Metabolic Syndrome in Childhood Obesity

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Objectives: *We determined the frequency of metabolic risk factors and the prevalence of Metabolic Syndrome in childhood obesity.* ***Subjects****: 186 obese children (97 females and 89 males), aged 11.2 ± 2.8 (6-16) years and 98 healthy children (46 females and 52 males), aged 10.9 ± 3.2 (6-16) years were recruited for the study, as study and control groups, respectively.* ***Methods****: Subjects were evaluated for anthropometry, blood pressure (BP) and biochemical cardiovascular risk factors. Metabolic syndrome was defined in presence of ≥ 3 of the following: (i) fasting triglyceride ≥ 100 mg/dL; (ii) high density lipoprotein – cholesterol < 50 mg/dL, except in boys aged 15 to 19 years, in whom the cut-off point was 45 mg/dL; (iii) fasting glucose ≥ 110 mg/dL; (iv) waist circumference > 75th percentile for age and gender and (v) systolic BP > 90th percentile.* ***Results:*** *We found that 144 (77.4%) children in the obese group had one, two or more cardiovascular risk factors. Using a pediatric definition, the prevalence of metabolic syndrome was 2.1%. In the control group, the clustering of one, two and three risk factors was very rare.* ***Conclusion:*** *Childhood obesity is associated with increased frequency of cardiovascular risk factors and metabolic syndrome.*

Key words*: Cardiovascular risk factors, Metabolic syndrome, Obesity.*

PEDIATRIC obesity is a complex and growing global problem(1). Childhood obesity increases the risk of obesity in adulthood and is associated with cardiovascular disease (CVD) risk factors such as hypertension, diabetes mellitus, and dyslipidemia(2). The metabolic syndrome (MetS), also called insulin resistance syndrome, has been described in many ways, in part owing to the lack of a 'gold standard' diagnostic test(3). There is now consensus that insulin resistance and obesity are part of one common pathologic mechanism termed the MetS, formerly known as syndrome X and insulin resistance syndrome(4,5).

The National Cholesterol Education Program's (NCEP) Adult Treatment Panel (ATP) III has recently acknowledged the importance of insulin resistance in the etiology of CVD and has identified a number of risk factors for the development of the metabolic syndrome(6). According to the recently released guidelines of NCEP, an individual would be classified as having the metabolic syndrome if three of the five criteria were met. Together, these risk factors predispose the individual to greater risk for developing CVD and type 2 diabetes(4,5).

Ferranti, *et al.*(3) defined pediatric metabolic syndrome using criteria analogous to ATP III as ≥3 of the following: (*a*) fasting serum TG ≥100 mg/dL; (*b*) serum HDL-C <50 mg/dL, except in boys aged 15 to 19 years, in whom the cut-off point was 45 mg/dL; (*c*) fasting blood glucose ≥ 110 mg/dL; (*d*) waist circumference >75th percentile for age and gender; and (*e*) systolic BP >90th percentile for gender, age and height.

Identification of causes and/or etiological factors for the development of metabolic syndrome is important so that suitable measures can be instituted to prevent and cure the syndrome(7). We aimed to detect the frequency of cardiovascular risk factors and to investigate the prevalence of metabolic syndrome in Turkish obese children

and adolescents, using criteria analogous to ATP III.

Subjects and Methods

This prospective study was undertaken in an outpatient clinic for pediatric endocrinology in a university hospital in Turkey in 2005. The study group consisted of 186 obese children (97 females and 89 males), aged 11.2 ± 2.8 (6-16) years and the control group comprised of 98 healthy children (46 females and 52 males), aged 10.9 ± 3.2 (6-16) years. The control group was selected from subjects of same age with normal growth and development and no endocrinological problems, who were admitted to general pediatric polyclinics. Written informed consent was obtained from parents or guardians of all consecutive obese patients or healthy children who were offered the study. The same investigator performed anthropometric measurements and complete physical examination including pubertal staging, neurological, mental and dysmorphic findings. Obese subjects were included in study after the exclusion of any with endocrinological disorders or obesity syndromes. Tanner classifica-tion was used for pubertal staging(8,9). BP was measured in each subject three times by the same observer, using a mercury-gravity manometer with proper cuff size in standard conditions. BP measurements were compared with reference values prepared according to age, sex and height(10).

Anthropometry: Body weight was measured to the nearest 0.1 kg with a balance scale (Baurer, PS 07), and height was measured to the nearest 0.1 cm with stadiometer (Hyssna Limfog, AB) with subjects lightly dressed and without shoes. Body mass index (BMI) was calculated as weight (kg) divided by height square (m^2). The degree of obesity was quantified using international cut off points for body mass index for overweight and obesity by sex between 2 and 18 years, according to Cole's reference data(11).

Waist circumference (WC) was measured midway between the lateral lower rib margin and the uppermost lateral border of iliac crest, and hip circumference was measured at the widest point over the great trochanters. Both circumferences were measured in the standing position and at the end of gentle expiration(12). The waist-to-hip ratio (WHR) was calculated. All measurements were taken 3 times at each site, and the mean of 3 values was used.

ATP III uses WC as a measure of central obesity, and percentiles for age and gender have been most associated with central obesity in children across genders and races(13). We have no nomograms for WC for our population, therefore, percentiles were compared to estimated value for percentile regression for European-American children and adolescents, according to gender and age(14). If WC exceeded 75th percentile for age and gender, it was accepted as abdominal obesity.

Laboratory investigations: Blood glucose, serum insulin and lipid levels were determined from blood samples taken after an overnight fast. Glucose, total cholesterol (TC), TG measurements were performed using enzymatic assays (Instrumentation Lab, MA, USA). HDL-C was measured by a direct enzymatic assay without precipitation (Instrumentation Lab, MA, USA). Low-density cholesterol (LDL-C) was estimated by Friedewald formula. Insulin measurement was done by using solid phase chemiluminescence immunoassay. Serum TC, TG, LDL-C and HDL-C were considered high or low when they fell above or below the recommended values(15). Homeostasis model assessment for insulin resistance (HOMAIR) was estimated by using glucose (mg/dL) / insulin (mmol/L), and insulin (mmol/L) × glucose (mmol/L)/22.5 formulae, respectively(16). HOMAIR >2.5 was defined as hyperinsulinemia(16). Oral glucose tolerance test was carried out only in obese subjects, using oral glucose (1.75 g/kg ideal body weight, maximum 75 g in 250 mL of water). Categorization of glucose tolerance status was made using the World Health Organization criteria(17).

Statistical analysis: Mean values and standard deviations of the clinical and laboratory data of the children and the frequency of cardiovascular risk factors were calculated. Independent *t* test was used to analyze the significance of difference between both groups. P value of <0.05 was regarded as significant.

Results

Clinical characteristics and cardiovascular risk

TABLE I–*Clinical and Laboratory Data of the Children Enrolled in the Study (Mean ± SD)*

	Obese male (n = 89)	Obese female (n = 97)	Control male (n = 52)	Control female (n = 46)
Age (years)	11.3 ± 2.9	11.1 ± 2.8	10.9 ± 3.2	11.1 ± 3.3
BMI (kg/m^2)	28.1 ± 9.1**	27.1 ± 3.8**	18.7 ± 2.0	17.0 ± 2.8
WC (cm)	90.8 ± 10.3**	87.7 ± 10.3**	65.3 ± 8.5	63.2 ± 7.8
WHR	0.90 ± 0.9**	0.86 ± 0.08*	0.79 ± 0.5	0.75 ± 0.6
Glucose (mg/dL)	92.4 ±14.1	92.2 ± 12.8	92.1 ± 9.6	92.6 ± 8.8
Insulin (µU/mL)	15.1±18.6**	17.7 ± 15.3**	7.2 ± 3.1	6.7 ± 2.8
TC (mg/dL)	161.3 ± 34.6*	162.1 ± 30.4*	129.8 ± 28.5	132.1 ± 25.3
TG (mg/dL)	101.8 ± 57.3*	99.8 ± 46.5**	73.1 ± 18.9	73.9 ± 22.7
HDL-C (mg/dL)	40.4 ± 10.8*	38.0 ± 12.9**	51.6 ± 15.9	48.6 ± 12.5
LDL-C (mg/dL)	101.1 ± 30.0**	99.4 ± 37.0*	79.4 ± 22.0	78.6 ± 17.8
HOMAIR	3.5 ± 4.3**	3.8 ± 3.1**	1.7 ± 0.6	1.6 ± 0.7
Systolic BP (mmHg)	108.2 ± 16.1	109.0 ± 10.1	99.9 ± 9.4	102.1 ± 11.1
Diastolic BP (mmHg)	69.4 ±7.5	69.5 ± 8.0	62.8 ± 8.9	63.7 ± 6.7

* P <0.05, ** P < 0.001, obese vs control for each sex. (Biochemistry normal values were determined according to the references 3, 15, 16 and 17).

factors of the boys and girls in this study are shown in *Table I.* Gender and age characteristics of two groups were similar. BMI, WC and WHR values of the obese children were significantly higher than those of non-obese children. Serum insulin, TC, TG, HDL-C, LDL-C, HOMAIR parameters showed significant differences between obese and control children. Blood glucose and BP measurements of the two groups were not significantly different for gender.

The frequencies of cardiovascular risk factors in obese and control children are presented in *Table II.* Hypertension, hyperinsulinemia, hypercholesterolemia, hypertriglyceridemia, low HDL-C, and high LDL-C frequencies of the obese children were significantly higher than those of control group in both sexes. Elevated systolic and diastolic blood pressures were detected in 17.7% and 15.1% of obese children, respectively. Hyperinsulinemia was shown in 52.2%. There was no subject with diabetes mellitus. Impaired glucose tolerance was found only in 1 (0.5%) subject. 11.3% of the obese children had high TC, 25.8% had high TG, 36.6% had low HDL-C, and 3.7% had high LDL-C.

The prevalence of metabolic syndrome was 2.1% in obese children (*Table III*). We detected that 79.0% of the obese children had one, two or more risk factors; the rest (20.9%) were free from any risk factor. These frequencies were much lower in the control group. The clustering of one, two and three risk factors was very rare - 12.2%, 7.1% and 0%, respectively.

Discussion

The combination of cardiovascular risk factors (abdominal type of obesity, insulin resistance, hyperinsulinemia, impaired glucose tolerance, dyslipidemia, and hypertension) has been well demonstrated in adults (18-20). Childhood metabolic syndrome(Mets) promotes the development of premature atherosclerosis and significantly increases CVD risk early in life. Recently, risk factors for metabolic syndrome in obese children have been studied and described(3, 21).

Diverse definitions of pediatric metabolic syndrome have been used in various populations. The Quebec family cohort study used skinfold measurements and mean blood pressure, criteria more cumbersome for the primary pediatrician and less closely based on ATP III than the present definition(22). When metabolic syndrome was

TABLE II–*Frequency of Cardiovascular Risk Factors in Both Groups*

	Obese male (n = 89)	Obese female (n = 97)	Control male (n = 52)	Control female (n = 46)	All obese (n = 186)	All control (n = 98)
Abdominal obesity	11 (11.1%)	9 (9.3%)	–	–	20 (10.7%)	–
Systolic hypertension	17 (19.1%)**	16 (16.5%)**	2 (3.8%)	2 (4.3%)	33 (17.7%)**	4 (4 .0 %)**
Diastolic hypertension	11 (12.4%)**	17 (17.5%)**	1 (1.9%)	1 (2.1%)	28 (15.1%)**	2 (2.0%)**
Hyperinsulinemia	42 (47.2%)**	55 (56.7%)**	2 (3.8%)	4 (8.6%)	97 (52.2%)**	6 (6.1%)**
Hypercholesterolemia	14 (15.7%)**	7 (7.2%)**	1 (1.9%)	3 (6.5%)	21 (11.3%)**	4(4.1%)**
Hypertriglyceridemia	24 (27%)**	24 (24.7%)**	1 (1.9%)	4 (8.6%)	48 (25.8%)**	5 (5.1%)**
Low HDL-C	25 (28.1%)**	43 (44.3%)**	2 (3.8%)	3 (6.5%)	68 (36.6%)**	5 (5.1%)**
High LDL–C	3 (3.4%)**	4 (4.1%)**	0	2 (4.3%)	7 (3.7%)**	2 (2%)**
IGTT	–	1(1%)			1 (0.5%)	

** $P < 0.001$, obese vs control both for each sex and all children studied. (The cut-offs for labeling as high or low were determined according to the references 3, 10, 14, 15, 16 and 17).

TABLE III–*Clustering of Risk Factors in the Obese and Non-obese Children*

	Obese		Control	
	n	%	n	%
No risk factor	39	20.9	79	80.6
+1 risk factor	82	44.1	12	12.2
+2 risk factors	61	32.8	7	7.1
+3 risk factors (MetS)	3	1.6	0	0
+4 risk factors (MetS)	1	0.5	0	0
Total	186	100	98	100

defined by BMI instead of WC, lipid levels >95th percentile (or <5th percentile for HDL), and oral glucose tolerance testing, 39% of obese children in US population had metabolic syndrome(23). The metabolic syndrome definition given by Cook, *et al.*(24), based on 1992 NCEP guidelines and devised before ATP III and wide recognition of metabolic syndrome, uses more restrictive lipid and abdominal circumference cut points, which leads to lower prevalence estimates in adolescents of approximately 4%. Using a pediatric definition in our study, the prevalence of metabolic syndrome was 2.1%. These results were similar to those reported by Ferranti, *et al.*(3), who showed that the incidence of metabolic syndrome in adolescents of the American population is 1.6%. There was no significant gender difference in the frequency of metabolic syndrome in both studies.

We found 147 (79.0%) children in obese group had one, two or more cardiovascular risk factors. These results were similar to those reported by Csabi, *et al.*(21) who found that 76.7% of the obese children had one, two or three cardiovascular risk factors. Chu, *et al.*(2) reported the prevalence of two or more cardiovascular risk factors four to five times greater in obese than in non-obese children. In our study, the number of obese subjects who had two risk factors was higher than those who had three or four risk factors. This finding might make us think that cardiovascular risk factors already cluster in obese children and that the duration of childhood obesity might be somewhat short for the development of metabolic syndrome.

In our study, BP measurements did not differ significantly in both groups, but we think it is inappropriate to compare the mean BP measurements in such a group with a wide age distribution. For this reason, BP measurements were compared with reference values prepared according to age and sex. Frequencies of systolic hypertension (17.7%) and diastolic hypertension (15.1%) in the obese group were higher than those in the control group, 4% and 2%, respectively. In some studies, higher blood pressure in the obese children was found when compared with those in non-obese children(2,21, 25). Qing *et al*(26) reported that systolic, as well as diastolic blood pressure was related to BMI, and this relationship similarly existed in non-obese children.

What is Already Known

- Development of cardiovascular risk factors and metabolic syndrome has its origin in childhood.

What this Study Adds

- Using a pediatric definition in our study, based closely on ATP III, the prevalence of metabolic syndrome was 2.1% in obese children.
- Potential risk factors for cardiovascular disease are strongly associated with obesity.

WC is a less accurate but more practical and lower-risk indicator of visceral obesity than abdominal CT or MRI, and is a method used by ATP III. Fat distribution is affected differentially by puberty in girls and boys(3).

Guidelines of NCEP ATP III were based on data from white populations and major problem is the defining levels of WC. Because we have no nomograms for WC for Turkish children, measurements were compared to estimated value for percentile regression for European-American children and adolescent, according to gender and age. Although puberty is a phase of increased insulin resistance, pubertal staging might not be necessary in this study because this study only dealt with prevalence of metabolic syndrome in obese and healthy children. Otherwise, our study should be interpreted in light of these limitations.

In conclusion, we showed development of cardiovascular risk factors and metabolic syndrome has its origin in childhood and they are strongly associated with obesity. The prevention and treatment of obesity in childhood therefore have a significantly role in reducing the risk for cardiovascular disease in adulthood.

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