td>
<td>0.07</td>
<td>---</td>
</tr>
<tr>
<td>BMI (percentile)</td>
<td>54 (1-99)</td>
<td>69 (1-100)</td>
<td>0.249</td>
<td>---</td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>100 (70-120)</td>
<td>110 (76-160)</td>
<td>0.000001</td>
<td>---</td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
<td>66 (50-80)</td>
<td>70* (50-110)</td>
<td>0.000003</td>
<td>---</td>
</tr>
<tr>
<td>duration of hyperlipidemia (years)</td>
<td>-</td>
<td>2 (1-8)</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>cIMT (mm)</td>
<td>0.45 (0.38-0.6)</td>
<td>0.5 (0.35-0.7)</td>
<td>0.000007</td>
<td>---</td>
</tr>
<tr>
<td>cholesterol (mmol/L)</td>
<td>3.88 (2.77-4.4)</td>
<td>6.13 (5.2-21.9)</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>LDL (mmol/L)</td>
<td>2.31 (0.3-3.2)</td>
<td>4.03 (2.5-20.5)</td>
<td>---</td>
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</tr>
<tr>
<td>HDL (mmol/L)</td>
<td>1 (0.57-1.75)</td>
<td>1.19 (0.26-2.71)</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>triglycerides (mmol/L)</td>
<td>0.98 (0.29-1.88)</td>
<td>2.28 (0.46-7.5)</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>creatinine (µmol/L)</td>
<td>43.3 (23.8-132.6)</td>
<td>70.7 (15.9-1272)</td>
<td>0.00005</td>
<td>---</td>
</tr>
<tr>
<td>glucose (mmol/L)</td>
<td>4.66 (3.5-5.94)</td>
<td>5 (2.5-15.93)</td>
<td>0.0003</td>
<td>---</td>
</tr>
<tr>
<td>albumin (g/L)</td>
<td>41 (30-50)</td>
<td>39 (10-49)</td>
<td>0.00003</td>
<td>---</td>
</tr>
<tr>
<td>proteinuria (mg/day)</td>
<td>0 (0-2260)</td>
<td>0 (0-13100)</td>
<td>0.001</td>
<td>---</td>
</tr>
<tr>
<td>CRP &gt;0.33 mg/dL</td>
<td>4/5%</td>
<td>26/31%*</td>
<td>0.000005</td>
<td>---</td>
</tr>
<tr>
<td>obesity</td>
<td>4/5%</td>
<td>10/12%</td>
<td>0.094</td>
<td>---</td>
</tr>
<tr>
<td>hypertension</td>
<td>0</td>
<td>35/42%</td>
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</tbody>
</table>

* The median and the range are expressed as numeric variables while the frequencies and percentages are written as categorical variables. ** Mann-Whitney U test or Pearson χ² test.
Discussion

Previous studies have shown increased cIMT in populations of children with arteriosclerotic risk factors as familial hyperlipidemia [4], primary hypertension [5], diabetes [6], metabolic syndrome [7], and chronic nephropathy [8], among others. Our results show that the median cIMT was higher in children with hyperlipidemia than in controls (0.5 mm vs. 0.45 mm) without a significant difference when the various causes of hyperlipidemia were compared. In addition to higher cIMT, hyperlipidemic children also had increased systolic and diastolic blood pressures, HDL, triglycerides and glucose serum levels as well as elevated CRP. Differences in creatinine, albumin and proteinuria are caused by renal disease-associated hyperlipidemia, however, such differences are not significant when primary hyperlipidemia is compared with controls.

Factors influencing the cIMT are varied. Bivariate analysis showed a positive correlation with cholesterol, LDL and triglyceride levels, although the highest correlation was seen with the presence of hypercholesterolemia. A weak but significant positive correlation with anthropometric variables as age, weight, height and BMI was found as previously reported in children [9] and adults [10]. Correlation with blood pressure was observed when the hypertensive state or figures of both systolic and diastolic blood pressures are analyzed which was in accordance with the report of Lande and Col [5].

The duration of hyperlipidemia is an important variable that lost its significance in the multivariate analysis. This is because the duration is not uniform in the different types of hyperlipidemia. It is shorter in the cases with renal transplant and longer in the cases with proteinuria or nephrotic syndrome, nevertheless, in the cases of primary hyperlipidemia, it is difficult to determine the onset time hence, we cannot exactly specify when hypercholesterolemia began.

The etiology of hyperlipidemia cases included in this work does not reflect the typical causality in the general population, where most cases are primary hyperlipidemia. However, it could represent the causes of hyperlipidemia found at tertiary care hospitals, as most cases are associated with renal disease. On the other hand, the control population comprising of only 35% of healthy children and 65% of nephrology outpatients may possess masked unknown risk factor for arteriosclerosis that could have clouded the analyses. However, cIMT data was not previously described in the population of Mexican children, and could help to design appropriate treatment for children with hyperlipidemia which together with adequate and timely screening programs for the disease would improve the prevention of CVD. With the exception of two cases with severe hyperlipidemia, we did not find atheromatous plaques, which show that the prevention of adulthood CVD in these children is possible.

cIMT has been used in several clinical trials in adults as variable outcome to measure the effect of different interventions to prevent CVD [11]. cIMT decreased in obese children treated with diet and exercise [12], as well as in hyperlipidemic children treated with pravastatin [13]. cIMT measurements have been recommended in children with hyperlipidemia after 10 years of age, and yearly if found in the upper tertile and in case of progression, a more aggressive treatment could be necessary [14]. The early use of statins in hyperlipidemic children has also been suggested to prevent the development of arteriosclerosis and consequent CVD at later ages [15].
We believe that the importance of this study lies in aiding future clinical trials on both non-pharmacological and pharmacological treatment of hyperlipidemia in Mexican children. However, further studies on the effect of different treatments for hyperlipidemic children, using cIMT as arteriosclerosis surrogate, upon long-term CVD are necessary to estimate the actual value of such assessments.

**CONCLUSION**

Regardless of what causes hyperlipidemia, cIMT is increased in children with this disease. The principal variables associated with increased cIMT are hypercholesterolemia, age and diastolic blood pressure.

**REFERENCES**


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**Cite this article**