The Prevalence of Metabolic Syndrome and Its Relation to Leptin Levels in Obese Children and Adolescents

Obez Çocuklar ve Adölesanlarda Metabolik Sendrom Prevalansı ve Leptin Düzeyleriyle İlişkisi

Mehmet BOYRAZ,[a]
Peyami CINAZ,[a]
Abdulbaki KARAOĞLU,[b]
Emre TAŞÇILAR,[b]
Aysun BİDECİ,[a]
Hamdi Cihan EMEKSİZ,[a]
Orhun ÇAMURDAN[a]

[a]Department of Pediatric Endocrinology, Gazi University Medical Faculty,
[b]Department of Pediatrics, Gülhane Military Medical Faculty, Ankara

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Yazışma Adresi/*Correspondence:*
Mehmet BOYRAZ
Gazi University Medical Faculty, Department of Pediatric Endocrinology, Ankara, TÜRKİYE/TURKEY
boyrazoglu@gmail.com

ABSTRACT Objective: In this study, we aimed to determine the prevalence of metabolic syndrome (MS) and frequency of metabolic risk factors in pubertal obese children, and to evaluate the relation between metabolic syndrome and plasma leptin levels. **Material and Methods:** In this study, 451 pubertal children and adolescents aged between 8-18 years admitted with complaints of excess weight. The ones with a body mass index standard deviation score (BMI-SDS) ≥1.81 were included in this study. In all cases, medical history, physical examination, anthropometric measurements, results of biochemical and hormonal assays were evaluated. MS was diagnosed according to International Diabetes Federation (IDF) consensus criteria. **Result:** Fifty five percent of the study group were males and 45% were females. The median ages for girls and boys were 12.3 (8.0-16.4) and 12.6 (8.9-16.2) years, respectively. There were 89 (19.8%) children with MS. It was found that leptin had a positive relationship with BMI, waist and hip circumference, insulin level, Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) and LDL cholesterol level, and a negative one with age and HDL cholesterol in all obese cases. However no relation was found between leptin and fasting blood glucose and triglyceride levels. On the other hand, leptin was higher in those with hypertension. **Conclusion:** An increased prevalence of obesity, together with metabolic risk factors such as dyslipidemia and abnormal blood pressure were observed in childhood, contributing to the onset of MS at younger ages. Leptin was markedly elevated in obese patients with MS. At the same time, it was found associated with metabolic risk factors. Therefore a high leptin level may be a risk factor for MS.

Key Words: Obesity; leptin; abdominal obesity metabolic syndrome

ÖZET Amaç: Bu çalışmada pubertal obez çocuk ve adölesanlarda metabolik sendom (MS) prevalansını, metabolik risk faktörlerinin sıklığını ve leptin düzeylerinin MS ve risk faktörleriyle ilişkisini test etmeyi amaçladık. **Gereç ve Yöntemler:** Bu çalışmaya; aşırı kilo yakınmasıyla başvuran 8-18 yaş arasında, beden kitle indeksi standart deviasyon skoru (BKİ-SDS) değeri ≥1,81 olan 451 obez çocuk ve adölesan alındı. Tüm olgularda tıbbi öykü, fizik muayene, antropometrik ölçümler, biyokimyasal ve hormonal testlerin sonuçları değerlendirildi. MS tanısı Uluslararası Diyabet Federasyonu (IDF) konsensus kriterlerine göre konuldu. **Bulgular:** Çalışma grubunun %55'i erkek ve %45 kız idi, ortanca yaş değeri kızlar için 12,3 yıl (8,0-16,4) ve erkekler için 12,6 yıl (8,9-16,2) idi. MS'li 89 (%19,8) çocuk vardı. Obez olgularda leptin düzeyleri ile bel ve kalça çevresi, insülin düzeyi, Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) ve LDL kolesterol arasında pozitif, yaş ve HDL kolesterol arasında negatif korelasyon bulundu. Ancak leptin düzeyi ile açlık şekeri ve trigliserid arasında anlamlı bir ilişki bulunmadı. Leptin düzeyleri hipertansiyonu olan obezlerde, hipertansiyonu olmayan obezlere göre daha yüksekti. **Sonuç:** Artan obezite prevelansı ile birlikte dislipidemi ve yüksek kan basıncı gibi metabolik risk faktörleri genç yaştaki bireylerde MS'nin başlamasına katkıda bulanabilir. MS'li obez çocuklarda leptin daha yüksekti, aynı zamanda metabolik risk faktörleriyle de ilişkiliydi. Bu yüzden leptin yüksekliği MS açısından bir risk faktörü olabilir.

Anahtar Kelimeler: Obezite; leptin; abdominal obezite metabolik sendrom

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Obesity is a multifactorial disease resulting from the interaction between genetic and environmental factors. It can also be defined as accumulation of excessive fat as a result of an imbalance between calorie intake and burn off. The incidence of obesity has increased three times since 1970, and today it has affected more than one billion people in the world.[1]

Recently, obesity prevalence has also increased.in children The environmental factors that lead to obesity are consumption of high-calorie diets, socioculturel level, expending more time in front of TV, sedentary life style and communication problems between child and parents.[2] Increasing prevalence of childhood obesity has led to more frequent complications occurring at earlier ages. Obesity by itself is a risk factor for cardiovascular diseases (CVD), and this risk augments the prevalence of hypertension, dyslipidemia, glucose metabolism disorder and atherosclerosis.

Simultaneous abdominal obesity, hypertension, dyslipidemia (high triglyceride level, low HDL level), insulin resistance or impaired glucose tolerance is defined as metabolic syndrome (MS).[3,4] MS is not a disease of only adults but also has increasingly become a threat for children and adolescents particularly after start of puberty in which it becomes obvious by the act of physiological insulin resistance. MS is related to increased CVD risk. There is still no consensus on criteria for the definition of MS in children.[3,5,6] However recently, The International Diabetes Federation (IDF) has defined the criteria for MS in children and adolescents.[4]

In most of the obese patients, leptin level is high due to enhanced adipose tissue. Inadequate response of these patients to increased leptin level demonstrates that obesity is affected by leptin resistance as well. In MS likewise obesity, there is a hyperleptinemic state and a positive relation between serum leptin level and adipose tissue mass, insulin resistance and type 2 diabetes mellitus.[7] However in literature the studies that investigated the relation between MS and leptin level in obese children are scarce.

In this study, we aimed to determine the prevalence of MS and frequency of metabolic risk factors in pubertal obese children, and to evaluate the relation between MS and plasma leptin levels.

MATERIAL AND METHODS

In this study, 451 pubertal children and adolescents aged between 8-17 years admitted to the pediatric endocrinology department of two distinct hospitals (Gazi University Hospital and Gulhane Military Medical School) between November 2008 and January 2011with the complaint of obesity and a body mass index standard deviation score (BMI-SDS) ≥1.81 were evaluated.[8] Obese patients were evaluated retrospectively in this study. Our study was approved by the ethics committee on January 19, 2011. The children receiving treatment for any reason, syndromic ones and patients having either an endocrinological disease or familial dyslipidemia were excluded from the study. During pubertal evaluation, Tanner Staging was used. A testis size ≥4 ml in males and the Tanner stage of breast development ≥ stage II in females were assumed as puberty.[9] Weight of each child was measured with light clothes and without shoes by the device BMI SECA (sensitive to 0.1 kg) in the morning after a starvation of 12 hours. For height measurement, Harpender Stadiometer (sensitive to 0.1 cm) was used. BMI was calculated by the weight (kg)/height (m^2) formula. To compare BMI across different ages and in both boys and girls, the BMI-SDS was considered. BMI-SDS was calculated with the Lambda, Mu, Sigma (LMS) method. The standard deviation score represents the number of SD above or below the considered population, mean value based on standardized tables for children. Obesity was defined as a BMI above 1.81 SD which corresponds to the 95th adjusted for age and gender.[11] Waist circumference was measured with a non elastic tape measure. The waist circumference was measured at the end of expiration in between the midpoint of the last rib and superior iliac crest.[11] Blood pressure was measured by a mercury sphingomanometer with an appropriate sleeve for the age of the patient, after a minimum of ten minutes rest. We used the National High Blood Pressure Education

Program Working Group (2004) normal values for children as a reference to evaluate blood pressure measurements.[12] Blood pressure ≥ 95th percentile for age, sex and height was accepted as hypertension. After a minimum of 12-14 hours fasting, samples for fasting blood glucose (FBG), lipid profile (TG, LDL, VLDL, HDL, total cholesterol) leptin and insulin levels were obtained. Presence of simultaneous LDL cholesterol ≥130 mg/dl, total cholesterol ≥200 mg/dl and HDL cholesterol <40 mg/dl was assumed as dyslipidemia.[13] Triglyceride level ≥95th percentile for age and sex was assumed as hypertriglyceridemia.[6,14] Olympus AU 2700 device was used to measureFBG and lipid profile. Insulin level was measured by electrochemiluminescence method using Roche Modular Analytics E-170 immunoassay analyzer (RocheDiagnostics, ABD). Before determining the leptin level, we waited for thawing of serum samples and kit reactives which had been preserved at -80 C°. Measurement was done properly by RIA method and using the kit of Leptin Irma Company with a lot number of 800897. Results were evaluated by the device Benthold LB2111 in a standard range of 0.5-90 ng/ml. A FBG of 100-126 mg/dl was assumed as impaired fasting glucose.[15] As insulin resistance index, HOMA-IR (HOMA-IR= FBG (mmol/l) x fasting plasma insulin (μIU/ml)/22.5) was used (1 mmol/l=18 mg/dl). A HOMA-IR value above 3.16 was accepted as insulin resistance.[16,17] The diagnosis of MS was made according to the IDF criteria. The IDF definition of MS for children aged 10 years or older includes BMI> 90th percentile for age and sex, and presence of two or more of the following findings: (1) Triglycerides >150 mg/dl; (2) HDL-cholesterol <40 mg/dl; (3) systolic blood pressure >130 mmHg, diastolic >85 mmHg; and (4) Plasma glucose >5.6 mmol/l or >100 mg/dl or known type 2 diabetes (Table 1).[6]

STATISTICAL ANALYSIS

The variables used in the study did not show normal distribution, therefore the differences between groups were evaluated with non-parametric Mann-Whitney U test. Spearman's rank correlation test was performed to investigate whether a linear relationship exists between variables. All data were evaluated as median and referred with minimum and maximum. If the cut of level for significance (p) was below 0.05, it was assumed as statistically significant. All statistical data were evaluated by SPSS package software (Version 16.0 Chicago, IL).

RESULTS

There were 451 obese cases in the study (55% males and 45% females). The median age of females and males were 12.3 (8.0-16.9) and 12.6 (8.9-16.2) years, respectively. Eighty nine cases (19.8%) had

TABLE 1: According to the IDF criterias for the diagnosis of MS in childhood.

Age	Obesity (waist circumference)	Triglyceride	HDL-C	Blood pressure	Fasting blood glucose
6-<10	90th percentile	Will not be the diagnosis of metabolic syndrome, but if you have the story family history of metabolic syndrome, type 2 diabetes, dyslipidemia, cardiovascular disease, hypertension and/or obesity, should be done further investigations			
10<16	90th percentile	150 mg/dl	40 mg/dl	Systolic ≥130/diastolic ≥85 mmHg	Type 2 diabetes/glucose ≥100 mmHg
16 +	Central obesity (waist circumference; male ≥94 cm, female ≥80 cm In addition, at least two of the following criteria - Triglyceride ≥150 mg/dl - HDL-C; male <40 mg/dl, female <50 mg/dl - Blood pressure; systolic ≥130 or diastolic ≥85 mmHg - Fasting blood glucose ≥100 mg/dl or Type 2 diabetes				

MS. Anthropometric and biochemical features of cases with and without MS are summarized in Table 2. Except LDL and total cholesterol levels, significant differences were found for all parameters between cases with and without MS (Table 2). In all obese patients, the frequency of abdominal obesity, hypertension, impaired fasting glucose, insulin resistance, dyslipidemia and type 2 DM were found as 61.8% (279), 25.7% (116), 4.4% (20), 34.3% (156), 41% (185) and 2.2% (10), respectively. Median leptin level was 32.1 ng/dl (5.9-92.5) in MS cases and 24.5 ng/dl (5.6-60.5) in cases without MS (p= 0.009). The leptin level was higher in hypertensive patients in comparison to normotensive ones (Table 3). Regarding correlation matrix between variables, there were positive linear correlations between leptin level and BMI, waist circumference, insulin level, HOMA-IR and LDL cholesterol level, and negative linear correlations between leptin level and age and HDL cholesterol levels ($p<0.05$) (Table 4).

DISCUSSION

Similar to adolescence, obesity is also a risk factor for CVD in children. Coexisting hypertension, dyslipidemia, insulin resistance, atherosclerosis, and hypertrophic cardiomyopathy enhances this risk as well.[5,6] Reinehr et al. reported the prevalence of hypertension as 38%, triglyceride and LDL cholesterol elevation as 25% and decrease in HDL cholesterol as 5% among 229 obese children.[18] In similar studies by Atabek and Pirgon and Atabek et al., the prevalence of insulin resistance, impaired glucose tolerance and dyslipidemia were reported as 37.1%, 24.3% and 54%, respectively.[19,20] In our study, the most common risk factors among obese cases were central obesity with the prevalence of 61.8%, dyslipidemia (41%), impaired fasting glucose (4.4%), insulin resistance (34.3%) and hypertension (25.7%). Regarding these results, obese children and adolescents should be screened particularly for insulin resistance, dyslipidemia and hypertension.

Although MS is predominantly a disease of adults, its prevalence has increased among children in the recent years. Although there is still no consensus for the diagnosis of MS in children, the diagnosis is usually made according to IDF criteria.[4] In our study, corrected IDF criteria were used. In United States, MS prevalence among 2430 adolescents aged between 12-19 years was reported as 4.2% (males 6.1% and females 2.1%) in The Na-

TABLE 2: Anthropometric and biochemical features of groups with and without metabolic syndrome.

	Group without MS (n=362)			Group with MS (n=89)			
	Median	Min	Max	Median	Min	Max	p value
Age (year)	12.5	8	16.9	12.8	8.5	16.2	0.498
Weight (kg)	69.9	42.9	119.0	81.8	59.6	137.0	<0.001
BMI (kg/m^2)	29.2	23.3	44.9	33.2	25.4	49.6	<0.001
BMI-SDS	2.10	1.81	2.92	2.69	1.92	3.46	<0.001
WC (cm)	83.0	67.0	112.0	89.9	78.8	120.0	<0.001
HC (cm)	101.0	81.0	160.4	108.5	89.0	170.0	<0.001
FBG (mg/dl)	81.0	69.0	107.0	92.0	69	120.0	<0.001
Insulin (mg/dl)	15.5	4.0	31.0	28.2	18.5	46.0	<0.001
HOMA.IR	3.3	0.8	6.7	6.6	4.0	10.9	<0.001
HDL-C (mg/dl)	44.0	16.0	108.0	29.5	16.0	48.0	<0.001
LDL-C (mg/dl)	97.0	19.0	289.0	95.0	45.0	153.0	0.363
Triglyceride (mg/dl)	122.0	14.9	231.0	233.5	72.0	335.0	<0.001
T.cholesterol (mg/dl)	165.0	107.0	346.8	165.5	111.0	232.6	0.476
Leptin (ng/ml)	24.5	5.6	60.5	32.1	5.9	92.5	0.008

MS: Metabolic syndrome; BMI: Body mass inex; WC: Waist circumference; HC: Hip circumference; FBG: Fasting blood glucose; HOMA-IR: Homeostasis Model Assessment of Insulin Resistance; HDL-C: High density lipoprotein cholesterol; LDL-C: Low density lipoprotein cholesterol.

TABLE 3: Anthropometric and biochemical features of obese groups with and without hypertension.

	Normotensive (n=336)			Hipertensive (n=115)			
	Median	Min	Max	Median	Min	Max	P value
Weight (kg)	62.6	31.0	121.0	82.5	56.6	137.0	<0.001
BMI (kg/m²)	26.6	17.2	44.7	31.3	25.1	49.6	<0.001
BMI-SDS	2.23	1.81	2.89	2.88	1.89	3.48	<0.001
FBG (mg/dl)	87.0	67.0	107.0	89.0	68.0	120.0	<0.001
Insulin (mg/dl)	12.0	4.0	30.0	27.1	8.6	46.0	<0.001
HOMA.IR	2.7	0.80	6.9	6.3	1.9	10.9	<0.001
HDL-C (mg/dl)	45.0	22.0	121.0	29.0	16.0	64.0	<0.001
LDL-C (mg/dl)	89.0	19.0	289.0	89.2	33.0	153.0	0.287
Triglyceride (mg/dl)	122.0	14.9	265.0	226.0	66.0	335.0	<0.001
T. cholesterol(mg/dl)	166.0	78.0	346.8	164.0	111.0	232.6	0.126
Leptin (ng/ml)	19.0	0.63	62.4	27.2	5.6	92.3	<0.001

BMI: Body mass index; FBG: Fasting blood glucose; HOMA-IR: Homeostasis Model Assessment of Insulin Resistance; HDL-C: High density lipoprotein cholesterol; LDL-C: Low density lipoprotein cholesterol.

tional Health and Nutrition Examination Survey (NHANES) III study. In the same report, the prevalence of MS in obese children was stated as 28.7%.[21] Duncan et al. found an increase in MS prevalence to 6.4% (males 9.2% and females 3.7%) in NHANES 1999-2000 study (991 adolescents, aged 12-19 years).[22] Additionally, they reported the MS prevalence in obese, overweight and normal weight patients as 32.1%, 7.1% and 1%, respectively.[22]

Rates for MS prevalence in obese children varied in studies conducted in different European countries (France 15.9%, Italy 13.9%, Spain 18%).[23-25] Although the studies on MS prevalence have increased in our country, there are still inadequate data. Atabek et al. examined 169 obese cases (age between 7-18 years) and reported 27.2% had MS.[20] Moreover, they pointed the MS rate in pubertal obese as 37.6%, and in prepubertal obese as 20%.[20] Similarly, MS was determined in 41.8% of 352 obese children.[26] In an another Turkish study including 1385 school age children, MS rate was determined as 2.2% in all children and 21% in the obese children. The National Cholesterol Education Program (NCEP) III criteria were used in all these Turkish studies we mentioned so far.[27] Finally, according to IDF criteria, we determined MS rate as 19.8% among obese children in our study.

TABLE 4: Correlation results of the between leptin level and anthropometric and biochemical values.

	Leptin (ng/ml)	
	r	p
Age (year)	-0.200	<0.001
BMI-SDS (kg/m²)	0.699	<0.001
WC (cm)	0.213	<0.001
HC (cm)	0.311	<0.001
FBG (mg/dl)	-	0.060
Insulin (mg/dl)	0.385	<0.001
HOMA.IR (mg/dl)	0.394	<0.001
HDL-C (mg/dl)	-0.152	<0.001
LDL-C (mg/dl)	0.133	0.001
Triglyceride (mg/dl)	-	0.060

BMI: Body mass index; WC: Waist circumference; HC: Hip circumference; FBG: Fasting blood glucose; HOMA-IR: Homeostasis Model Assessment of Insulin Resistance; HDL-C: High density lipoprotein cholesterol; LDL-C: Low density lipoprotein cholesterol.

Apparent increase in childhood obesity increased the importance of obesity-related factors like leptin.[28] Leptin is a product of obesity gene, and only expressed in adipose tissue. It is either free or bound to leptin binding protein. It does not only define the amount of fat content, but also the energy imbalance and prolonged starvation as well. Excess calorie intake increases the leptin level while inadequate intake decreases it. Although leptin level is high in obese cases, it is in fact an anti- obesity hormone. It prevents MS development. However, knowledge till now suggests the presence of leptin

resistance.[7] Studies up to now were generally conducted in adults. There are a few studies in literature regarding childhood MS and the role of leptin.

Leptin synthesis, transport and clearance differs between males and females. In comparison to males, females possess higher leptin levels. Serum leptin level increases in parallel to the increase in body fat mass, and reaches its maximum level just before puberty. Therefore it is proposed that leptin might trigger the onset of puberty. The difference in leptin levels regarding genders may explain the reasons for delayed entrance of boys to puberty and higher amount of fat mass in girls in comparison to boys.[29] In this study, in accordance with the literature, we found a higher level of leptin in girls. Moreover, another relation was detected between hypertension and high leptin level. Increment in sympathetic activity may arise due to the vasoconstrictor effect of leptin.[30] Additionally, it may indirectly affect renin, aldosteron and angiotensin. Despite these suggestions, the exact mechanism between leptin and hypertension have not been defined until now.[31]

Hyperinsulinemia and insulin resistance increase leptin level, and leptin decreases the effect of insulin.[32,33] Detection of significant positive correlation in between HOMA-IR, insulin and leptin levels in our study supports this conclusion.

We determined a relationship between MS and plasma leptin level in our study. Chu et al. reported that leptin and BMI were the markers of hyperinsulinemia and MS.[34] Park et al. reported that leptin did not have any role in MS.[35] The relationship between leptin and MS may be different in different ethnicities. Further studies are needed to enlighten this issue.[35] Contrary to leptin, an association was detected between insulin level and MS. The studies in literature revealed the critical role of insulin resistance in pathopyhsiology, and its effect on the other components of MS.[36] Although the complex relation of insulin resistance with obesity, hypertension and hyperlipidemia could not be completely elucidated, in consideration of current knowledge, the declaration 'MS is carried on the horns of insulin resistance!' is not a mistake.

In conclusion, an increased prevalence of obesity, together with metabolic risk factors such as dyslipidemia, hyperinsulinemia and abnormal blood pressure, were observed in adolescents, contributing to the onset of MS at younger ages. Therefore the important consideration is early diagnosis and treatment of metabolic risk factors in obese children and adolescents. Leptin was markedly elevated in obese children and adolescents with MS. A strong association was determined between leptin and anthropometric and biochemical parameters in obese children. A high leptin level may be a risk factor for MS.

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