Preclinical Changes in the Mechanical Properties of Abdominal Aorta in Obese Children

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Obesity in childhood has been associated with the development of early cardiovascular abnormalities. The aim of the present study was to investigate whether preclinical functional changes are detectable in the abdominal aorta of obese children. One hundred consecutively seen obese children and 50 healthy controls were studied. The groups were matched in terms of age and gender. The pulsatile wall-motion of the abdominal aorta was determined using a B-mode ultrasound technique. The following mechanical property parameters were measured or computed: lumen diastolic and systolic diameters, relative aortic strain, elastic modulus, and stiffness. Compared to controls, obese children had higher blood pressure values and higher concentrations of total cholesterol, triglycerides, insulin, and C-reactive protein. Homeostasis model assessment (HOMA) score, a parameter of insulin resistance, was significantly higher in obese children than in controls (3.2 ± 1.9 *v* 1.4 ± 0.5, *P* < .001). Aortic mechanical parameters were significantly different in obese children as compared to controls: stiffness was higher (3.00 ± 1.45 *v* 2.22 ± 0.87, *P* < .001) as was elastic modulus (0.38 ± 0.18 *v* 0.24 ± 0.10 N/m^2, *P* < .001). Obese girls with insulin resistance (ie, in the highest tertile of HOMA, >3.7) had increased aortic stiffness (3.79 ± 2.25) compared to obese girls in the lowest tertiles of HOMA (2.67 ± 1.09 , *P* = .045), even after adjustment for traditional cardiovascular risk factors (*P* = .031). The present findings suggest that preclinical changes in the aortic elastic properties are detectable in obese children. Insulin resistance seems to play an important role in the increased rigidity of the aortic wall in obese girls.

OBESITY is a major public health issue in the United States and Europe, with a rapidly increasing prevalence among children.[1] During the past 30 years, there has been a dramatic increase in the prevalence of overweight and obesity in children.[2] It is now clear that obesity in childhood causes a wide range of serious complications, increasing premature illness and death risk in adulthood.[3] In particular, overweight children are very likely to become obese adults and to develop hypertension, dyslipidemia, and type 2 diabetes.[4-6] Obesity in children has also been associated with the development of early cardiovascular abnormalities. Autopsy studies have shown that the presence of fatty streaks and fibrous plaques in the aorta and coronary arteries of children and young people was related to body mass index (BMI).[7,8]

Recent improvements in imaging technologies have allowed the study of early structural and functional atherosclerotic changes in the arteries of human beings.[9] Quantitative measurement of arterial intima-media thickness (IMT) by high resolution B-mode ultrasound is associated with traditional and nontraditional cardiovascular risk factors, including obesity.[10-12] Moreover, IMT is an independent predictor of clinical events in adult populations.[13,14] However, before atherosclerosis becomes morphologically evident by echographically demonstrable atheromatous lesions, mechanical changes of the arterial wall with functional consequences may occur.[15,16]

Although most ultrasound studies have focused on the carotid artery, because it is located rather superficially on the neck and can be easily visualized, autopsy studies have shown that the first atherosclerotic lesions actually begin to develop in the abdominal aorta of children as young as 3 years old.[17] Thus, the present study was designed to evaluate whether preclinical mechanical changes are detectable by B-mode ultrasound in the abdominal aorta of obese children. In addition, we investigated the relation between parameters of aortic distensibility and metabolic cardiovascular risk factors, including parameters of insulin resistance.

MATERIALS AND METHODS

The study population consisted of 100 obese children (60% males; mean age, 10.0 ± 2.6 years) consecutively recruited from subjects attending the Outpatient Center for Pediatric Obesity and Endocrinology of Cardarelli Hospital in Naples, Italy.

Obesity was defined as BMI greater tham the 95th percentile of the reference values stated in the Centers for Disease Control growth chart.[18]

The control group consisted of 50 children, who were relatives or friends of the obese children studied. The groups were matched in terms of age and gender. All children included in the study were nonsmokers and took no medications. None had a history of diabetes or impaired glucose tolerance (fasting blood glucose > 110 mg/dL), hypercholesterolemia (total cholesterol > 200 mg/dL), and/or hypertension (systolic blood pressure > 140 mm Hg, diastolic blood pressure > 90 mm Hg). None of the children's parents reported a history of cardiovascular disease.

Written informed consent was acquired from the subjects' parents.

Clinical and Biochemical Assessment

Tanner stage was assessed by an expert pediatrician in all subjects. Blood pressure was measured 3 times at 1-minute intervals in each subject during the ultrasound examination, using a standard mercury sphygmanometer with an appropriate cuff size, whose bladder width

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was approximately 40% of the arm circumference of the child.[19] The measurements were then averaged for statistical analyses.

Blood samples were collected at 9 AM by venipuncture from all subjects after an overnight fast. Determinations of total cholesterol, triglycerides, apolipoprotein B, and apolipoprotein A-1 were performed by classical enzymatic assay. High-density lipoprotein (HDL)-cholesterol was measured after precipitation of very-low-density lipoprotein (VLDL)- and low-density lipoprotein (LDL)-cholesterol with phosphotungstic acid. LDL-cholesterol concentration was calculated using Friedewald's formula.

An oral glucose tolerance test was performed in all subjects. After an overnight fast, they received an oral glucose load of 1.75 g/kg body weight, until a maximum of 75 g. Blood samples for determination of glucose and insulin were collected just before and 30, 60, 90, 120, and 180 minutes after the glucose load. Plasma insulin was measured by a radioimmunoassay that uses polyclonal antibodies. The estimate of insulin resistance by homeostasis model assessment (HOMA) score was calculated with the formula: fasting serum insulin (μU/mL) $\times$ fasting plasma glucose (mmol/L)/22.5, as described by Matthews et al.[20]

B-Mode Ultrasound Studies

Echographic B-mode evaluation of the abdominal aorta was done by an expert sonographer (C.A.) at the Department of Radiology and Imaging Techniques of Cardarelli Hospital, using a Duplex-Scanner (Siemens Elegra, Issaquah, WA) with a 5-MHz transducer. All children were studied after resting supine for at least 10 minutes in a dark and quiet room. The abdominal aorta was scanned from the branching site of the superior mesenteric artery to the iliac bifurcation using longitudinal and cross-sectional views to verify the absence of atherosclerotic plaques or other anatomical abnormalities. The pulsatile wall-motion of the abdominal aorta was determined at 3 to 5 cm distal to the branching site of the superior mesenteric artery, taking care to avoid exaggerated force during the abdominal scanning. Particular attention was paid to ensure vertical alignment of the aorta and to avoid drifting of the probe. Using this protocol, optimal images showing aortic pulsatility were obtained in 95 of 100 obese children and in 48 of 50 controls.

Quantitative readings of abdominal aorta ultrasound scans were performed at the end of each examination by the same sonographer, who selected the best images of the aorta wall motion and measured the systolic and diastolic diameters for 5 consecutive cardiac cycles, using the caliper of the instrument. Then the measures were averaged for statistical analyses. In particular, to measure systolic diameters, the images were reviewed frame by frame on the monitor and the maximum systolic expansion frozen to allow precise measurement of the diameter. In the same way, the diastolic diameter was estimated as the mean of the minimal values of aortic lumen diameters during the same 5 cardiac cycles.

The following mechanical property parameters of the abdominal aorta were measured or computed from echographic and pressure measurements: lumen diastolic diameter; lumen systolic diameter; relative aortic strain, which represents the systolic expansion in diameter normalized for the minimum diastolic diameter: (systolic diameter $-$ diastolic diameter)/diastolic diameter; elastic modulus (Em), defined as the arterial pulse pressure divided by strain: 133.3 $\times$ (systolic blood pressure $-$ diastolic blood pressure)/strain; and stiffness (β), defined as the natural logarithm of the ratio of systolic blood pressure to diastolic blood pressure divided by arterial strain. A previous study from our group performed in hypercholesterolemic children indicated that the ultrasound method described is sufficiently sensitive to detect differences in aortic elastic properties. [15]

To evaluate the reproducibility of vascular measurements in the present analysis, ultrasound scans were performed by the same observer in 21 participants on 2 different occasions, 1 to 7 days apart. For aortic systolic diameter, the intraobserver coefficient of variation in replicate blind determination was 1.5% and 2.2% for diastolic diameters.

Table 1. Clinical and Biochemical Parameters in Obese Children and Controls

	Obese (n = 95)	Controls (n = 48)	*P*
Age (yr)	10.0 ± 2.6	10.2 ± 2.2	.58
Weight (kg)	57.0 ± 16.6	35.4 ± 9.3	.001
Height (cm)	142.8 ± 14.5	140.1 ± 13.8	.29
Systolic BP (mm Hg)	120.1 ± 14.8	100.8 ± 12.4	.001
Diastolic BP (mm Hg)	75.9 ± 7.4	66.0 ± 7.8	.001
Total cholesterol (mg/dL)	163.8 ± 28.1	153.9 ± 19.8	.02
Triglycerides (mg/dL)	79.8 ± 35.9	60.2 ± 20.4	.001
Fasting glucose (mg/dL)	81.9 ± 9.1	78.7 ± 8.6	.05
Fasting insulin (μU/mL)	16.0 ± 10.6	7.2 ± 2.0	.001
HOMA score	3.2 ± 1.9	1.4 ± 0.5	.001
C-reactive protein (μg/L)	4.5 ± 2.4	3.5 ± 0.3	.001

NOTE. Values are means ± SD. To convert the value for triglycerides to millimoles per liter, multiply by 0.0113; to convert the value for cholesterol to millimoles per liter, multiply by 0.02586, to convert the value for glucose to millimoles per liter, multiply by 0.05551.

Abbreviations: BMI, body mass index; BP, blood pressure; HOMA, homeostasis model assessment.

Statistical Analyses

Statistical analyses were performed using the Statistical Package for Social Sciences (SPSS version 11.0, SPSS Inc, Chicago, IL). The results are reported as means ± SD, unless otherwise indicated. Comparisons between obese children and controls were performed using independent-sample Student's *t* tests. Analysis of covariance (ANCOVA) was used to evaluate the presence of confounding variables in the relationship between obesity status and vascular parameters.

RESULTS

The clinical characteristics of the study groups are presented in Table 1. Years of education of children parents were similar in the 2 groups (mean ± SD, 8.9 ± 3.0 in obese *v* 8.5 ± 3.2 years in the control group, $P = .45$). Compared to controls, obese children had higher blood pressure values and higher concentrations of total cholesterol, triglycerides, insulin, and C-reactive protein. HOMA, a parameter of insulin resistance, was significantly higher in obese children than in controls.

Elastic modulus and stiffness were both significantly higher in obese children than in controls, and this difference was present even after dividing the entire group into boys and girls (Table 2).

In univariate analyses, we could not find any association between aortic mechanical parameters and cardiovascular risk factors, nor did we find any association between aortic parameters and indexes of insulin resistance.

However, obese girls (n = 13) in the highest tertile of HOMA (>3.7) had significantly greater aortic stiffness (3.79 ± 2.25) than obese girls (n = 25) in the lowest 2 tertiles of HOMA (2.67 ± 1.09; $P = .045$), even after adjustment for traditional cardiovascular risk factors (age, total cholesterol, and triglycerides, $P = .031$). Statistical adjustment for fasting blood glucose was not done because it is one of the parameters used to calculate HOMA; moreover, adjustment for blood

Table 2. Mechanical Properties of the Abdominal Aorta in Obese Children and Controls

	Entire Group			Boys			Girls		
	Obese (n = 95)	Controls (n = 48)	*P*	Obese (n = 57)	Controls (n = 27)	*P*	Obese (n = 38)	Controls (n = 21)	*P*
DD	9.32 ± 1.88	8.91 ± 1.97	.22	9.40 ± 1.95	9.58 ± 1.90	.68	9.22 ± 1.79	8.03 ± 1.75	.017
SD	10.99 ± 2.41	10.73 ± 2.02	.51	11.05 ± 2.41	11.49 ± 1.82	.40	10.91 ± 2.43	9.75 ± 1.86	.063
STRAIN	0.18 ± 0.07	0.22 ± 0.09	.004	0.17 ± 0.06	0.21 ± 0.08	.029	0.18 ± 0.08	0.22 ± 0.10	.075
EM	0.38 ± 0.18	0.24 ± 0.10	.001	0.38 ± 0.18	0.25 ± 0.12	.001	0.39 ± 0.20	0.23 ± 0.09	.001
STIF	3.00 ± 1.45	2.22 ± 0.87	.001	2.97 ± 1.32	2.21 ± 0.97	.010	3.05 ± 1.64	2.23 ± 0.75	.011

Abbreviations: DD, diastolic diameters (mm); SD, systolic diameters (mm); EM, elastic modulus (N/m^2); Stif, stiffness.

pressure was not done when comparing stiffness index because blood pressure is included in the index. Similar results were found using fasting insulin as an index of insulin resistance: obese girls in the highest tertile of fasting insulin (>18 μU/mL) had higher values of stiffness (4.11 ± 2.25) than obese girls in the lowest tertiles (2.50 ± 0.84, $P = .003$).

DISCUSSION

Epidemiological studies have shown that obesity in childhood predicts not only obesity in adulthood,[21] but also an increased risk of cardiovascular morbidity and mortality.[22,23] Furthermore, postmortem studies suggested that obese children were at increased atherosclerotic risk.[7,8,24]

In recent years, the development of noninvasive methods has allowed the detection of in vivo abnormalities in arterial structure and function in childhood and adolescence.[15,16,25-27]

In the present study, using high-resolution B-mode ultrasound, we demonstrated early changes in the mechanical properties of the aortic wall, as defined by increased stiffness and elastic modulus, in obese children. Our data are consistent and complement a recent observation of Tounian et al, who reported decreased common carotid distensibility and endothelium-dependent brachial arterial reactivity in 48 children with severe obesity.[28]

Modifications in mechanical aortic parameters in obese children could be due to a rearrangement of the wall material or to an impairment of endothelial function, which is partly responsible for smooth muscle tone and mechanical properties of the arterial wall through the release of vasoactive substances.[29,30] Furthermore, even though stiffness is considered relatively independent of blood pressure, we cannot exclude that higher blood pressure was an important factor conditioning the higher aortic stiffness in obese children.

In the obese girls, the higher tertile of serum fasting insulin concentrations and of HOMA were associated with significantly higher values of aortic stiffness and elastic modulus as compared to the lower tertiles. This association was present even after adjustment for traditional cardiovascular risk factors. To our knowledge, this is the first demonstration of an association between higher arterial stiffness and indexes of insulin resistance in obese children, even though confined only to girls. Fasting serum insulin concentrations were significantly associated with indexes of carotid stiffness in nondiabetic participants in the Atherosclerosis Risk in Communities (ARIC) study and this association was slightly stronger among obese people than among their leaner counterpart.[31] In univariate regression analyses, Tounian et al found no association between parameters of stiffness and fasting insulin concentrations and area under the curve of insulin concentration versus time during the oral glucose tolerance test.[28] However, their sample size was relatively small and no analysis was reported for different genders.

We cannot explain why the association of indexes of insulin resistance with aortic stiffness is present only in the female gender in obese children; it could be due to a different process of arterial remodeling in obese girls and in obese boys, with a more important role of insulin in influencing this process in the female gender.

In conclusion, the present study demonstrates an increased stiffness of abdominal aorta in obesity in children and suggests that the joint effect of insulin resistance and obesity can have a considerable impact on preclinical arterial changes and could play an important role in the early pathophysiology of macrovascular disease, at least in the female gender.

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