Ultrasonography measurement of carotid intima-media thickness in pediatric patients with obesity, familial hyper-cholesterolemia and type 1 diabetes

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Abstract

Ultrasonography measurement of carotid intima-media thickness in pediatric patients with obesity, familial hypercholesterolemia and type 1 diabetes.

Purpose. To evaluate by ultrasonographic images carotid intima-media thickness (IMT) as an early marker of cardiovascular risk (CVR) in patients with clinical and laboratory diagnosis of familial hypercholesterolemia (FHC), type 1 diabetes (DBT-1) and Obesity (OB), compared to a healthy control group.

Materials and Methods. A prospective, descriptive, and cross-sectional study. We evaluated the IMT of common carotid (cc) arteries and included in a single dichotomic variable other structural modifications of the wall (atheromatous plaques and intima irregularities). US was blinded to the blood tests results (as recommended by the 2007 Mannheim consensus) from 121 patients (aged 6 to 18 years): 24 FHC, 40 DBT-1, 43 OB, and 14 controls. Patients with other diseases that could alter the arterial wall were excluded. Variables were analyzed using the Statistix 8 program.

Results. The three groups had a higher IMT than the control group, with these differences being statistically significant. Mean IMT (mm) were 0.59 (0.31-2.15), p: 0.006, CI 0.06 to 0.36 in FHC; 0.48 (0.3-0.85), p: 0.001, CI 0.06-0.14 in obesity; and 0.46 (0.25-0.65), p: 0.0004, CI 0.03-0.13 in DBT-1. Control group: 0.37 (0.30-0.45). The major difference was observed in FHC patients. No association was found between IMT and the levels of HbA1c and lipids. In the OB group there was no association between IMT and BMI Z-score. Atheromatous plaques and intima irregularities were found in 31% of FHC patients, 8% of DBT-1 patients, and 6% of OB patients.

Conclusion. Ultrasonographic IMT measurements demonstrated that patients with chronic diseases and increased CVR at adulthood presented early changes in the carotid intima-media at childhood. This allows clinical prevention strategies and therapeutic guidance.

INTRODUCTION

Measuring intima-media thickness (IMT) is now a standard diagnostic procedure in assessing cardiovascular risk (CVR) in adults.

There has also been an increase in the number of pediatric publications evaluating IMT in children from high-risk groups, such as those with arterial hypertension (AHT), type 1 diabetes (DBT-1), chronic kidney disease, obesity, dyslipidemia and homocystinurias (1).

This study is based on the need to find a non-invasive, low-cost, and readily-available method, such as ultrasound, for assessing the carotid artery in patients with a diagnosis of familial hypercholesterolemia (FHC), obesity and type 1 diabetes.

There is no definition of normal IMT values in the pediatric population in our environment. Therefore, a blind study was conducted in cooperation with the Nutrition Department to measure IMT in patients free from these conditions (control group), who were classified according to age (prepubertal and pubertal), gender and body mass index (BMI).

MATERIALS AND METHODS

This is a prospective, descriptive and cross-sectional study. We evaluated 121 patients with an age range between 6 and 18 years, in 107 cases (43 obese, 24 with FHC, 40 with DBT 1) and 14 controls.

The responsible adult accompanying the child and the child signed an informed consent/assent to participate in the study. The informed consent/assent was previously approved by the Hospital Ethics Committee.

Inclusion criteria

Age between 6 and 18 years, under follow-up at the Nutrition Department. Obese Patients: BMI above the 97th percentile; patients with familial hypercholesterolemia: LDL cholesterol levels above 190 mg%, family history of hypercholesterolemia, with or without history of early cardiovascular disease; DBT-1; insulin-requiring childhood-onset diabetes.

Control group patients: children and adolescents free from these conditions, with no family history of early cardiovascular disease, who presented for regular follow-up of other conditions (ambulatory surgical condition: for example, phimosis). In these subjects, lipid profile and blood glucose levels were measured as part of their preoperative testing.

Exclusion criteria for all groups

Patients with any other condition that may alter the arterial wall, such as congenital heart disease, chronic kidney disease, transplant recipients, rheumatic disease or HIV infection, and adolescent patients who admitted smoking.

Ultrasound

In all patients we measured the IMT of common carotid arteries (CCA), considering as normal the values obtained in the control group. Plaque is defined as a focal structure that encroaches into the arterial lumen of at least 0.5 mm or 50% of the surrounding IMT value or demonstrates a thickness >1.5 mm as measured from the media-adventitia interface to the intima-lumen interface.

A state-of-the-art Toshiba Xario ultrasound system with high-frequency lineal transducer (7-12MHZ) was used. US was blinded to blood tests results. Technique: patient lying down in the supine or semi-supine position with the head slightly hyperextended and rotated 45° away from the side being examined, as recommended by the 2007 Mannheim Consensus. Image was focused on the posterior wall of each common carotid artery, in a segment 1 cm proximal to the carotid bifurcation on each side (Table 1). Only the intima (echogenic line) and the media (hypoechoic...
Additional data included an assessment of the internal and external common carotid arteries by color Doppler and pulsed Doppler, and the Peak Systolic Velocity (PSV), as well as the Internal Carotid Artery/Common Carotid Artery PSV ratio were recorded in cases of stenosis.

**Anthropometric measurements and clinical examination**

- Weight and height.
- BMI: weight (kg) / height (cm), expressed in percentiles (Pc) and as z score ($z = \frac{\text{measured value} - \text{median}}{1 \text{SD}}$).
- Obesity was defined as BMI at or above 95th percentile for gender and age. Reference: percentiles curves of the Argentine Society of Pediatrics (SAP), 2001 /6.
- Waist circumference (to estimate central obesity).
- Blood pressure: hypertension was considered if systolic or diastolic pressure was at or above 95th percentile for gender, age and height.

**Blood tests**

Blood glucose, total cholesterol, LDL, HDL and triglycerides were measured in fasting patients by standard methods. In diabetic patients, glycosylated hemoglobin was also estimated.

**Data analysis plan**

We compared the neck vessels ultrasound findings of each group of patients with the control group and evaluated the IMT in both CCAs, the peak systolic velocity in CCA (CCA PSV), and ICA (ICA PSV) and their ratio (ICA/CCA), calculating an average from the left and right vessels values.

Results were expressed as mean and mean standard deviation for normal distribution variables, and as median and interquartile range for non-normally distributed variables. Differences between the population of patients with FHC, OB or DBT-1 and normal controls were analyzed using the T test for Gaussian distribution or the Wilcoxon test for non-Gaussian distribution.

Lineal regression was performed to investigate the relationship between the various variables representative of each condition (LDL, Hba1c, ZBMI, time of evolution) and outcome variables (intima media thickness).

$p \leq 0.05$ was assumed as significant and the Statistix 8 software was used.

**RESULTS**

From June 2009 to May 2010 we studied 107 patients (24 FHC, 40 DBT-1 and 43 OB) and 14 control children and adolescents, who underwent a neck vessels ultrasound.

Subjects in the group of diabetic patients were older than controls, but according to data from the literature, it is estimated that this difference does not affect the evaluation $(1,3,4)$. Despite the low number of controls studied, all ages were represented.

No differences were found when analyzing ultrasound findings of each group according to gender; therefore findings were reported by pathological group. Other structural alterations of the vessels walls were grouped in a single dichotomous variable (atheromatous plaques, intima irregularities).

Compared to controls, the 3 groups of patients had a greater intima-media thickness, with differences being statistically significant (Table 2).

**Comparison of findings from different groups**

The highest difference was found in patients with FHC. No association was found between the LDL-Cholesterol value and the IMT. Sixty-two point five percent of patients with FHC were receiving drug the-
Ultrasonography measurement of carotid intima-media thickness

Table 2: Ultrasound of neck vessels in the various groups.

<table>
<thead>
<tr>
<th></th>
<th>FHC</th>
<th>DBT-1</th>
<th>OBESE</th>
<th>CONTROLS</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMT (mm) Mean</td>
<td>0.59*</td>
<td>0.46 ‡</td>
<td>0.48**</td>
<td>0.37</td>
</tr>
<tr>
<td>Range</td>
<td>3.4</td>
<td>0.1</td>
<td>0.11</td>
<td>0.13</td>
</tr>
<tr>
<td>SD</td>
<td>FHC vs. Controls* p: 0.006; Cl: 0.06-0.36</td>
<td>DBT-1 vs. Controls ‡ p: 0.0004; Cl: 0.039-0.13</td>
<td>Obese vs. controls; * * p: 0.001; Cl: 0.062 – 0.14</td>
<td></td>
</tr>
<tr>
<td>CCA PSV</td>
<td>136.3</td>
<td>103.00</td>
<td>88.2</td>
<td>77</td>
</tr>
<tr>
<td>Mean (54.4; 195.4)</td>
<td>121.5</td>
<td>94.572</td>
<td>75.4</td>
<td>70.1</td>
</tr>
<tr>
<td>Range</td>
<td>38.5</td>
<td>30.6</td>
<td>23.3</td>
<td>27.3</td>
</tr>
<tr>
<td>SD</td>
<td>0.97</td>
<td>0.9916</td>
<td>0.89</td>
<td>0.9</td>
</tr>
<tr>
<td>ICA/CCA</td>
<td>(0.54; 1.73)</td>
<td>(0.44; 1.66)</td>
<td>(0.65; 1.46)</td>
<td>(0.5; 1.5)</td>
</tr>
<tr>
<td>Range</td>
<td>0.29</td>
<td>0.27</td>
<td>0.19</td>
<td>0.28</td>
</tr>
<tr>
<td>At: atheromatous alterations (n)</td>
<td>9* At: plaque: 5</td>
<td>3 Irregular intima: 3</td>
<td>3 Irregular intima: 3</td>
<td></td>
</tr>
</tbody>
</table>

At: atheromatous


data not shown). In the group of diabetic patients, no association was found between IMT and levels of plasma lipids and HbA1c. In the group of obese patients, the BMI z-score was 3.2 for males and 2.08 for females (p: 0.0046; CI: 1.9193-0.36; T Test), but this difference had no impact on ultrasound findings. No association was found between IMT and BMI z-score.

Thirty-one percent of patients with FHC (p: 0.009), 8% of diabetic patients and 6% of obese patients had structure alterations of the endothelium, including atheromatous plaques and endothelial irregularities. When studying the characteristics of the 15 patients with these alterations, it was found that they had a greater IMT (0.45 vs. 0.72 mm), p: 0.04; CI 0.5-0.86; T Test), higher LDL cholesterol (215 vs. 109 mg%, p: 0.01; CI 25-186, T Test) and lower HDL-cholesterol (37 vs. 47 mg%; p: 0.0001; CI: 6-14; T Test).

**DISCUSSION**

Cardiovascular disease (CVD) is a leading cause of death in the general population (1). With the exception of high-risk groups (such as children with chronic kidney disease, FHC, Kawasaki disease, obesity and DBT-1), CVD is extremely rare in children, although there is no doubt that its pathophysiologic basis, atherosclerosis, begins early in childhood (3,4).

The pathological basis for CVD is arterial damage in the form of arteriosclerosis. Arteriosclerosis is a broad term that usually describes diffuse thickening and stiffening of large- and medium-sized arteries and is observed in different conditions. The pathological changes include the media and intima.

Atherosclerosis is a form of arteriosclerosis and causes characteristic focal lesions in the intima of large- and medium-sized arteries (1).

Evidence shows that the pathogenesis of atherosclerosis begins in childhood. Pathology studies have demonstrated the presence of early precursors of atherosclerosis, such as fatty streaks and intimal thickening in children arteries (3).

The main risk factors for arteriosclerosis and athe-
Rosclerosis are common, although such processes have different pathogeneses. It can be said that arteriosclerosis leads to diffuse stiffening of arteries, whereas atherosclerosis leads to focal and patchy narrowing and/or atherothrombosis (8-9).

There are two main theories on the pathogenesis of arterio/atherosclerosis: hemodynamic and metabolic.

The hemodynamic theory claims that hemodynamic damage to the arterial wall is the first and most important event initiating arterio/atherosclerotic processes. According to the metabolic theory, the arterial wall is damaged by lipids, oxygen radicals and mediators of inflammation (6,7).

Until the 1950s, arterio/atherosclerosis was believed to develop only in adulthood. Atherosclerotic lesions were first described in coronary arteries of young men killed during the Korean War, which shed new light on the pathogenesis of CVD. The first reports from large population-based studies from the US published in the subsequent decades identified risk factors of CVD and arterio/atherosclerosis (6,7).

In general, three groups of factors damaging arterial walls are included: hemodynamic (blood pressure), metabolic (dyslipidemia, insulin resistance, homocystinuria) and inflammatory. However, a relationship is postulated among all these main factors.

Many observational studies and atherosclerosis regression trials of drug therapy have established that IMT of the carotid arteries, as measured non-invasively by B-mode ultrasound, is a valid marker for the progression of atherosclerotic disease in adults (7).

Introduction into clinical practice of noninvasive methods of arterial imaging caused an eruption of reports on early arterial damage present in children (8,9). The general principle of noninvasive evaluation of arterial structure is based on ultrasound imaging of arterial walls using high-definition imaging equipment and devices allowing measurement of IMT.

The standard sites of IMT measurement in adults are the CCA, carotid bulb, and ICA. Usually, CCA is measured 1–2 cm below the bifurcation (a site that is easily visualized both in children and adults).

The Mannheim carotid intima–media thickness consensus standardizing IMT measurements in adults has been recently updated (9-11).

An important component of carotid US is to adequately document the location, internal characteristics, and surface of plaque (10, 11). Plaque can be simply characterized as homogeneous or heterogeneous. Homogeneous plaques may be fibrous or calcified and have a uniform internal architecture with a smooth surface. Heterogeneous plaques and ulcerated plaques are unstable or friable with the potential for embolic transient ischemic attacks and cerebrovascular accidents. These symptomatic plaques have lower calcium content but larger amounts of intra-hemorrhage lipids, which make them appear hypoechoic (12) (Fig. 2).

Some authors found that obese children have significantly increased CCA-IMT in comparison with healthy controls (1). However, it should be stressed that obesity usually is related not only to metabolic abnormalities (which are known cardiovascular risk factors), but there is also an intermediate phenotype in adolescents with primary AHT (13). However, there are studies in obese normotensive children compared to healthy controls where no significant differences were found in IMT between groups (13).

In the studies by Pilz et al. and Beauloye et al., it was found that IMT correlated with BMI, systolic blood pressure, insulin levels and insulin resistance, and with hypoadiponectinemia (14, 15).

Atherogenesis starts in early childhood and a strong association exists between raised LDL cholesterol levels in young adults and risk of subsequent coronary-artery disease (16).

B-mode ultrasound can reliably assess IMT of the arterial wall, and pathological findings have been reported in some young patients with FHC (17); therefore it is postulated that IMT might serve as a marker of atherosclerosis in children with this disorder and might contribute to the decision of whether or not to start lipid-lowering treatment.

Children with FHC are prone to early development and progression of atherosclerosis. Abnormal cholesterol levels contribute to premature atherosclerosis and to the development of cardiovascular events in these individuals. There is evidence that cholesterol plays a direct causal role in atherogenesis, which is strongly supported by a large number of experimental, epidemiological and clinical studies (18-19).

In the group of patients with FHC, we found higher IMT values (compared to the mean in healthy patients) and structural pathology, such as atheromatous plaque and wall thickening. This suggests that further follow-up of this group of patients in particular is warranted and that, perhaps, a multidisciplinary working group on cardiovascular risk assessment should be established, as it is well documented (and supported by a large number of studies in adults) that ultrasound follow-up is an efficient marker for treatment initiation and adjustment, and prevention of future complications.
In children, signs of subclinical atherosclerosis, such as increased IMT in CCA have been detected in a large number of studies (20).

Adult patients with diabetes show a higher risk (2 to 10 fold) of developing atherosclerotic lesion compared with the normal population (21, 22). As shown by autopsy studies, atherosclerotic processes begin in childhood and progress rapidly in the presence of risk factors (22, 23). It is important to consider the age of the onset of diabetes, therefore IMT measurement should be performed in all pediatric patients with diabetes.

Although in many studies IMT was measured in healthy children, the largest study to date on normative IMT data in children and adolescents was published by Jourdan and ESCAPE Study Investigators (24). The results obtained by the ESCAPE study fit the normative values obtained in the Stanislas Study in young adults and in the study by Denarie et al (25, 26). The main result of the study was that IMT significantly increases during adolescence, and is related to height, BMI, systolic blood pressure and pulse pressure.

Table 3 summarizes the results of the main intima-media thickness measurement studies conducted in children.

In this study, we evaluated the existence of differences in IMT measurement in children with obesity, FHC and DBT-1, comparing them to eutrophic children free from these conditions.

In the three groups of patients, IMT was found to be greater than in the control group and, even if the population size was small, as this is a descriptive study, this difference was statistically significant. IMT values found in our study were similar to those reported in the literature.

In obese patients, no structural pathology was found, although the IMT was greater than in the control group (perhaps due to the sample size or the characteristics of the population). This should be further investigated to obtain more conclusive results.

**CONCLUSION**

This is the first study in our country on early markers of cardiovascular risk in the pediatric population.

IMT measurement can describe the process of changes in arterial wall due to atherosclerosis and provide information not only in patients at risk, but also in the apparently healthy population.

This noninvasive method has multiple clinical applications, ranging from prevention (determination of populations with increased cardiovascular risk) to therapeutic guidance in pediatric patients at high risk because of progressive atherosclerotic processes and who must receive therapy. In the future, this method might allow for the institution of treatment with lipid-
lowering drugs, which to date has a restricted use in the pediatric population.

Our study shows that 3 groups of patients with chronic diseases with increased cardiovascular risk in adulthood (FHC, DBT-1 and obesity) had early alterations in the carotid intima-media in childhood.

Results show the need for further investigation since, even if the sample size was small, both for the group of patients and the control group, results were statistically significant. It would be important to continue, in particular, with the recruitment of controls for future studies, which has been difficult at our institution because patients generally present with conditions that may alter results.

References


