Abdominal obesity is an independent risk factor for increased carotid intima- media thickness in obese children

Bülent Hacıhamdioğlu[1], Vedat Okutan[2], Yılmaz Yozgat[2], Düzgün Yıldırım[3], Murat Kocaoğlu[3], Mustafa Koray Lenk[2], Okan Özcan[1]

Departments of [1]Pediatrics, [2]Pediatric Cardiology, and [3]Radiology, Gülhane Military Medical Academy and Medical Faculty, Ankara, Turkey

SUMMARY: Hacıhamdioğlu B, Okutan V, Yozgat Y, Yıldırım D, Kocaoğlu M, Lenk MK, Özcan O. Abdominal obesity is an independent risk factor for increased carotid intima-media thickness in obese children. Turk J Pediatr 2011; 53: 48-54.

We aimed in this study to investigate carotid intima-media thickness (IMT) in obese children and evaluate the relationship of IMT to various cardiovascular risk factors. One-hundred four obese children (9.3 ± 2.5 years) and 30 healthy age-matched control subjects were enrolled in the study. All children were assessed for fasting levels of glucose, insulin, lipid profile, skinfold thickness (SFT), waist circumference (WC), and blood pressure (BP). Insulin resistance was estimated by the homeostasis model assessment (HOMA) index. Carotid IMT measurements and non-alcoholic fatty liver disease (NAFLD) were diagnosed with ultrasonographic findings. IMT was significantly higher in obese children compared to controls (0.49 ± 0.05 vs. 0.40 ± 0.02 mm, p<0.001). Significant positive correlations were found between increased carotid IMT and body fat percentage (BFP), body mass index (BMI), age, height, systolic BP, WC, SFT, triglyceride and insulin levels, and insulin resistance index. In a linear logistic regression analysis, the only parameter affecting the increase in carotid IMT was WC (β: 0.589, p<0.001). Furthermore, IMT was increased significantly in obese children with NAFLD when compared to obese children without NAFLD (0.54 ± 0.04 vs. 0.48 ± 0.05 mm, p<0.001). Children with abdominal obesity are at increased risk for atherosclerosis, and WC can be used to determine the atherosclerosis risk in obese children.

Key words: obesity, children, cardiovascular disease, intima-media thickness, waist circumference.

The prevalence of childhood obesity has been increasing at an alarming rate in both developed and developing countries. The highest prevalence of childhood obesity has occurred in developed countries; however, its prevalence is increasing in developing countries such as Turkey[1-4]. Childhood obesity is a risk factor for atherosclerosis and is associated with increased mortality due to cardiovascular disease in adulthood, independent of adult weight[5,6]. Recent studies in children indicate that atherosclerosis starts at an early age and is linked to obesity[7].

High-resolution B-mode ultrasound measurement of the carotid intima-media thickness (IMT) is a marker of early atherosclerosis, which correlates with coronary artery disease in adults and is associated with myocardial infarction and stroke[8,9]. Previous studies have shown a significantly increased IMT in obese children[10-14].

Abdominal obesity, an excessive accumulation of both central subcutaneous and visceral fat, has emerged as an important predictor of metabolic complications and adverse health effects and increased cardiovascular and metabolic risks in children and adolescents[15-17]. Although visceral fat (body adipose tissue located within the abdominal cavity around the visceral organs) can be accurately assessed by imaging techniques such as computed tomography and magnetic resonance imaging,

use of these techniques may not be feasible clinically[18]. Measuring waist circumference (WC) is a simple, effective way of measuring abdominal obesity in adults and children and may be a better predictor of cardiovascular disease risk than body mass index (BMI)[19]. In particular, WC is a better indicator of visceral fat in children than BMI[20,21].

Non-alcoholic fatty liver disease (NAFLD), which is characterized by fatty infiltration of liver cells, is a highly prevalent condition that resembles alcohol-induced liver injury but occurs in patients who do not abuse alcohol. A NAFLD diagnosis is based on blood testing, imaging studies and a liver biopsy, which is the best diagnostic tool for confirming NAFLD. NAFLD is strongly associated with obesity, type 2 diabetes and dyslipidemia[22], and is the primary hepatic complication of obesity and insulin resistance (IR). Ultrasonography is an easy and noninvasive method for diagnosing fatty liver in children with obesity[23]. Recent studies have clearly documented that adults and children with NAFLD have significantly greater carotid IMT[24,25].

In the present study, we examined the association between increased IMT and the presence of conventional cardiovascular risk factors such as visceral obesity, hypertension, dyslipidemia, and IR in obese children. We also investigated possible IMT changes in an obese population with NAFLD.

Material and Methods

We studied 104 children with obesity consecutively recruited from the outpatient clinic of the Department of Pediatrics, Gülhane Military Medical Hospital, in Ankara, Turkey, along with 30 healthy age-, gender-, and pubertal stage-matched control subjects. Exclusion criteria included a history of familial hypercholesterolemia or hepatic infectious or endocrine diseases, syndromic obesity, the use of medication that alters blood pressure, glucose and lipid metabolism, and smoking and alcohol consumption. Obesity was defined as a BMI over the 95th percentile[26]. The study was conducted according to the Declaration of Helsinki, and the study protocol was approved by the Ethical Committee of the Gülhane Military Medical Committee. Signed informed consent was obtained for each subject over 12 years of age, and informed parental consent was obtained for all children regardless of age.

Each child underwent a complete physical examination and anthropometric measurement, including pubertal staging according to the Tanner criteria. Height and weight were measured in postabsorptive conditions and with an empty bladder. Height was measured to the nearest 0.5 cm on a standard height board, and weight was determined to the nearest 0.1 kg on a standard physician's beam scale with the subject dressed only in light underwear and no shoes. We also measured triceps and subscapular skinfold thickness (SFT) to the nearest 1 mm with Lange skinfold calipers (Holtaın Ltd., Crymych, UK). Both measurements were taken on the subjects' right side in accordance with standard procedures. The subscapular SFT was measured immediately below the inferior angle of the scapula. The body fat percentage (BFP) estimate was calculated by a formula presented by Slaughter et al.[27]:

For boys, BFP = 0.783 × (subscapular SFT [mm] + triceps SFT [mm]) + 1.6

For girls, BFP = 0.586 × (subscapular SFT [mm] + triceps SFT [mm]) + 9.7

Waist circumference (WC) was measured three times at the end of gentle expiration using a flexible tape, midway between the lowest rib and the superior border of the iliac crest[19]. BMI was calculated as weight (in kilograms) divided by height (in meters) squared. Blood pressure (BP) was measured with a standard mercury sphygmomanometer after the subjects had rested at least 10 minutes (min). Systolic BP was recorded at the appearance of sounds, and diastolic BP was recorded at the disappearance of sounds.

Blood samples were obtained by venipuncture at 0800 after an overnight fast. All children were assessed for levels of fasting serum total high-density lipoprotein (HDL) and low- density lipoprotein (LDL) cholesterol, triglycerides, plasma glucose, and insulin. The estimate of IR was calculated by a homeostasis model assessment (HOMA-IR) score, as described by Matthews et al.[28]:

HOMA-IR = fasting plasma insulin level (μU/ml) × fasting plasma glucose level (mmol/L)/22.5

After clotting, the serum was separated and immediately analyzed. Plasma concentrations of glucose, total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides were measured using an Olympus 2700 Analyzer (Olympus Diagnostica GmbH, Hamburg, Germany). Insulin levels were measured with the Roche Modular Analytics E-170 immunoassay (Roche Diagnostics, Indianapolis, IN, USA).

Ultrasound imaging: The same sonographer, who was blinded to the participants' laboratory values and risk factor levels, conducted all of the examinations. Scans were obtained at rest; the subjects lay quietly for 10 min before the first scan. The participants were examined in the supine position. High-resolution B-mode ultrasonography of the right common carotid artery was performed with a GE Logic 9 Ultrasound Imager (Milwaukee, WI, USA) with a 14-MHz linear transducer. Longitudinal images of the common carotid artery were obtained by combined B-mode and color Doppler ultrasound examinations. The IMT of the common carotid artery far wall was measured with the electronic calipers of the machines, as previously described[29]. On a longitudinal, two-dimensional ultrasound image of the carotid artery, the posterior wall of the carotid artery was displayed as two bright white lines separated by a hypoechogenic space. The IMT was assessed at the far wall as the distance between the interface of the lumen and intima (first echogenic line) and the interface between the media and adventitia (second echogenic line). The mean carotid artery IMT was calculated for each child as the average of three consecutive measurements of the maximum far wall thickness obtained from the common carotid artery 10 mm below the carotid bulb.

The diagnosis of fatty liver was based on the results of abdominal ultrasonography, which was conducted by trained technicians with a GE Logic 9 Ultrasound Imager and a 5-MHz convex transducer. Of four known criteria (hepatorenal echo contrast, liver brightness, deep attenuation, and vascular blurring), the participants were required to have hepatorenal contrast and liver brightness to be given a diagnosis of NAFLD[30,31]. Abdominal ultrasonography was applied only to obese children.

Statistical methods

Data are expressed as mean ± SD. Differences between the subject characteristics in the obesity and control groups were analyzed with the independent-sample *t*-test. Correlation was assessed using Pearson's test (r). Relationships between IMT and constant variables were examined after adjusting for weight, BMI, WC, BFP, insulin, HOMA-IR, fasting glucose, systolic and diastolic BP, total cholesterol, triglycerides, and LDL cholesterol using general linear regression models (backward analysis). Differences were deemed significant at $p<0.05$. All statistical analysis was performed using the Statistical Package for Social Sciences (SPSS/ Windows version 11.5; SPSS, Inc., Chicago, IL, USA).

Results

The study population characteristics are shown in Table I. The obesity and control groups showed no significant difference in terms of gender composition, age, height, and pubertal/prepubertal stage. Subjects in the obese group had a significantly higher body weight, BMI, systolic BP, SFT, BFP, and WC. Total cholesterol, LDL cholesterol, fasting glucose, fasting insulin, and HOMA-IR levels were significantly elevated in obese children. HDL cholesterol, triglycerides and diastolic BP were not different between the two groups. The obese group had significantly higher carotid artery IMT than did the controls (0.49 ± 0.05 versus 0.40 ± 0.02 mm; $p<0.001$).

Table II displays the correlations between carotid artery IMT and other measurements in obese children. When IMT was considered as a continuous variable in the whole population of obese children, it was positively correlated in the univariate analysis with WC ($r = 0.58$, $p<0.001$), weight ($r = 0.55$, $p<0.001$), BMI ($r = 0.57$, $p<0.001$), triceps SFT ($r = 0.52$, $p<0.001$), subscapular SFT ($r = 0.46$, $p<0.001$), height ($r = 0.45$, $p<0.001$), age ($r = 0.41$, $p<0.001$), BFP ($r = 0.40$, $p<0.001$), fasting insulin level ($r = 0.31$, $p=0.001$), HOMA-IR ($r = 0.31$, $p=0.001$), triglycerides ($r = 0.21$, $p=0.027$), and systolic BP ($r = 0.19$, $p=0.04$). No significant relationships were found between carotid artery IMT and diastolic BP, total cholesterol, LDL cholesterol, HDL cholesterol, or fasting glucose level.

Table I. Characteristics of the Study Population

	Obese children (n:104)	Control group (n:30)	p
Age (y)	9.3±2.5	9.3±2.8	0.95
Gender (girl/boy)	39/65	11/19	0.93
Pubertal state (prepubertal/pubertal)	57/47	16/14	0.88
Weight (kg)	50.8±15.5	31.1±10.3	<0.001
Height (cm)	139.1±15.2	132.9±14.5	0.052
BMI (kg/m^2)	25.5±2.8	17.5±2.9	<0.001
WC (cm)	84.7±10.1	73.6±7.8	<0.001
Triceps SFT (mm)	26.7±4.67	14.7±2.2	<0.001
Subscapular SFT (mm)	28.29±5.37	15.9±2.4	<0.001
BFP (%)	43.5±8.1	25.8±3.2	<0.001
Systolic BP (mmHg)	114.9±6.7	109.3±10.8	0.001
Diastolic BP (mmHg)	69.4±8.1	70.5±5.7	0.515
Total cholesterol (mg/dl)	168.6±35.8	131.9±16.8	<0.001
LDL cholesterol (mg/dl)	97.6±33.4	70.0±17.8	<0.001
HDL cholesterol (mg/dl)	47.4±8.5	45.1±5.8	0.16
Triglycerides (mg/dl)	108.28±57.7	91.8±51.4	0.16
Fasting glucose (mg/dl)	92.5±8.4	82.4±6.2	<0.001
Fasting insulin (IU/ml)	13.0±7.2	6.0±2.2	<0.001
HOMA-IR	2.9±1.8	1.22±0.4	<0.001
Carotid IMT (mm)	0.49±0.05	0.40±0.02	<0.001

BMI: Body mass index. WC: Waist circumference. SFT: Skinfold thickness. BFP: Body fat percentage. BP: Blood pressure. LDL: Low-density lipoprotein. HDL: High-density lipoprotein. HOMA-IR: Homeostasis model assessment-insulin resistance. IMT: Intima-media thickness.

In the linear logistic regression analysis, WC was the only parameter significantly associated with increased carotid IMT (β: 0.589, p<0.001).

Non-alcoholic fatty liver disease (NAFLD) was diagnosed in 21 obese children (20.2%). However, 83 obese children (79.8%) were not diagnosed with NAFLD by the ultrasonographic examinations. The obese children with NAFLD had significantly higher carotid artery IMT than did the other obese children (0.54 ± 0.04 vs. 0.48 ± 0.05 mm; p<0.001). Furthermore, subjects in the obese group with NAFLD had a significantly higher weight, insulin level, HOMA-IR, BMI, SFT, BFP, and WC (p<0.05) than those without NAFLD.

Discussion

Enhanced carotid IMT is an established marker for early, preclinical atherosclerosis. Increased carotid artery IMT has been previously demonstrated in children with familial hypercholesterolemia, type 1 diabetes, and hypertension[32-34]. Many studies have shown increased carotid IMT in obese children when compared to healthy subjects. In these studies, different factors were correlated with increased carotid IMT[10-14]. Reinehr et al.[12] reported that BMI, BFP, BP, fasting glucose, and high-sensitive C-reactive protein correlated with increased carotid IMT. Atabek et al.[13] showed that IR is an independent risk factor for increased carotid artery IMT in obese children. In our study, increases in carotid IMT correlated with WC, weight, BMI, triceps SFT, subscapular SFT, height, age, BFP, fasting insulin level, HOMA-IR, triglycerides, and systolic BP. No significant relationships were observed between carotid artery IMT and diastolic blood pressure, total-LDL-HDL cholesterol levels, or fasting glucose level. In the present study, serum cholesterol levels in obese children were significantly higher than in healthy subjects; however, we did not find a significant relationship between carotid artery IMT and cholesterol levels. This

Table II. Relationship Between Carotid Artery Intima-Media Thickness and Related Cardiovascular Risk Factors in Obese Children

Variables	r	p
WC	r=0.58	p<0.001
Weight	r=0.55	p<0.001
BMI	r=0.57	p<0.001
Triceps SFT	r=0.52	p<0.001
Subscapular SFT	r=0.46	p<0.001
Height	r=0.45	p<0.001
Age	r=0.41	p<0.001
BFP	r=0.40	p<0.001
Insulin	r=0.31	p=0.001
HOMA-IR	r=0.31	p=0.001
Triglyceride	r=0.21	p=0.027
Systolic blood pressure	r=0.19	p=0.044

WC: Waist circumference. BMI: Body mass index. SFT: Skinfold thickness. BFP: Body fat percentage. HOMA-IR: Homeostasis model assessment-insulin resistance.

might be due to the fact that our subjects did not have very high lipid levels as do those with familial hypercholesterolemia.

The association between WC and IMT has been rarely studied in obese children. Recently, Beauloye et al.[14] showed that adiponectin levels are associated with increased IMT. In that study, WC was not correlated with IMT; however, Hassinen et al.[35] showed that increased WC was associated with increased carotid IMT in elderly women. Maffeis et al.[36] reported that WC in obese girls was independently associated with certain cardiovascular risk factors. In our study, we showed that WC is an independent risk factor for increased IMT.

In this study, we demonstrated the effect of WC on carotid IMT in obese children. Abdominal obesity may be a better predictor than overall obesity for the risk of cardiovascular disease, and WC is a simple, yet effective, surrogate measure of abdominal obesity[19]. BMI is used as an indicator of overall adiposity, whereas WC has been advocated as an indicator of central obesity because it is a good predictor of abdominal fat and is related to the development of cardiovascular diseases, type 2 diabetes mellitus, and premature death[20,21]. Furthermore, in our study, the degree of obesity and the combination of classic cardiovascular risk factors (IR, BP, hypertriglyceridemia) appeared to explain, at least in part, the effect of adiposity on carotid IMT. We conclude that abdominal obesity plays an important role in the development of atherosclerosis.

For a long time, hepatic steatosis was considered a benign manifestation with little or no clinical significance, but this idea has changed recently. Abdominal obesity, type 2 diabetes, IR, hypertension, and dyslipidemia are typical components of metabolic syndrome (MetS) that coexist as pathological conditions frequently associated with NAFLD. This opinion strongly supports the notion that NAFLD may be the hepatic manifestation of MetS. The importance of NAFLD and its relationship with MetS is now increasingly recognized, and this has stimulated an interest in the possible role of NAFLD in the development of cardiovascular disease[38]. Recent cross-sectional studies have repeatedly demonstrated a marked increase in carotid artery IMT in adult patients with NAFLD[24,25]. Pacifico et al.[39] also showed that NAFLD is a risk factor for increased carotid IMT in obese children. In our study, we showed that obese children with NAFLD had increased carotid IMT values compared to obese children without NAFLD. However, we did not find evidence to support that NAFLD is an independent risk factor for atherosclerosis, because our NALFLD group had higher insulin, WC and BMI levels, which are also associated with increased carotid IMT.

Although the higher risk for cardiovascular disease associated with NAFLD might well be

explained by the close association of NAFLD and MetS components[36], the possible biological mechanisms linking NAFLD and accelerated atherosclerosis are still poorly known. NAFLD in its more advanced form might act as a stimulus for further increased IR and dyslipidemia, leading to accelerated atherosclerosis[40,41]. Another possible underlying mechanism linking NAFLD and atherosclerosis may be increased oxidative stress and chronic inflammation[41]. Decreased concentrations of adiponectin, an adipose-secreted cytokine with antiatherogenic properties, may represent another possible underlying mechanism linking NAFLD and atherosclerosis[43].

Our study had some limitations. We estimated BFP with SFT, but this method is not the best way to determine BFP. Furthermore, a liver biopsy, not ultrasonograpy, is the gold standard to diagnose NAFLD. However, biopsy is an invasive and expensive process. We could not determine any inflammatory markers secreted from adipose tissue, which might provide data to explain the association between abdominal obesity and atherosclerosis. Furthermore, the number of controls (normal-weight children) was low compared with the obese group.

Our results suggest that abdominal obesity may have an important role in the pathogenesis of early atherosclerosis in obese children. Children with abdominal obesity are at increased risk for atherosclerosis, and WC can be used as a parameter for determining the risk of atherosclerosis in children with obesity. NAFLD may also be a risk factor for atherosclerosis in obese children.

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