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Original/*Síndrome metabólico*

Higher HDL levels are a preventive factor for metabolic syndrome in obese Turkish children

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Abstract

Aim: **The definition of childhood metabolic syndrome has not been described clearly. Childhood obesity is increasing gradually, and the incidence of childhood metabolic syndrome is also rising. We aimed to show metabolic syndrome components and preventive factors for metabolic syndrome in obese children**

Methods**: In the present study, 187 obese children and adolescents 5–18 years old were investigated retrospectively. Demographic data, anthropometric measurements, body mass index, blood pressure values, insulin levels, oral glucose tolerance test results, total cholesterol, high density lipoprotein, and triglyceride levels were obtained from hospital records. A body mass index > 95th percentile was considered obese. Insulin resistance was calculated according to the oral glucose tolerance test with 1.75 g/kg glucose maximum 75 g glucose. The insulin sensitivity index and homeostatic model assessment-insulin resistance (HOMA IR) were calculated and compared. Metabolic syndrome was diagnosed according to the modified WHO criteria adapted for metabolic syndrome in children.**

Results**: Abnormal glucose homeostasis was detected in 53% of subjects. Dyslipidaemia was present in 45.7% and hypertension in 16.6% of the patients. Metabolic syndrome was identified in 24.6% of obese children and adolescents. High HOMA-IR values and fasting glucose levels, elevated triglycerides and lower HDL levels were an indication of metabolic syndrome.**

Conclusion**: Obesity and insulin resistance are significant factors for the development of metabolic syndrome in children and adolescents. In obese children higher HDL levels are preventive factor for metabolic syndrome. Preventing obesity and insulin resistance may decrease the prevalence of metabolic syndrome.**

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Key words: *Childhood obesity. HDL levels. Insulin resistance. Metabolic syndrome.*

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LOS NIVELES DE HDL MÁS ALTOS SON UN FACTOR PREVENTIVO PARA EL SÍNDROME METABÓLICO DE LOS NIÑOS TURCOS QUE SUFREN DE OBESIDAD

Resumen

Objetivo: **El síndrome metabólico infantil no ha sido definido aún con claridad. La obesidad infantil se está incrementando progresivamente al igual que la incidencia del síndrome metabólico infantil. Nuestro objetivo ha sido mostrar los componentes del síndrome metabólico y sus factores preventivos en los niños obesos.**

Metodología**: Este estudio analizó de forma retrospectiva a 187 niños y adolescentes obesos de entre 5 y 18 años. Los datos demográficos, las medidas antropomórficas, los índices de masa corporal, los valores de presión sanguínea, los niveles de insulina, los resultados de test de tolerancia a la glucosa oral, el total de colesterol, las lipoproteínas de gran densidad y los niveles de triglicéridos fueron obtenidos de registros hospitalarios. Una masa corporal con un índice superior a 95 percentiles fue considerada como obesidad. La resistencia a la insulina se calculó de acuerdo con el test de tolerancia a la glucosa oral con 1,75 g/kg de glucosa y un máximo de 75 gramos de glucosa. Se calculó y comparó el índice de sensibilidad a la insulina y la evaluación del modelos homeostático-resistencia a la insulina (HOMA IR). El síndrome metabólico fue diagnosticado de acuerdo con los nuevos criterios de la OMS adaptados a los síndromes metabólicos infantiles.**

Resultados**: Se observó una homeostasis de glucosa anormal en el 53% de los casos. La dislipidemia estaba presente en el 45,7% de los pacientes y la hipertensión en un 16,6%. El síndrome metabólico fue identificado en un 24,6% de los niños y adolescentes obesos. Altos valores de HOMA-IR y de glucosa, triglicéridos elevados y niveles bajos de HDL eran indicadores de síndrome metabólico.**

Conclusión**: La obesidad y la resistencia a la insulina son factores significativos para el desarrollo del síndrome metabólico en niños y adolescentes. En niños obesos altos niveles de HDL son un factor preventivo del síndrome metabólico. Prevenir la obesidad y la resistencia a la insulina puede reducir el predominio del síndrome metabólico.**

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Palabras clave: *Obesidad infantil. Niveles de HDL. Resistencia a la insulina. Síndrome metabólico.*

Introduction

Body mass index (BMI), calculated according to weight and height (kg/m^2), is used to define overweight and obesity in childhood. A BMI between the 5th and 85th percentile is considered normal, whereas a BMI between the 85th and 95th percentile indicates overweight. A child is considered obese if BMI exceeds the 95th percentile for their age. The prevalence of childhood obesity has increased dramatically and steadily in the last four decades and has become an important worldwide public health issue[1,2]. The prevalence of childhood obesity has been reported by many investigations to be 1.8–3.7% in in most regions of the world[3-9]. Currently, the childhood obesity prevalence is 17% in the United States[1]. The obesity prevalence in Turkish children parallels that of many countries and is considerably lower in those 6–17 years of age compared with most European countries[3]. Metabolic syndrome (MS) increases in frequency with the rise in obesity prevalence. Obesity plays a central role in MS, which also includes hyperinsulinemia/insulin resistance (IR), hypertension and dyslipidaemia[10].

The frequency of MS components are as follows: 9.8–17.9% for abdominal obesity, 21.0–23.4% for elevated triglycerides (TGs), 18.3–23.3% for reduced high-density lipoprotein-cholesterol (HDL-C), 4.9–7.1% for elevated blood pressure (BP), and 0.8–1.7% for impaired fasting blood glucose[11]. The existence of MS is a major risk factor for cardiovascular disease (CVD) in children. CVD and changes in the CV system may begin without any clinical signs or symptoms. The assessment of subclinical CV changes and risk factors are important for preventing these diseases. Hypertension, obesity, IR, and dyslipidaemia are modifiable risk factors for CVDs. It was previously thought that obese children will not develop CVD until they reach adulthood, but they can develop short-term CV complications. Cardiac hypertrophy and ventricular dysfunction have been reported in children with MS[12,13]. IR is defined as a decreased tissue response to insulin. In turn, pancreatic β-cells increase their production and secretion of insulin as a compensatory mechanism and physiological response[14]. IR can be determined by several methods and differs according to the National Cholesterol Education Program Adult Treatment Panel (NCEP ATP III) and World Health Organisation (WHO). The hyperinsulinemic/euglycemic clamp test is the gold standard method to assess IR. However, the insulin sensitivity index and Homeostasis Model Assessment (HOMA) IR index are frequently used to determine insulin sensitivity, and the oral glucose tolerance test (OGTT) is another method for measuring insulin levels in patients[15,16]. A correlation exists between IR and MS, in that IR is independent of obesity and a basic factor in the pathophysiological mechanism of MS[16].

The study was conducted because no other study has been performed on this subject in the inner northern region of Turkey.

Methods

A total of 187 obese children 5–18 years of age who were admitted to the School of Medicine at Gaziosmanpasa University between January 2012 and May 2014 were included in this study. Participants were diagnosed as obese according to BMI, considering the growth curve for each sex and the cut-off points proposed by the WHO[17]. Weights were measured using a digital scale (Seca Corp., Chino, CA, USA). Measurements were made while the patients were barefoot and wearing light clothing. Height was measured using a portable stadiometer (Seca) together with weight. Body mass index (BMI) was calculated as weight in kg divided by height in meters squared (kg/m^2). If the BMI was > the 95th percentile, patients were considered obese[18]. BP was measured using a sphygmomanometer and an appropriate collar for each child. BP was classified according to the criteria proposed by The Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents, with consideration of sex, age, and the height percentile as follows: normal BP (systolic or diastolic BP < 90th percentile), prehypertensive (90–95th percentile), and hypertensive (BP ≥ 95th percentile)[18, 19]. Biochemical data were obtained retrospectively from tests conducted at a biochemistry laboratory. Total cholesterol (TC), HDL-C, TGs and fasting blood glucose levels were determined using the enzymatic colorimetric method. All samples were obtained after a 12-h fast. Dyslipidaemia was defined according to TC, HDL-C and TG levels. The cut-off values for TC, HDL, TG and fasting glucose levels were 200, 35, 150 and 110 mg/dl, respectively. Abnormal glucose homeostasis was determined according to the fasting glucose level, HOMA-IR level and 2-h OGTT values. Insulin and glucose levels were measured at 0, 30, 60, 90 and 120 min. HOMA-IR, fasting glucose and 120-min OGTT values were considered positive if they were greater than 3.16, 110 mg/dl and 140–200 mg/dl, respectively. HOMA-IR was calculated as the product of basal insulin and fasting glucose values divided by 22.5[20]. Patients were diagnosed with MS according to the WHO criteria[21]. (Table I)

Descriptive analyses were performed to provide information on general characteristics of the study population. Kolmogorov-Smirnov test was used to evaluate whether the distribution of continuous variables were normal. Therefore, two independent sample t-test or Mann-Whitney U-test was used to compare the continuous variables between groups. The continuous variables were presented as the mean ±standard deviation and median. Categorical variables were presented as a count and percentage. Chi-Square test was used to compare the categorical variables between groups. Kappa statistics were used for measuring agreement between the guidelines. A p-value <0.05 was considered significant. Analyses were performed using commercial software (IBM SPSS Statistics 18.0 (SPSS, Inc., Chicago, IL, USA).

Table I

	NCEP	*WHO*
Hypertansion		
Blood Pressure> %95 p	X	X
Obesity		
Waist circumference 102 cm (M), 88 cm (F)	X	X
BMI> %95P		X
Dyslipidaemia		
HDL <40mg/dl (M), 50mg/dl (F)	X	
HDL <35mg/dl (M), 39mg/dl(F)	X	X
Triglyceride > 150 mg/dl	X	X
Total cholesterole		X
Insulin resistance		
Fasting insulin		X
Fasting Glucose>110mg/dl or DM	X	X
HOMA-IR		X
OGTT 120th min		X

*Three out of five criteria are necessary to diagnose metabolic syndrome according to the NCEP
**One indicator of insulin resistance and hyperinsulinemia was a glucose level > 110 mg/dl, and two out of three criteria are necessary to diagnose metabolic syndrome according to the WHO criteria.

Results

A total of 187 obese children and adolescents (112 females and 75 males; mean age, 12.2 ± 2.9 yr) were assessed in this study. The distributions of subjects according to age were 40% (n = 75) for 5–11-yr-olds and 60% (n = 112) for 12–18-yr-olds. Abnormal glucose homeostasis was identified in 53% of subjects with impaired glucose tolerance (10% according to 120-min OGTT values, 3.2% impaired fasting glucose levels and % 50.3 HOMA-IR > 3.16). The frequency of abnormal glucose homeostasis in girls was higher than that in boys. Fasting glucose levels were > 110 mg/dl in six patients (3.2%). No patient had type II diabetes mellitus. Nineteen patients had 120-min OGTT glucose levels of 140–200 mg/dl (10.1%). HOMA-IR was > 3.16 in 94 patients (50.3%). No difference was observed between girls and boys with respect to HOMA-IR. Mean HOMA-IR values were 3.82 in girls and 3.76 in boys. Age is an important factor for and directly proportional to HOMA-IR. Dyslipidaemia was present in 45.7% (low HDL, 15.1%; high TGs, 31.5%; and high total cholesterol, 8%) and hypertension in 16.6% of patients. Mean TG values of the patients were 119.5 mg/dl in girls and 121.5 mg/dl in boys. Mean HDL values were 47.15 and 46.98 mg/dl in girls and boys, respectively. Mean HDL values were lower in those aged 12–18 years compared with 7–11 years ($p < 0.05$). Coexistence of dyslipidaemia was detected in 14 children. Seven individuals were girls (6.8%) and the remaining were boys (9.6%). Dyslipidaemia and IR were identified together in 29 (28.15%) girls and 19 (26.02%) boys. Impaired glucose tolerance according to the 120-min OGTT results was seen in six boys (8.2%) and 12 girls (10.8%). MS was diagnosed in 46 (24.6%) patients. The MS prevalence was 29.6% (n = 30) in girls and 23.2% (n = 16) in boys according to the WHO guidelines. MS frequency of patients aged 12–18 years was significantly higher than of patients 5–11 years ($p < 0.05$). MS increased with age. The most frequent component of MS was IR. (Table II)

Discussion

No consensus definition exists for metabolic syndrome in children, and many attempts have been made to define MS in the paediatric population. The most often used MS criteria in paediatric studies have been variably adapted from the definitions of adult MS. In particular, the childhood MS criteria of the NCEP ATP

Table II

	Metabolic Syndrome (-)			*Metabolic Syndrome (+)*			
Age	11.69	3.01	12.00	13.46	2.41	14.00	<0.001*
BMI	29.96	8.07	29.00	30.56	4.39	30.00	0.115
BPs	110.39	12.96	110.00	114.46	12.03	112.50	0.068
BPd	70.91	12.97	70.00	75.11	11.38	75.00	0.072
FG	83.93	12.85	85.00	90.29	15.30	89.00	0.007*
HOMA-IR	3.11	2.22	2.56	5.59	2.46	5.13	<0.001*
OGTT 120.min	111.25	30.95	105.00	103.93	23.77	105.00	0.153
HDL	48.78	12.21	46.00	43.23	11.32	41.75	0.010*
TG	106.66	52.89	96.70	153.58	67.42	150.00	<0.001*
TC	160.41	37.51	157.10	171.41	48.02	170.35	0.127

**p<0.05*
FG: Fasting glucose. BPs: Sistolic blood pressure. BPd: Diastolic blood pressure. TC: Total cholesterole TG: Triglycerid

III and WHO are used worldwide to identify children with MS[1]. Many diagnostic protocols use similar criteria to define MS. Generally, MS criteria modified for children by the WHO and the diagnostic criteria offered by the NCEP ATP III are used to diagnose MS in children and adolescents. The modified WHO MS criteria for children were used in this study. The prevalence of MS is nearly 20% in obese children in Turkey[14]. The MS prevalence differentials according to diagnostic criteria were used to define MS. In a study by Tavare et al., MS prevalence was 40.4% according to NCEP III criteria but 24.6% according to the International Diabetes Federation[22]. There are several definitions for MS, in each of which diagnosis is based on the existence of dyslipidaemia, hypertension, impaired glucose tolerance and obesity with IR. Only the values show minimal changes[23].

In this study, the prevalence of MS in obese children and adolescents (24.6%) matched that found in the literature. The prevalence of MS ranges between 0.7 and 43% in many countries[24]. MS is represented by a set of risk factors for CVDs in children and adolescents, and each of the components determines an unfavourable cardiovascular profile for young people[20]. In this study, the MS prevalence was higher in children aged 12–18 years compared with younger children. Pubertal endocrinological changes may affect this prevalence, and HDL levels were lower in children 7–11 years of age.

Some investigators claim that the most common component of MS is low HDL, and the least common is high BP, whereas others claim that waist circumference is the most common and high fasting glucose the least common. The most prevalent component of MS in many investigations is high TG levels[25-27]. In this study, HDL levels were higher in obese children than in obese children without MS. Low HDL-C levels are the most significant risk factor for early atherosclerosis in children with MS. According to some investigators, a low HDL level is the most common component of MS and a preventive factor against CVD[28]. Hyperinsulinemia increases vascular resistance and causes proliferation of vascular smooth muscle cells. Insulin is a potent growth factor that indirectly stimulates growth factors such as insulin-like growth factor-1. This is one of the mechanisms of hypertension development in patients with MS[12,16]. Results are summarized in figure 1.

Many tissues respond to endocrine hormones, and adipose tissue is a highly insulin-responsive organ that helps regulate glucose and lipid homeostasis in the body. White adipose tissue (WAT) stores TGs, which are broken down to produce energy if the caloric need arises. WAT secretes adipokines such as leptin, which act in energy sensing and pubertal development[15]. Obesity and IR are hypothesised to play a major role in dyslipidaemia in both individuals with normal glucose tolerance and those with impaired

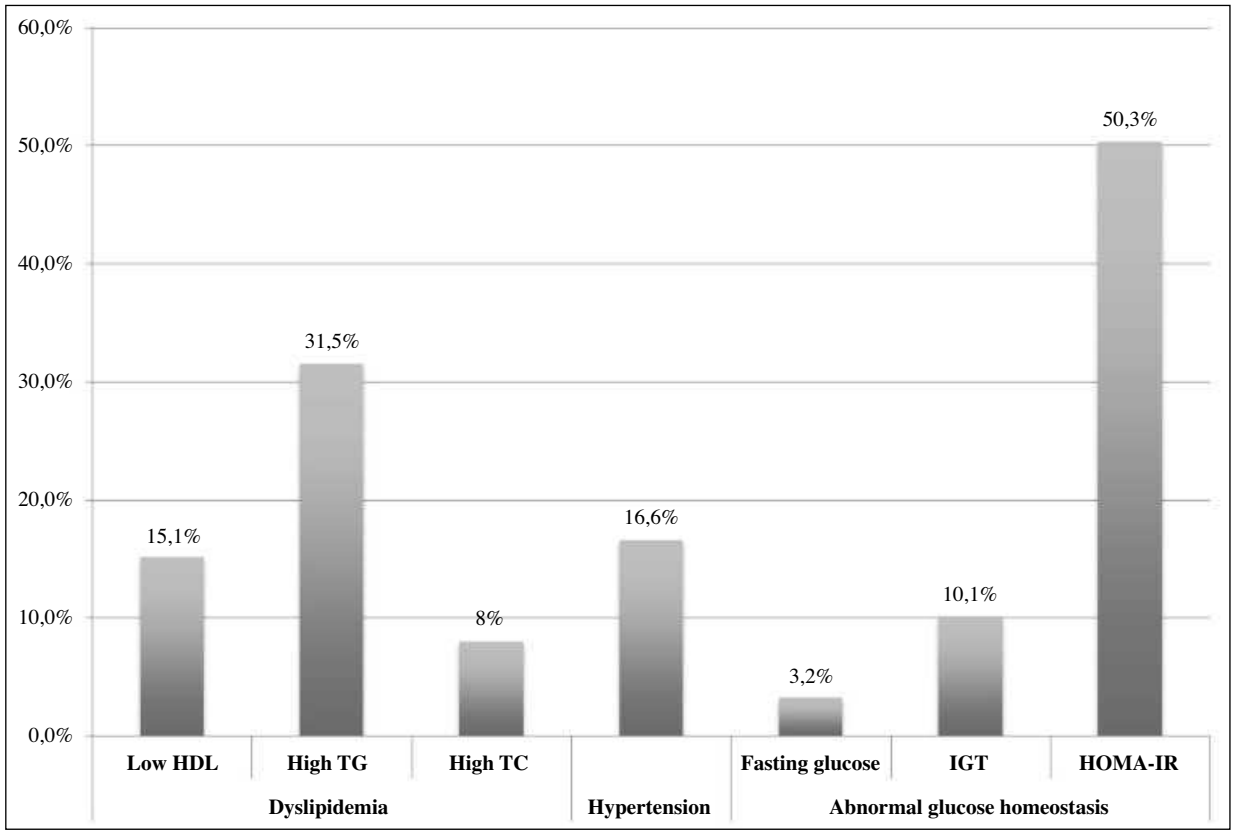

Fig. 1.

glucose tolerance and type 2 diabetes[10]. The major component of MS was IR in obese children in this study. One treatment method for MS involves exercise and diet, which are remedies for IR. IR is observed in adolescents and particularly in obese children[29]. Children with IR do not always develop MS. Hyperinsulinism and abnormal glucose homeostasis occur; however, fasting glucose levels and OGTT values are normal. Hyperinsulinism is seen more often in obese children than is impaired fasting glucose[30]. Visceral fat increases IR, and this contributes to the development of hypertension. Hyperinsulinism increases renal sodium uptake and the renin–angiotensin aldosterone system, which contributes to increased blood pressure[31].

Multiple studies have shown that MS parameters are associated with a greater cardiovascular risk in adults. Thus, childhood obesity must be prevented during the early years. Management of obesity includes diet, regular exercise, and oral antidiabetic agents.

Conclusion

Childhood obesity has close relationships with CVD, adulthood obesity, and MS. Obesity, physical inactivity and a poor diet must be addressed in obese children, in whom low HDL levels are very important, as they contribute to the development of MS.

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