The mechanical properties and stiffness of aorta in obese children

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Obesity in children has also been associated with the development of early cardiovascular abnormalities. The aim of this study was to investigate the relationship between aortic stiffness and some risk factors in obese children. Sixty obese children and 60 age- and sex-matched healthy controls were assessed. The mechanical property parameters were measured or computed: lumen diastolic and systolic diameters, aortic strain and elastic modules. Compared to controls, obese children had altered stiffness values of the aorta, whereas strain was not different. Compared to controls, obese children had higher systolic and diastolic blood pressure values. Insulin level, homeostasis model assessment (HOMA) score, and total cholesterol, triglycerides, low-density lipoprotein (LDL), and leptin levels were significantly higher, while adiponectin, high-density lipoprotein (HDL) levels and quantitative insulin sensitivity check index (QUICKI) scores were significantly lower in obese children than in controls. Obesity in children increases aortic stiffness, which suggests that the joint effect of insulin resistance, serum leptin and adipokine levels and obesity can have a considerable impact on preclinical arterial changes and could play an important role in the early pathophysiology of macrovascular disease.

Key words: obesity, aortic stiffness, children, echocardiography.

It is well known that obesity in childhood causes a wide range of serious complications, increasing premature illness and death risk in adulthood.[1] In addition, overweight children are very likely to become obese adults and to develop hypertension, dyslipidemia and type 2 diabetes.[2,3] Obesity in children has also been associated with the development of early cardiovascular abnormalities. Previous 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).[4,5] Therefore, screening for early detection of vascular changes may play an important role in childhood obesity. Recent studies have shown that measurement of aortic strain and distensibility helps in the early detection of arteriosclerosis.[6,7] Two-dimensional transthoracic echocardiography (2DE) is a valuable method for the assessment of the aortic stiffness index, as a good characteristic of arterial elasticity.[8,9] The aim of this study was to investigate the relationship between aortic stiffness and some risk factors in obese children.

Material and Methods

Study Population

Sixty obese children (30 male/30 female) followed by the Department of Pediatrics of Adnan Menderes University were enrolled in the study. Ages ranged from 5 to 15 years (mean: 10.2 ± 3.0 years) and weight from 25.5 to 124 kg (mean: 62.9 ± 21.4 kg). BMI was calculated as weight (kg) / height (m^2). We considered children to be obese if their BMI exceeded the age-and sex-specific cut-off points proposed for children by Cole et al.[10] The control group consisted of 60 age- and sex-matched healthy children,

selected from subjects of the same age with normal growth and development. All children included in this study were nonsmokers and took no medications. Subjects with valvular or congenital heart disease, left ventricular ejection fraction <55%, and conduction or rhythm disturbances were also excluded. All study procedures were approved by the ethics committee at Adnan Menderes University, and written informed consent was obtained from the parents.

Clinical and Laboratory Assessment

After clinical and demographic data recording, systolic and diastolic blood pressures (Ps and Pd, respectively) were measured in the supine position with a mercury cuff sphygmomanometer with an appropriate cuff size from the right arm after 15 minutes (min) of rest. The first and the fifth Korotkoff sounds were taken for the Ps and Pd. The average of three consecutive measurements was accepted as the blood pressure measurement.

Blood samples were collected at 9 a.m. by venipuncture from all subjects after an overnight fast. Determinations of blood

Table I. Clinical, Biochemical and Echocardiographic Characteristics of the Study Group.

	Obese children (n=60)	Control group (n=60)	p
Age (years)	10.2 ± 3.0	10.3 ± 3.0	0.92
Gender (Male/Female)	30/30	30 / 30	1
Weight (kg)	62.9 ± 21.4	37.1 ± 13.7	< 0.001
Height (cm)	145.5 ± 16.2	143.9 ± 18.6	0.61
BMI (kg/m^2)	28.7 ± 17.1	17.1 ± 2.5	< 0.001
Systolic BP (mmHg)	105.7 ± 10.4	95.2 ± 7.7	< 0.001
Diastolic BP (mmHg)	67 ± 5.3	62.9 ± 6.4	< 0.001
Fasting glucose (mg/dl)	89.5 ± 8.0	88.6 ± 7.6	0.54
Fasting insulin (μU/ml)	6.6 ± 2.6	4.2 ± 2.0	< 0.001
HOMA score	1.4 ± 0.5	0.9 ± 0.5	< 0.001
QUICKI score	0.36 ± 0.02	0.39 ± 0.13	< 0.001
Total cholesterol (mg/dl)	131.1 ± 18.2	94.5 ± 10.3	< 0.001
Triglycerides (mg/dl)	85.5 ± 16.1	63.2 ± 16.6	< 0.001
HDL (mg/dl)	40 ± 7.3	52 ± 8.3	< 0.001
LDL (mg/dl)	98 ± 6.5	72 ± 11.4	0.01
Leptin (ng/ml)	16.2 ± 14.5	9.0 ± 10.2	0.002
Adiponectin (μg/ml)	71.7 ± 42.3	89.2 ± 26.7	0.008
Echocardiographic findings			
EF (%)	72.4 ± 5.9	73.6 ± 4.9	0.22
FS (%)	36.2 ± 2.9	36.8 ± 2.4	0.19
E/A	1.6 ± 0.1	1.5 ± 0.1	0.18
IVSt (cm)	1.17 ± 0.2	0.9 ± 0.10	< 0.001
LVPWt (cm)	1.0 ± 0.1	1.3 ± 3.7	0.54
LVEDD (cm)	0.7 ± 0.1	0.6 ± 0.08	< 0.001
Aortic stiffness parameters			
S	0.5 ± 0.2	0.5 ± 0.1	0.10
Ep	102 ± 45	54.8 ± 11	< 0.001
Ep*	1.6 ± 0.8	0.82 ± 0.1	< 0.001

BMI: Body mass index. BP: Blood pressure. HOMA: Homeostasis model. QUICKI: Quantitative insulin sensitivity check index. HDL: High-density lipoprotein. LDL: Low- density lipoprotein. EF: Ejection fraction. FS: Fractional shortening. E: Early diastolic peak. A: Late diastolic peak. IVSt: Interventricular septum thickness. LVPWt: Left ventricular posterior wall thickness. LVEDD: Left ventricular end diastolic diameter. S: Aortic strain. Ep: Pressure strain elastic modules. Ep*: Normalized pressure strain.

glucose, total cholesterol and triglycerides were performed by enzymatic assay. The cholesterol content of lipoprotein fractions was measured on lipoproteins separated by sequential ultracentrifugation.[11] Plasma insulin was measured by radioimmunoassay using polyclonal antibodies. The degree of insulin resistance (IR) was determined with the use of a homeostatic model (homeostasis model assessment [HOMA]).[12] HOMA score was calculated as the product of the fasting plasma insulin level (in microunits per milliliter) and the fasting plasma glucose level (in millimoles per liter), divided by 22.5. The quantitative insulin sensitivity check index (QUICKI index) (1/log insulin + log glycemia in mg/dl) was also calculated for IR. Plasma adiponectin concentrations were determined using a validated sandwich enzyme-linked immunosorbent assay (ELISA) using an adiponectin-specific antibody as described previously.[13] Serum leptin level was also measured by ELISA method.

Echocardiographic Assessment

Echocardiographic evaluation was performed in all cases at rest and on clinically stable, supine patients with a Philips HD11 XE system using a 3.5 MHz transducer by the same cardiologist. Measurements were determined with standard techniques in accordance with the recommendations of the American Society of Echocardiography.[14] In the examination, myocardial and valvar motion, as well as anatomical substrates of flow abnormalities were evaluated. The diameter of the abdominal aorta, systolic functions (ejection fraction [EF] and fractional shortening [FS]) and diastolic functions (early (E) and late (A) diastolic peak flow velocities, and E/A ratio) were measured using two-dimensional, M-mode, color Doppler echocardiography. Interventricular septum (IVSt), left ventricular posterior wall thickness (LVPWt) and left ventricular end diastolic diameter (LVEDD) were recorded. The aortic diameter was measured at maximum systolic expansion (Ds) and minimum diastolic expansion (Dd). All aortic measurements were made as previously described by Lacombe et al.[15] and Okubo et al.[16] Aortic strain (S) was calculated from the changes in aortic diameter as measured by echocardiography using the formula (S = (Ds-Dd)/Dd). Pressure strain elastic modulus (Ep) was calculated from S, and the changes in brachial artery pressure were determined by the formula (Ep=(Ps-Pd)/S). Pressure strain (Ep*), normalized by diastolic pressure, was calculated using the formula (Ep* = Ep/Pd). While S is the mean strain

Table ll. Correlation between Anthropometric, Biochemical and Echocardiographic Features in Obese Children.

	Strain (S)		Pressure strain elastic modulus (Ep)		Normalized pressure strain (Ep*)	
	r	p	r	p	r	p
BMI (kg/m^2)	0.21	0.02	0.28	0.002	0.24	0.007
Systolic BP (mmHg)	0.45	< 0.001	0.03	0.74	-0.074	0.42
Diastolic BP (mmHg)	0.33	< 0.001	-0.40	< 0.001	-0.53	< 0.001
Fasting glucose (mg/dl)	0.03	0.72	0.04	0.67	0.98	< 0.001
Fasting insulin (μU/ml)	0.05	0.58	0.25	0.006	0.24	0.008
HOMA score	0.05	0.53	0.23	0.01	0.22	0.01
QUICKI score	-0.06	0.53	-0.13	0.13	-0.12	0.16
Total cholesterol (mg/dl)	0.08	0.38	0.33	< 0.001	0.32	< 0.001
Triglycerides (mg/dl)	-0.002	0.98	0.28	0.001	0.29	0.001
HDL (mg/dl)	0.09	0.30	-0.41	< 0.001	-0.40	< 0.001
LDL (mg/dl)	-0.15	0.08	0.49	< 0.001	0.46	< 0.001
Leptin (ng/ml)	-0.03	0.73	0.10	0.25	0.10	0.25
Adiponectin (μg/ml)	-0.05	0.59	0.11	0.20	0.10	0.26

BMI: Body mass index. BP: Blood pressure. HOMA: Homeostasis model. QUICKI: Quantitative insulin sensitivity check index. HDL: High-density lipoprotein. LDL: Low- density lipoprotein.

of the aortic wall, Ep and Ep* are the mean stiffness of the aorta. Whereas S and Ep* are dimensionless ratios, Ep has the dimension newtons per square meter (i.e. force/unit area).

Statistical Analysis

The data were analyzed using the Statistical Package for the Social Sciences (SPSS) 15.0 for Windows evaluation version. The differences between the groups were explored using the Student's t-test and the Mann-Whitney U test. Differences in proportions between groups were assessed for statistical significance using the chi-square test. Pearson's correlation coefficients were used to investigate the associations between anthropometric, biochemical features and echocardiographic features. A p value of less than 0.05 was considered to be significant.

Results

The clinical data, biochemical characteristics, echocardiographic findings, and aortic measurements of the 60 obese children and 60 healthy controls are shown in Table I. All groups were the same age and gender. BMI values in the obese and control groups were found to be 28.7 ± 17.1 and 17.1 ± 2.5 kg/m^2, respectively ($p<0.001$). Compared to controls, obese children had higher systolic and diastolic blood pressure values. Insulin level, HOMA score, total cholesterol, triglycerides, low-density lipoprotein (LDL), and leptin levels were significantly higher, while high-density lipoprotein (HDL), adiponectin levels and QUICKI scores were significantly lower in obese children than in controls.

Systolic (EF, FS) and diastolic (E/A) functions were not different between the obese patients and the control group. However IVSt and LVEDD were significantly larger in obese children than controls (Table I). Both Ep and Ep* values showed significant differences between the obese children and the control group, whereas S was not significantly different. The correlation coefficients between the anthropometric, biochemical values and aortic stiffness parameters in obese children are shown in Table II. A moderate correlation was found between Ps, Pd, total cholesterol, HDL, and LDL values and aortic stiffness parameters.

Discussion

This study has shown that aortic stiffness is altered among children with obesity. The results demonstrate that systolic and diastolic aortic diameters increase with obesity, and obese children have enlarged aortic diameters, suggesting early vascular remodelling. Our findings are in agreement with previous results showing that obesity is associated with structural and functional elastic abnormalities.

Increased arterial stiffness is an important risk factor and predictor of cardiovascular mortality in a variety of diseases.[17-19] 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.[20,21] There are numerous techniques for assessing the early stages of vascular disease and stiffness, including pulse wave analysis or direct measurements. Direct measurement of arterial stiffness requires invasive techniques unsuitable for routine clinical practice. It is demonstrated that pulsatile changes in ascending aortic vessel diameter can be indirectly registered during routine 2DE.[8] Aortic elastic properties rely on aortic and blood pressure data. These non-invasive measurements have been confirmed as the determinants of aortic distensibility, with a high degree of accuracy in comparison with invasive means.[8] Increase in stiffness (Ep, Ep*) and decrease in S are a consequence of more rigid arteries. Physiologically, a higher Ep and Ep* and lower S induce an increase in the pulse pressure load of the heart's left ventricle. The direct consequences are left ventricular hypertrophy, an increase in Ps and a decrease in Pd. The combination of a higher demand for coronary flow as a result of the left ventricular hypertrophy and the reduced supply due to a decrease in Pd lead to an increased susceptibility to coronary ischemia. In the present study, we showed that aortic stiffness was significantly altered in obese children compared to the control group. In addition, obese children with metabolic syndrome were associated with increased aortic stiffness.

Visceral adipocytes have an elevated lipolytic activity that results in increased free fatty acids

release in the portal vein with an accumulation (liver, pancreas, and muscles) that contributes to IR. Furthermore, other mechanisms could be involved, such as increases in circulating proinflammatory cytokines or leptin.[22,23] Indeed, high levels of leptin have been documented in individuals with obesity and found to be correlated with reduction in arterial distensibility.[23] In addition to hypothalamic receptors, receptors for leptin have been observed on the vascular endothelium and on smooth muscle cells.[24,25] Accordingly, leptin can exert receptor-mediated influence on vessel tone and growth and, in cell culture, stimulate vascular smooth muscle proliferation and migration.[26] In addition, leptin induces oxidative stress in endothelial cells, and this action triggers the transcription of oxidant-sensitive genes that participate in atherogenesis. Finally, leptin increases sympathetic nervous activity, and chronic administration of leptin was shown to increase blood pressure in several experimental models. It is possible that high levels of leptin that are observed in obesity could contribute to its adverse effects on cardiovascular health. It also has been proposed that an increase in circulating proinflammatory cytokines may contribute to the development of cardiovascular disease in obese individuals.[22,27] Adipokines are an exciting new link between obesity and IR but also obesity and cardiovascular disease, hypertension, as well as hyperlipidemia.[28] In this study, we found significantly higher leptin and lower adiponectin levels in the obese group than control group. Similarly, we found that insulin sensitivity check indexes, HOMA and QUICKI, were significantly different between obese children and the control group.

We concluded that obesity in children increases aortic stiffness, and we suggest that the joint effect of IR, serum leptin and adipokine levels and obesity can have a considerable impact on preclinical arterial changes and could play an important role in the early pathophysiology of macrovascular disease.

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