

Relation of age and sex with carotid intima media thickness in healthy children

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Background/aim: To investigate the age- and sex-associated carotid intima media thickness (cIMT) changes in healthy children to determine the age- and sex-specific normal range of values for childhood.

Materials and methods: This study examined 91 healthy school-age children aged 7–15 years prospectively. Standardized sonographic cIMT measurements and analyses were performed. Body mass index and blood pressure were obtained, and atherosclerotic risk factors were investigated. Age- and sex-specific cIMT measurements for different age groups were calculated and the relation with sex was investigated.

Results: Regarding the total study group, mean cIMT measurements for age groups 7–9, 10–12, and 13–15 years were 4.1 ± 0.5 mm, 4.4 ± 0.6 mm, and 4.6 ± 0.4 mm, respectively. cIMT did not differ between boys and girls in the same age group. Age related analyses showed significant variations among the age groups with positive correlation between cIMT and age.

Conclusion: Our results suggest that age-related physiologic thickening of the carotid artery intima-media occurs not only in adults but also in children and that sex is not a factor for cIMT differences in childhood.

Key words: Carotid artery, intima-media thickness, ultrasonography, aging, children, sex differences

1. Introduction

Atherosclerosis is the leading cause of mortality all over the world and the atherosclerotic process begins and progresses in childhood when the risks of cardiovascular disease already exist (1). Obesity and hypertension are well-known cardiovascular risk factors and causes of subclinical cardiovascular disease in childhood (2,3). Carotid intima-media thickness (cIMT) is a noninvasive ultrasound biomarker of early atherosclerosis and cardiovascular disease (4). In healthy adults, cIMT increases with age and thus age is one of the most important determinants for cIMT studies (5). It has also been shown that the differences in cIMT between healthy younger and older people are prominent (6). Although there are many studies about the age- and sex-related cIMT differences in healthy adults, studies in healthy children are scarce (7,8). The effect of age and sex has to be understood for the assessment of a measured cIMT value as to whether it is normal or pathological. We aimed to determine age-

and sex-associated changes of cIMT in healthy Turkish children.

2. Materials and methods

2.1. Subjects

Overall, 194 children were enrolled in the study. Blood pressures and body mass indices (BMIs) of the children were measured. Blood pressure was measured after 15-min rest from the right arm in a sitting position with a calibrated, age-specific sphygmomanometer. A blood pressure value below the 90th percentiles for height and sex (9) and a body mass index between the 15th and 85th percentiles for age (BMI percentiles for 5–19 years as per the World Health Organization 2007 definitions) were accepted as normal for the study group (10).

There were 103 children (53.1%) excluded from the study, because 72 (37.1%) had BMIs that were not between the 15th and 85th percentiles according to age, 12 (6.2%) had high blood pressure, 10 (5.1%) had a history of chronic

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drug intake, 8 (4.1%) were smokers, and 1 (0.5%) had a risk of cardiac disease. The remaining 91 healthy school-age children with a mean age of 11.7 ± 2.6 years (range: 7–15 years) constituted the study group. All subjects and their parents gave informed consent to the examinations after explanation of the study design. The study was done in the radiology and pediatric cardiology departments in a period of 2 months in 2013.

2.2. Ultrasonography examination

All of the carotid artery ultrasound studies were performed by the same pediatric radiologist. Ultrasonography examinations were performed using the Logiq E9 ultrasound system (GE Medical Systems, Wauwatosa, WI, USA) equipped with an ML 6–15 transducer (active matrix array probe, 6–15 MHz, linear). Patients were in the supine position with the head slightly extended and rotated to the contralateral direction from the examination side. The far wall of the left main carotid artery, 2 cm proximal to the bulb, was focused on and several longitudinal images were used to measure the IMT with the automatic IMT measurement program of the ultrasound system. The mean of at least 3 measurements was recorded as the cIMT value (Figure) (6).

2.3. Statistical analyses

All data obtained in the study were recorded and analyzed with SPSS for Windows 15. Descriptive statistics, including mean \pm standard deviation, median (interquartile range), minimum, maximum, frequency, and percentage, were calculated. The variables were investigated to determine whether or not they were normally distributed. Mann–Whitney U test and Kruskal–Wallis variance analyses were used. The Mann–Whitney U test was performed to test the significance of pairwise differences using Bonferroni correction to adjust for multiple comparisons. Correlation analysis was performed between age, systolic

blood pressure, and cIMT measurements. A multiple linear regression model was used to identify independent predictors of cIMT. A 2-sided P-value of less than 0.05 was considered to be statistically significant.

3. Results

The mean BMI value for girls was 19.4 ± 2.4 kg/m² and for boys was 20.1 ± 1.9 kg/m² ($P = 0.08$). Regarding the total study population, IMT increased with age. The mean cIMT for age groups 7–9, 10–12, and 13–15 years were 4.1 ± 0.5 mm, 4.4 ± 0.6 mm, and 4.6 ± 0.4 mm, respectively. Median cIMT at age 7–9 years was 3.9 mm (3.6–6.0 mm), at age 10–12 years was 4.2 mm (3.6–5.9 mm), and at age 13–15 years was 4.6 mm (3.6–5.6 mm). The mean cIMT was 4.4 ± 0.5 mm for all study groups. Measurements of cIMT according to age and sex are shown in Table 1.

There was no statistically significant difference for the measurement of cIMT values between boys and girls ($P = 0.07$). The patients were divided into 3 age groups (7–9 years, 10–12 years, and 13–15 years). The differences in measurements of cIMT values were statistically significant ($P = 0.001$) among age groups. There was also a statistically significant difference between the age groups of 7–9 years and 13–15 years ($P < 0.001$). cIMT values were found to increase with age ($r = 0.339$, $P = 0.001$). Systolic blood pressure and cIMT values did not have a significant correlation ($r = 0.139$, $P = 0.161$).

When cIMT measurement values were examined with linear regression analysis according to sex, age, and blood pressure parameters, only age was found to affect the cIMT values (Table 2).

4. Discussion

This study indicates that sex has no relationship with cIMT in children, whereas age has a positive relationship with cIMT. We found that cIMT values increased significantly with age in children.

Atherosclerosis is known to begin in childhood and the risk of cardiovascular diseases can be raised by increased cIMT values (7). It is important to recognize early subclinical atherosclerosis by noninvasive methods in childhood to eliminate the clinical risks. B-mode ultrasonography can identify early vascular changes, such as thickening of vessel walls and impairment of arterial vasodilatory functions. Adult ultrasonographic studies have shown that cIMT represents an excellent marker for subclinical atherosclerosis (11). Recently, similar ultrasonographic assessment of cIMT was carried out in children and high-risk children showed greater cIMT than normal children (7,11).

Our results showed a wide range of cIMT values (3.6–6.0 mm) in normal school-age children. The range of cIMT values reported by Ishizu et al. (7) was 3.5–5.5 mm,

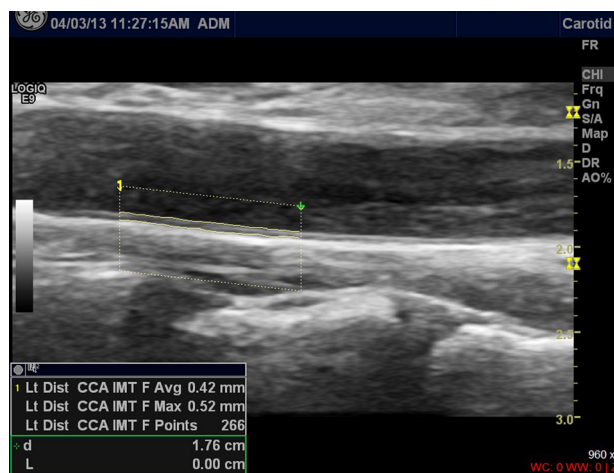


Figure. Automated measurement of cIMT is demonstrated between 2 parallel lines in the region of interest.

Table 1. Carotid artery IMT measurements (mm) according to various parameters.

	n (%)	Median (IR)	Mean (SD)	Minimum	Maximum
All groups	91 (100)	4.4 (0.9)	4.4 (0.5)	3.6	6.0
Boys	47 (51.6)	4.4 (1.1)	4.6 (0.6)	3.6	6.0
Girls	44 (48.4)	4.2 (0.8)	4.2 (0.5)	3.6	5.4
Age					
7	10 (11.0)	3.9 (0.6)	4.1 (0.4)	3.7	5.0
8	9 (9.9)	4.0 (0.8)	4.2 (0.7)	3.6	6.0
9	8 (8.8)	3.9 (0.6)	4.0 (0.3)	3.7	4.6
10	8 (8.8)	3.8 (1.4)	4.2 (0.8)	3.7	5.8
11	9 (9.9)	4.3 (0.6)	4.3 (0.4)	3.6	5.7
12	13 (14.3)	4.7 (1.0)	4.6 (0.6)	3.7	5.9
13	8 (8.8)	4.7 (1.0)	4.6 (0.5)	3.6	5.2
14	17 (18.7)	4.7 (0.5)	4.8 (0.3)	4.4	5.4
15	9 (9.9)	4.2 (1.2)	4.4 (0.6)	3.8	5.4
Age groups					
7–9	27 (29.7)	3.9 (0.6)	4.1 (0.5)	3.6	6.0
10–12	30 (33.0)	4.2 (1.1)	4.4 (0.6)	3.6	5.9
13–15	34 (37.4)	4.6 (0.6)	4.6 (0.4)	3.6	5.4

n: number, IR: interquartile range, SD: standard deviation.

Table 2. Linear regression analysis of cIMT according to age.

	β	P	95% CI
Age*	6.54	0.007	1.81–11.26
Sex	2.16	0.104	–4.44 to 8.76
Systolic blood pressure	5.21	0.163	–3.57 to 13.83

*: There was a positive relationship only between age and cIMT.

by Böhm et al. (8) was 4.8–5.6 mm, and by Sass et al. (11) was 4.3–5.5 mm. The mean cIMT value in our study was 4.4 ± 0.5 mm, whereas it was reported as 4.4 ± 0.5 mm and 4.9 ± 0.3 mm in studies by Ishizu et al. (7) and Sass et al. (11), respectively. Our results were similar to those of Ishizu et al. (7) and different from those of Böhm et al. (8) and Sass et al. (11). Transducer properties may be a reason for this discrepancy. For cIMT measurement we used a 6–15 MHz active matrix array probe. Ishizu et al. (8) used a 5–13 MHz active matrix array probe, whereas Böhm et al. (8) used a 10 MHz linear probe and Sass et al. (11)

used a 7.5 MHz linear probe. Active matrix array probes with high MHz values provide high-resolution images with more sensitive measurements. This may be a reason for the discrepancy of cIMT values between studies. Our results show that the wide range of cIMT values should be kept in mind when determining whether the measured cIMT is pathological or not. If a measurement of cIMT is higher than 6 mm, a possible risk for atherosclerosis may be predicted in children. However, this value is not a cut-off point, and further studies may settle this issue more clearly.

In a study conducted with 369 French patients, Sass et al. (11) found that cIMT was influenced by sex at ages above 18 and was higher in males. They suggested that this might be due to the protective effect of estrogen in females. In the same study, no relationship between sex and cIMT was reported in pediatric patients under 18 years of age (11). Ishizu et al. (7) reported in their study that sex and cIMT had no relationship in healthy Japanese children of 5–14 years old. In another study including 267 healthy German children (6–17 years), Böhm et al. (8) found a positive relationship between sex and cIMT in males. Although the study was based on healthy children of 6–17 years old, they excluded the 6–7 and 16–17 age groups from their statistical calculations (8). In our study, we found no relationship between sex and cIMT. We think that the differences in the results of all these studies could be race-related physiological changes. In a study including a total of 2268 patients (mean age: 42.0 ± 11 years) with Hispanics ($n = 1542$), Asians ($n = 266$), non-Hispanic whites ($n = 285$), and blacks ($n = 175$), the average cIMT was reported to be significantly lower in Hispanics (0.55 mm) and Asians (0.54 mm) relative to those of non-Hispanic whites (0.59 mm) and blacks (0.58 mm) (12). To our knowledge there is no study of children based on race-related cIMT changes in the literature. Further studies based on the same study model conducted in various races are required for concrete evidence in children.

In healthy adults, the relationship between cIMT and age was shown in several studies, and age was reported to be the most important parameter that defines cIMT (11,13). The effect of aging on early atherosclerotic lesions in children is not clear. There are few studies concerning this effect in children, with contradictory results (7,11). Sass et al. (11) reported no significant correlation between age and cIMT. However, the age group examined in that study was 10–18 years, and school-age children of 6–9 years old were not evaluated. This could be the reason for the nonsignificant correlation between age and cIMT. On the other hand, Ishizu et al. (7) reported a significant positive correlation between age and cIMT in their study with 60 healthy school-age children (5–14 years). Böhm et al. (8) also reported a similar result in their study with 267 healthy children (6–17 years). In our study, we also found a significant positive correlation between age and cIMT. These results have shown that age related physiologic thickening of the cIMT is not only an

issue for adults but also for school-age children. However, the mechanism of the age-related physiologic thickening of the arterial intima-media is controversial in childhood. It was reported that an increase of physiological blood pressure with age is related with an increase of arterial wall thickening in healthy adults (14). Although Böhm et al. (8) indicated a positive correlation between blood pressure and cIMT in healthy children, we found no correlation between blood pressure and cIMT, similar to the study by Ishizu et al. (7), who attributed wall thickening in childhood to physical growth accompanied with an increment in blood volume. Despite the controversy about the mechanism of thickening in the intima-media, these data suggest that age-dependent physiologic thickening of the arterial wall starts in childhood. Physiological growth of organs may be a factor for the increment of cIMT in childhood. Further studies focused on the mechanism of age-dependent physiological thickening of arterial walls could clarify this process. Our results revealed the importance of the age factor in the formation of the control group in study designs investigating cIMT in childhood. Therefore, caution should be taken to match the age distribution of the control group with that of the study group.

Our study suffered from a few limitations. First, the study population was small. Thirty-seven percent of the study group was excluded for not meeting the criterion of BMI being between the 15th and 85th percentiles according to age. The percentage of excluded patients was much higher than we expected and consequently the group remained small. Second, we used noninvasive diagnostic parameters for healthy children. Thus, invasive cardiovascular risk factors (serum lipids, glucose level, and markers of inflammation) were not assessed. Third, only one pediatric radiologist did the sonographic examinations by an automated measurement method (15) for cIMT, and thus we did not evaluate interobserver variation.

In conclusion, our results suggest that age-related physiological thickening of the carotid artery intima-media occurs not only in adulthood but also in childhood and that sex is not a factor influencing cIMT in children. Further comprehensive studies with larger series invasively assessing cardiovascular risk factors are required to establish the mechanism of age-related changes in cIMT and the effects of other speculated factors, such as sex, blood pressure, BMI, height, and serum lipid values.

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