Metabolic syndrome in obese Turkish children and adolescents: comparison of two diagnostic models

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SUMMARY: Çizmecioğlu FM, Hatun Ş, Kalaça S. Metabolic syndrome in obese Turkish children and adolescents: comparison of two diagnostic models. Turk J Pediatr 2008; 50: 359-365.

There is no consensus on whether or not the diagnostic criteria of metabolic syndrome (MS) defined for adults [National Cholesterol Education Panel (NCEP) and World Health Organization (WHO)] can be used in childhood as well.

We aimed to compare prevalence of metabolic syndrome among obese children and adolescents using WHO and NCEP guidelines.

A total of 112 obese children and adolescents were assessed. MS was diagnosed according to both modified WHO and NCEP criteria using cut-off values for children.

Abnormal glucose homeostasis was identified in 46.6% of the subjects. Fasting glucose levels for all subjects were less than 110 mg/dl and no subjects had type 2 diabetes. Overall, dyslipidemia was present in 42.9% and hypertension in 42.9% of the subjects.

While 24% of the subjects were diagnosed as MS according to NCEP, a rate of 38.8% were diagnosed according to WHO-defined MS. There was a moderate agreement between NCEP and WHO guidelines.

More children were diagnosed as MS based on the WHO guidelines. This may lead to better monitoring for these children and prevention of their chronic diseases in the future. Therefore, we recommend using WHO guidelines in the diagnosis of MS with a specific emphasis on definition of abnormal glucose homeostasis.

Key words: metabolic syndrome, childhood and adolescence, diagnostic criteria.

Obesity and related problems have been shown to increase in adult life, but also and more importantly in childhood and adolescence. It has been reported that 10% of school children are overweight[1]. As a result of the increase in obesity, cardiovascular diseases, type 2 diabetes and metabolic syndrome (MS) seen mostly in adults have begun to become serious problems in children as well. Insulin resistance plays a key role in this metabolic process that results in chronic diseases such as type 2 diabetes and cardiovascular diseases in young adults. It has been shown that MS increases the risk of type 2 diabetes and cardiovascular diseases, and insulin resistance accounts for 46.8% of the cardiovascular diseases reported in a year in the United States[2,3].

Although the diagnostic criteria of MS are nearly the same today, the World Health Organization (WHO) and United States (US) National Cholesterol Education Program (NCEP) Adult Treatment Panel have determined some differences in these criteria[4,5]. MS components, which are abnormal glucose homeostasis, central obesity, hypertension and dyslipidemia, are defined for adults. The same parameters, with the same or different cut-off values, have also been used in children and adolescents[2,3,6,7]. However, there is no consensus on whether or not the diagnostic criteria of MS defined for adults (NCEP and WHO) can be used in childhood as well. Correct identification of the syndrome in childhood is important to prevent or reduce the high morbidity of chronic diseases

in young adults. Moreover, there are some important questions that need to be answered urgently to identify the high-risk group for MS and those who require treatment among the obese children and adolescents.

Therefore, we believe that diagnostic criteria of MS and cut-off values of these parameters need to be re-evaluated in childhood. The purpose of this study was to determine prevalence of MS among Turkish obese children and adolescents according to WHO and NCEP guidelines and to compare the rates identified by these definitions.

Material and Methods

Subjects

Subjects were children and adolescents 2-18 years of age who presented with obesity complaint to the pediatric outpatient clinic of a University hospital, between January 2002 and June 2004. Data were collected retrospectively. Subjects who had secondary or known genetic causes of obesity were excluded. A total of 112 obese (body mass index [BMI] >95th percentile) children and adolescents were assessed carefully in terms of family history, blood pressure, and skin findings such as acanthosis nigricans.

Anthropometric Assessments

Height and weight were measured using SECA stadiometer and beam balance by the same pediatric endocrinologist. Waist circumference was measured using a non-stretchable tape measure with the subject standing comfortably with his or her weight evenly distributed on both feet, and the feet about 25-30 cm apart. The measurements were taken midway between the inferior margin of the last rib and the crest of the ilium, in a horizontal plane at the end of expiration.

Subjects were evaluated according to pubertal stages. Tanner stage I was defined as pre-puberty, Tanner stage II-IV as mid-puberty and Tanner stage V as post-puberty.

Laboratory Assays

Subjects underwent standard oral glucose tolerance test (OGTT) (1.75 g/kg glucose, with the maximum of 75 g) with plasma insulin and blood glucose concentrations were measured at 0, 30, 60, 90, and 120 minutes. Fasting serum lipid concentration was measured after an 8 hour overnight fast as total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol and triglycerides. Glucose was measured by enzymatic method on AEROSET system. Coefficients of variation (CV) for within run value of serum glucose were 0.8% SD 0.76, mean 95.2 mg/dl. Plasma insulin concentration was measured by chemiluminescence enzyme immunoassay method using Immulite 1000 system (Diagnostic Product Corporation, USA). Recovery values for observed and expected and observed/expected% were 28.5, 26.5 and 108% in 280 µIU/ml and 59.7, 60.5 and 99% in 960 µIU/ml, respectively. Serum lipids were measured by enzymatic method on AEROSET system. For triglyceride, CV of within run values was 0.5% SD 0.95, mean 188.9. For total cholesterol, CV of within run values was 0.7 SD 1.84, mean 268.5. HDL cholesterol intra- and interassay CV were 2.3 and 1.6, respectively. Insulin resistance and sensitivity indexes were estimated using the Homeostasis Model Assessment (HOMA-$_{IR}$) and fasting glucose/insulin.

Definition of Metabolic Syndrome Components

Hypertension: Blood pressure was measured three times by auscultation method with appropriate cuff size after 20 minutes of rest. The average of the last two blood pressure measurements was defined as hypertension if it was >95th percentile according to their age and height percentile[8].

Obesity: Obesity was defined according to both BMI and waist circumference. BMI percentiles were calculated by Epi Info 2000 (CDC, Atlanta) packet program based on WHO/Centers for Disease Control (CDC) reference population[9]. Subjects with BMI ≥95 were defined as obese. Additionally, in order to define abdominal obesity, subjects whose waist circumferences were available and who were aged >8 years (n=66) were evaluated using cut-off values reported by Cruz et al.[10]. Abdominal obesity was accepted to be greater than cut-off point across sex and age groups.

Dyslipidemia: Abnormal fasting lipids were defined based on normative data for children across sex and age groups. Dyslipidemia was

defined if the level of triglyceride and/or total cholesterol was greater than reference values and/or HDL level was <35 mg/dl[11].

Abnormal glucose homeostasis and hyperinsulinemia: Abnormal glucose homeostasis was defined in presence of any of following criteria. Impaired fasting glucose (IFG) was defined as fasting plasma glucose ≥110 mg/dl and/or ≥100 mg/dl. We used both formerly recommended cut-off IFG value ≥110 mg/dl and the new cut-off value recommended by the American Diabetes Association (ADA) of IFG ≥100 mg/dl[12]. Glucose at 120 minutes during the standard OGTT between 140 and 200 mg/dl was defined as impaired glucose tolerance. Hyperinsulinism was defined as fasting insulin and/or peak insulin levels above cut-off values. For fasting insulin level, it was defined from any of following norms for pubertal stage: pre-pubertal (≥15 mU/L), mid-puberty (Tanner stages II-IV, ≥30 mU/L)[7], and post-pubertal (≥20 mU/L). Post-pubertal hyperinsulinism was defined according to adult WHO criteria, and cut-off value for peak insulin level was ≥150 mU/L[7,12-14].

Definition of Metabolic Syndrome

In diagnosis of MS, we assessed all subjects according to both NCEP and WHO guidelines using cut-off values for childhood across sex and age groups. Definitions of MS according to different guidelines are summarized in Table I.

According to NCEP, MS was diagnosed in the presence of any three of the following five parameters: fasting serum glucose ≥110 mg/dl, abdominal obesity, hypertension, elevated triglyceride and decreased HDL.

We modified NCEP by decreasing IFG cut-off value from 110 mg/dl to 100 mg/dl as recommended by the ADA. Other criteria for NCEP and modified NCEP were the same.

Definition of components of MS was made following modified WHO criteria adapted for children (Table II). In diagnosis of MS according to WHO guidelines, hyperinsulinism and/or impaired glucose tolerance were essential plus any two of following three criteria: BMI ≥95, hypertension and dyslipidemia (high triglyceride and/or low HDL and/or elevated total cholesterol)[7].

Table I. Diagnosis of Metabolic Syndrome According to Different Guidelines

	Obesity		Abnormal glucose homeostasis			Dyslipidemia			Hypertension
	BMI	Abdominal	IFG	IGT	Hyperinsulinismm	TG ↑	HDL ↓	T.Chol. ↑	
NCEP[a]		X	110 mg/dl	X		X	X		X
Modified NCEP[b]		X	100 mg/dl	X		X	X		X
Modified WHO[c]	X			X	X	X	X	X	X

[a] (Refs. 5,16).
[b] Modified by taking the IFG value as 100 mg/dl.
[c] (ref. 7).
NCEP: National Cholesterol Education Program. WHO: World Health Organization. BMI: Body mass index. IFG: Impaired fasting glucose. IGT: Impaired glucose tolerance. TG: Triglyceride. HDL: High-density lipoprotein. T. Chol: Total cholesterol.

Table II. Definition of Components of Metabolic Syndrome in Modified WHO Criteria Adapted for MS in Childhood

MS component	Definition
Obesity	BMI ≥95th centile
Abnormal glucose homeostasis	Any of following: a. Fasting hyperinsulinemia b. Impaired fasting glucose c. Impaired glucose tolerance
Hypertension	Systolic blood pressure ≥95th centile for age and sex
Dyslipidemia	Any of following: a. High triglycerides b. Low HDL c. High total cholesterol

MS: Metabolic syndrome. BMI: Body mass index. HDL: High-density lipoprotein.

Statistical Analysis

Data were analyzed using SPSS software version 10.0. Mann-Whitney U test and chi-square test were used to assess differences between groups. α error was 0.05 and differences between groups were significant when $p<0.05$. Kappa statistics were used for measuring agreement between the guidelines.

Results

A total of 112 children were assessed. Mean age was 11.7±3.4 decimal years (median 12, range 1.8-17.6). Forty-one percent of the patients (n=46) were male and 59% (n=66) were female. Distribution of subjects according to pubertal stages were 30.4% pre-pubertal (n=34), 33% mid-pubertal (n=37) and 36.6% (n=41) post-pubertal.

Abnormal glucose homeostasis was identified in 46.6% of the subjects (fasting hyperinsulinemia 20.5%, peak hyperinsulinism 34.8% and impaired glucose tolerance 8.9%). Fasting glucose levels for all subjects were less than 110 mm/dl, and no subjects had IFG or type II diabetes. However, in 5.4% of the subjects, fasting glucose levels were above 100 mg/dl.

Overall, dyslipidemia was present in 42.9% (low HDL 23.2%, high triglycerides 24.1% and high total cholesterol 8.9%) and hypertension in 42.9% of the subjects.

Eighteen percent of the subjects (n=20) had BMI ≥95th percentile and 82% (n=92) had BMI ≥97th percentile. Subjects who underwent waist measurement and were older than 8 years (n=66) were evaluated according to the cut-off values for waist circumference reports of Cruz et al.[10]. Eighty-nine percent of the subjects (age ≥8 years, n=59) had abdominal obesity while abdominal obesity was not observed in 12% (n=7). However, of the 7 subjects, 5 had BMI ≥97th percentile and 2 had BMI ≥95th percentile (Table III).

Table III. Percentages of Metabolic Syndrome Components

Metabolic syndrome components	%
Abnormal glucose homeostasis[a]	46.6
• fasting hyperinsulinemia[a1]	20.5
• peak hyperinsulinism[a2]	34.8
• impaired glucose tolerance (IGT)[a3]	8.9
Dyslipidemia[b]	42.9
• low HDL[b1]	23.2
• high TG[b2]	24.1
• high total cholesterol[b3]	8.9
Hypertension[c]	42.9
Obesity	
• BMI ≥95th percentile	18.0
• BMI ≥97th percentile	82.0
• Abdominal obesity[d]	89.0

HDL: High-density lipoprotein. TG: Triglyceride.
BMI: Body mass index.
Cut-off values for above criteria.
[a1] Fasting insulin level is ≥15 mU/L in pre-pubertal subjects, ≥30 mU/L in mid-puberty (Tanner stages II-IV), ≥20 mU/L in post-pubertal subjects.
[a2] Peak insulin level is ≥150 mU/L in all subjects.
[a3] IGT: Glucose at 120 minutes during the standard oral glucose tolerance test between 140 and 200 mg/dl.
[b1] HDL level was <35 mg/dl.
[b2, b3] TG and total cholesterol levels are greater than cut-off point across sex and age groups.
[c] Blood pressure is ≥95th percentile according to subjects' age and height percentile.
[d] Waist circumference is greater than cut-off points across sex and age groups.

MS Diagnosis by Different Diagnostic Models

While the prevalence of MS according to NCEP was 24%, it was 38.8% by WHO guidelines. If we define IFG level as 100 mg/dl in modified NCEP, MS prevalence increases to 30%. There was a moderate agreement between NCEP and WHO guidelines. Kappa value was 0.55 ($p<0.000$) for WHO and modified NCEP, while it was 0.43 for WHO and NCEP guidelines ($p<0.000$) (Table IV).

In Table V, MS-related parameters such as BMI, waist circumference, blood pressure, serum lipids, fasting and peak insulin levels, fasting and 120-minute glucose levels and insulin resistance indexes were compared across subjects with and without MS according to WHO guidelines. Parameters except total cholesterol, HDL and fasting glucose were statistically significant. Median $HOMA\text{-}_{IR}$ and glu^0/ins^0 values were very similar according to three models and were 4.3, 4.5 in patients with MS and 2.3, 8.9 in patients without MS, respectively. These results were consistent with other diagnostic models as well.

Metabolic syndrome presence was found to be 43% in girls and 32.5% in boys according to modified WHO guideline ($p>0.05$, chi-square test): 28.6% before puberty, 29.4% in puberty and 52.8% in post-pubertal children. Based on the cross-sectional data in this study, as puberty stage progresses, MS increases ($p=0.02$, chi-square test). Distribution of sex and puberty were similar for MS definition according to NCEP and modified NCEP (data not shown).

Discussion

The high correlation between obesity and type II diabetes has changed our approach to obesity in childhood. There is insulin resistance to some degree in obese children and particularly in adolescents. However, while some of these children develop MS and eventually type II diabetes, others may have innocent obesity not accompanied with metabolic disturbances[15]. Nevertheless, at least one cardiovascular risk

Table IV. Comparison of NCEP and WHO Guidelines in MS Diagnosis

	NCEP		Modified NCEP	
WHO	MS (-)	MS (+)	MS (-)	MS (+)
MS (-)	43 (61.4%)	5 (7.1%)	42 (58.3%)	5 (6.9%)
MS (+)	11 (15.7%)	11 (15.7%)	9 (12.5%)	16 (22.2%)
Kappa	0.43 (p=0.000)		0.55 (p=0.000)	

NCEP: National Cholesterol Education Program. WHO: World Health Organization. MS: Metabolic syndrome.

Table V. MS-Related Parameters Across Subjects With and Without MS According to WHO

	Metabolic syndrome (-)			Metabolic syndrome (+)			
	Mean±SD	Range	Median	Mean±SD	Range	Median	p
BMI (kg/m^2)	28.7±3.9	21.2-39.2	28.4	31.5±4.6	24-39	31	0.003*
WC (cm)	91±11	63-118	90	98±12	78-118	98	0.002*
BPs	116±15	80-160	115	134±18	100-180	140	0.000*
BPd	75±10	40-100	80	87±12	60-120	85	0.000*
TG (mg/dl)	106±54	21-299	105	165±88	48-324	147	0.004*
HDL (mg/dl)	41.7±7.9	26-60	42	38.8±14.2	19-81	36	0.072
TC (mg/dl)	163±26	114-216	166	165±30	122-216	169	0.821
FI (mIU/dl)	11.5±6.8	4.2-43	10.5	20.6±7.5	8.3-35	21	0.000*
FG (mg/dl)	81±9.5	56-105	81	82±11	65-102	79	0.560
PI (mIU/ml)	88±53	10-236	76	225±107	95-464	200	0.000*
†Glucose (120) (mg/dl)	108±18	73-154	108	114±26	47-146	115	0.000*
Glu^0/ins^0	8.9±4.3	2.0-17.8	7.6	4.5±1.6	2.2-7.8	4.6	0.000*
$HOMA_{IR}$	2.3±1.4	0.7-9.3	2	4.3±1.7	1.3-6.9	4.8	0.000*

*: $p<0.05$.
BMI: Body mass index. WC: Waist circumference (cm). BP: Blood pressure. TG: Triglyceride. TC: Total cholesterol. FI: Fasting insulin. FG: Fasting glucose. PI: Peak insulin. †; Glucose at 120 mins.

factor develops in 60% of overweight children and adolescents[16]. Therefore, it is important to determine MS risk in obese children. Early diagnosis of MS in childhood is essential if the progression from obesity to insulin resistance, MS and type II diabetes is considered. MS may be overlooked in children since the diagnosis is based on the criteria for adults.

In this study, when we used modified WHO criteria with cut-off values for children, prevalence of MS was 38.8%, whereas the rate was 24% when NCEP guidelines were used. In the literature, MS prevalence among children and adolescents was reported as 4.2% in the general population and 19.5% in the obese population according to NCEP guidelines compared to 8.4% and 38.9% according to WHO criteria, respectively[17]. In this study, almost 40% prevalence of MS shows that 1 of every 3 obese children is under the threat of chronic diseases (i.e. MS, cardiovascular diseases, type II diabetes). Our results based on WHO criteria are consistent with the literature, although NCEP results in this study were higher than the literature. This may be due to using the childhood cut-off values in this study. One of the limitations of this study is that our results are not representative of the general population. The other limitation concerns the missing values; since we used retrospective data, information about some of the variables was not available.

In studies of children and adolescents, IFG is detected at very low percentages compared to higher ratios of impaired glucose tolerance. Moreover, hyperinsulinemia may be observed in subjects with normal fasting glucose[18-21]. It is suggested to take IFG level as ≥100 mg/dl according to the ADA recommendation[12,22]. Complying with this recommendation, we modified NCEP in our study and used fasting glucose level ≥100 mg/dl. Using this modified NCEP, we observed that MS prevalence increased from 24% to 30%.

We noticed a similar problem in use of waist circumference or BMI index for definition of obesity in childhood. It is suggested to take waist circumference into consideration along with BMI. If we had considered only waist circumference, as is suggested in NCEP, we would have overlooked 7 MS diagnoses.

Abnormal glucose homeostasis has a wide range from insulin resistance to diabetes. Saad et al.[23] reported a case at the age of 9 who progressed from normal glucose tolerance to impaired glucose tolerance and finally developed type 2 diabetes within five years. The striking point was that this girl had a high level of insulin from the beginning, while her fasting and 120 min glucose levels were normal. Particularly in childhood, it is important to identify abnormal glucose homeostasis in the early stage before developing diabetes. Therefore, a different approach is necessary for children in evaluation of glucose homeostasis. In our study group, using WHO criteria, although average fasting insulin level was 20.6 mU/L, average peak insulin was 225 with upper limit of 464.2 mU/L, and none of the patients in the study had fasting glucose level ≥110 mg/dl. However, 5.4% of subjects had fasting glucose level ≥100. Therefore, using only fasting levels and IFG ≥110 mg/dl can be misleading. Our results showed high rates of insulin resistance and low rates of glucose intolerance. Almost half of the subjects in the study had overall abnormal glucose homeostasis, while impaired glucose tolerance was 8.9%. Type 2 diabetes was not detected in any of the subjects. In obese children, abnormal glucose homeostasis reflects beta cell insufficiency and insulin resistance, especially in genetic susceptibility. Since IFG and impaired glucose tolerance emerge in the late period in children, hyperinsulinemia should be included in the diagnostic criteria and cut-off points should be defined according to age. One of the evidences for this suggestion is that hyperinsulinism consistently exists among MS patients in all three models. $HOMA_{IR}$ was significantly higher in MS patients than in those without MS. It was also higher than the cut-off point for diagnosis of insulin resistance for adolescents as reported by Keskin et al.[24].

The aim of this study was to compare prevalence of MS among obese children and adolescents using WHO and NCEP guidelines. There is no consensus on whether or not the diagnostic criteria of MS defined for adults (NCEP and WHO) can be used in childhood as well. Adapting MS diagnosis models used in adults to children with childhood cut-off levels may prevent underestimation of MS in children.

National Cholesterol Education Program (NCEP) criteria for MS diagnosis in childhood should be modified considering the cut-off values for their ages. We suggest that IFG is 100 mg/dl.

In case of diagnosis according to WHO criteria, definition of hyperinsulinemia is important. Abnormal glucose homeostasis should be defined in presence of hyperinsulinemia and/or impaired glucose tolerance as well as two other criteria.

It takes a long time before abnormal glucose homeostasis progresses to become impaired glucose tolerance. For this reason, use of modified WHO criteria for early diagnosis of MS is essential for preventive medicine.

Children in this study were a selected group who referred to the pediatric department of a University hospital. Population-based epidemiological studies are needed in order to obtain MS prevalence in childhood and to decide on the diagnostic model that is appropriate for children and adolescents.

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