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Homeostatic model assessment of insulin resistance as a predictor of metabolic syndrome: Consequences of obesity in children and adolescents

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KEYWORDS

Insulin resistance;
Metabolic syndrome;
HOMA-IR;
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Abstract *Background:* Obesity and/or insulin resistance have gained increasing attention as the core manifestations of metabolic syndrome.
Objective: To evaluate insulin resistance according to homeostasis model assessment of insulin resistance index HOMA-IR in obese children and adolescents with or without metabolic syndrome at risk of type 2 diabetes mellitus.
Design and subjects: 60 obese children and adolescents were recruited, metabolic syndrome was diagnosed according to the modified WHO criteria adapted for children and adolescents. Insulin resistance was calculated using the HOMA-IR.
Results: Metabolic syndrome (MS) was found in 42 subjects (70%), using modified WHO guidelines for diagnosing MS. On comparing MS-related parameters between the groups with (MS+) and without metabolic syndrome (MS−), median body mass index, waist circumference, waist/height ratio, and blood pressure, total cholesterol and triglyceride were significantly higher in the MS + group. Basal insulin level as well as HOMA-IR was also significantly different between MS+ and MS-groups. The presence of insulin resistance according to HOMA-IR was identified in 53% of obese children and adolescents. This HOMA-IR age and sex limit was exceeded by 70% children in the MS + group, but only by 43% children in the MS-group ($p < 0.001$). HOMA-IR was positively correlated with the majority of anthropometric and biochemical parameters. The correlation was strongest with body mass index, waist circumference and diastolic blood pressure.
Conclusions: HOMA-IR might be a reliable surrogate measure of insulin resistance and a strong predictor of type 2 diabetes in obese adolescents allowing the development of preventive measures and treatment when needed.

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Introduction

The prevalence of overweight and obesity in children is increasing worldwide at an alarming rate in both developing and developed countries.[1] Obesity is associated with a heterogeneity of metabolic abnormalities, e.g., dyslipidemia, insulin resistance, hyperglycemia, and hypertension that may provide a plausible biologic link between obesity and the increased risk of cardiovascular morbidity and mortality. Metabolic syndrome (MS) has been defined as a cluster of risk factors for atherosclerosis that include insulin resistance, dyslipidemia, abdominal obesity and often hypertension. The clustering of these risk factors for cardiovascular disease (CVD) is referred to as (MS).[2,3] Patients with MS are at increased risk of cardiovascular disease (CVD) and type 2 diabetes mellitus (DM). Obesity and/or insulin resistance (IR) have gained increasing attention as the core manifestations of the syndrome.[4] MS has generated a great deal of interest in recent years, comprised of a constellation of anthropometric, physiologic, and biochemical abnormalities, MS is a risk factor for CVD and diabetes among adults.[5] Diagnosis of MS aims to detect patients at risk for cardiovascular and metabolic diseases.

The first criterion of MS was presented in 1998 by the World Health Organization (WHO), with emphasis on risk factors for diabetes mellitus type 2 (T2D).[6] In 2001, the Adult Treatment Panel III (ATP) presented a definition of MS focused on cardiovascular diseases. Finally, in 2007 the International Diabetes Federation (IDF) developed a criterion addressed to children aged 10 and older.[7] Of MS components, insulin resistance is believed to have a central role in metabolic dysfunction, leading to problems such as hyperlipidemia, hepatic steatosis, and atherosclerosis, which may progress to cardiovascular diseases and T2D.[8,9] The impairment of the homeostatic relation between plasma insulin and glucose concentrations is a symptom of insufficient insulin efficiency that can be evaluated using the so called HOMA-IR.

Homeostatic model assessment for insulin resistance (HOMA-IR), a relation between fasting glucose and insulin has been recognized as the most sensitive and specific method for measuring insulin resistance and risk for T2D.[10]

Aim of the work

The present study aimed to evaluate the prevalence of metabolic syndrome and role of dysregulated glucose homeostasis as consequences of obesity in children and adolescents at risk for T2D.

Patients and methods

A total of 60 obese children and adolescents aged 8–18 years; 38 boys and 22 girls were enrolled from attendants of pediatric genetic and endocrinology unit and pediatric outpatient clinic of Menoufia University Hospitals, Egypt. Some female adolescents especially from rural areas refuse to share in our study that is why we have higher male: female ratio in our sample of patients 1.7:1. We included in our study both children and adolescents to have a relatively larger sample of patients. Written consent had been taken from every child included in the study or their participant parents. While collecting data, those who had secondary or known genetic causes of obesity were excluded. Children and adolescents were assessed carefully in terms of family history, blood pressure, and skin findings as acanthosis nigricans.

Anthropometric assessments

All anthropometric measurements were taken with stress on body height and weight that were measured in light clothes using a portable stadiometer. Body mass index (BMI) was calculated as weight divided by the square of the height (kg/m^2). Obesity was defined according to both BMI and waist circumference. BMI percentiles were calculated according to international survey study.[11] Subjects with BMI $\geqslant$ 95 were defined as obese. To define abdominal obesity, waist circumference was measured using non stretchable tape measure with the participant standing comfortably with his or her weight evenly distributed on both feet, and the feet about 12–15 cm apart. The measurements were taken midway between the inferior margin of the last rib and the crest of the ileum, in a horizontal plane at the end of expiration.

Waist circumference (WC) was measured at the high point of the iliac crest to the nearest 0.1 cm at the end of normal expiration with a non stretchable tape. Hip circumference was measured around the point with the maximum circumference over the buttocks. Waist/hip ratio (WHR) and waist/height ratio (WHtR) were calculated. Blood pressure was measured under standard conditions. Measurements were obtained for each participant three times by the auscultation method with appropriate cuff size after 20 min of rest.[12] 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. All measures were evaluated according to appropriate centiles.[13]

Pubertal staging was evaluated according to Tanner and Whitehouse.[14] Tanner stage I was defined as pre-puberty, Tanner stages II–IV as mid-puberty and Tanner stage V as post puberty.[15]

Laboratory assays

All participants performed an oral glucose tolerance test (OGTT) as follows: after a 12 h overnight fast, a venous catheter was inserted in an ante-cubital vein; fasting blood sample was withdrawn for estimation of fasting plasma insulin (FI), and fasting blood glucose (FBG). Participants then ingested 1.75 mg/kg glucose (maximum 75 g), and blood samples were withdrawn again after 30, 60, 90 and 120 min for estimation of plasma insulin and blood glucose. The glucose oxidase method was used in the determination of blood glucose levels. Insulin levels were measured using a radioimmunoassay kit.

The venous blood sample was also analyzed for lipid profile including: total cholesterol (TC), triglycerides (TG), low density lipoprotein (LDL), and high density lipoprotein-cholesterol (HDL). Serum lipids including, serum total cholesterol (TC) and low density lipoprotein cholesterol (LDL-C), were assayed by standard enzymatic methods with the use of Beckman synchron CX5 chemistry analyzer (Diamond Diagnostics, USA).[16] LDL is not directly measured in the routine lipid panel; instead it is calculated by the Friedewald equation.

This equation is: LDL Cholesterol = Total Cholesterol − HDL cholesterol-(Triglycerides/5).[17]

For abnormal glucose homeostasis and hyperinsulinemia: abnormal glucose homeostasis was defined in the presence of any of the following criterion: Impaired fasting glucose (IFG) ⩾100 mg/dl according to the new cutoff value recommended by the American Diabetes Association (ADA).[18] Glucose at 120 min 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 cutoff values. For fasting insulin level, it was defined from any of the following norms for pubertal stage: pre-pubertal (⩾15 mU/L), mid-puberty (Tanner stages II–IV, ⩾30 mU/L), and post-pubertal (⩾20 mU/L).[19]

The estimate of insulin resistance was calculated as proposed by Matthewes et al. for homeostasis model assessment for insulin resistance (HOMA-IR) index. HOMA-IR was computed as follows: [fasting insulin (mU/L) × fasting glucose (mmol/L)]/22.5.[20] HOMA-IR cut-off value for diagnosing insulin resistance/impaired insulin sensitivity from 95th percentile according to pubertal stage.[21]

Definition of components of MS was made following modified WHO criteria adapted for children and adolescents.[22] Diagnosis was made in the presence of obesity (BMI > 95th percentile) plus two or more of the following risk factors:

Glucose homeostasis (hyperinsulinemia, pre-pubertal (⩾15 mU/L), mid-puberty (⩾30 mU/L), and post-pubertal (⩾20 mU/L), fasting glucose ⩾100 mg/dl and impaired glucose tolerance: 120 min ⩾ 140 mg/dl), elevated blood pressure (systolic blood pressure (SBP) >95th percentile for age sex and height), dyslipidemia (TG > 105 mg/dl for children <10 years and >136 mg/dl for children ⩾10 years, TC levels are greater than cutoff point across sex and age groups. HDL-Cholesterol <35 mg/dl).[23] Children not fulfilling the MS diagnostic criteria were included to the group without metabolic syndrome (MS−).

Statistical analysis

Quantitative data are expressed as mean ± standard deviation and qualitative data are expressed as number and percent. All parametric data were analyzed by the independent Student's *t*-test in categorical groups. All non-parametric data were analyzed by Chi-square test. Pearson's correlation coefficient was calculated to assess the strength of relationship between HOMA-IR and other variables. A *p*-value of <0.05 was considered statistically significant.

Results

The clinical characteristics of the study group of obese children and adolescents are shown in Table 1. There were no major sex differences except of greater WC and WHR in girls. Using modified WHO criteria, MS was found in 42 subjects. According to the HOMA-IR index, IR was identified in 53% obese children and adolescents, 70% of which were in the group of MS+. The comparison of the clinical and laboratory features between the groups with (MS+) or without metabolic syndrome (MS−) is shown in Table 2. Median BMI, WC, WHtR, and BP were higher in the MS + group. Serum levels of TG were higher, and HDL-C levels were lower in the group with MS than in those without. FG and glucose 120 were significantly higher in the MS + group. Basal insulin as well as HOMA-IR was also significantly different between MS+ and MS-groups. HOMA-IR was positively correlated with major MS-related parameters. The correlation was strongest with BMI, WC and DBP (Table 3).

Discussion

The prevalence of obesity among children and adolescents is progressively increasing around the world.[24] MS is highly

Table 1 Clinical characteristics of the studied groups.

	Boys (N = 38)			Girls (N = 22)			*t* test	*P*-value
	Mean ± SD	Med	*R*	Mean ± SD	Med	*R*		
Age (Y)	12.05 ± 2.54	11	8–18	12.50 ± 2.17	12	9–18	0.69	0.493
BMI (kg/m^2)	28.35 ± 1.84	28.25	25.1–32.1	27.84 ± 1.91	27.6	25.2–32.1	1.02	0.311
WC (cm)	92.36 ± 6.62	92	83–102	87.90 ± 4.84	88	80–101	2.99	0.004
HC (cm)	85.81 ± 5.96	83.5	79–99	88.31 ± 5.19	88.5	80–96	1.64	0.107
WHR	1.07 ± 0.06	0.005	0.98–1.28	0.99 ± 0.04	0.97	0.94–1.09	4.96	<0.001
WHtR	0.44 ± 0.10	0.45	0.30–0.70	0.44 ± 0.10	0.40	0.30–0.60	4.96	0.944
SBP	119.87 ± 10.96	125	100–135	120.36 ± 8.31	77.5	100–135	0.19	0.844
DBP	76.44 ± 6.25	75	65–85	76.81 ± 4.76	70	70–85	0.24	0.811
TC (mg/dl)	184.47 ± 22.84	192	102–215	190.05 ± 9.64	190	165–202	1.05	0.213
TG (mg/dl)	120.45 ± 22.75	128	80–165	101.91 ± 19.78	93	82–140	3.18	0.002
HDL (mg/dl)	35.50 ± 2.92	35	31–42	35.22 ± 2.50	35	31–42	0.36	0.715
LDL (mg/dl)	136.26 ± 5.89	136.5	120–145	136.05 ± 3.81	135.5	130–142	0.17	0.863
FG (mg/dl)	90.15 ± 10.58	89.5	70–108	95.90 ± 22.04	92	70–183	1.36	0.178
FI (mIU/dl)	20.19 ± 9.64	18.55	11.4–54.2	21.49 ± 10.62	19.05	11.6–38.5	0.48	0.630
$HOMA_{IR}$	4.48 ± 2.0	4.18	2.09–10.55	4.98 ± 2.25	4.42	2.32–11.0	0.88	0.380
Glucose 120 (mg/dl)	109.24 ± 6.71	108	98–124	111.0 ± 6.45	108	102–124	0.99	0.324

SBP, systolic blood pressure; DPB, diastolic blood pressure; TC, total cholesterol; FG, fasting blood glucose level; FI, fasting insulin level; HDL, high density lipoproteins; LDL, low density lipoproteins; TG, triglycerides; HOMA-IR, homeostasis model assessment of insulin resistance; waist, waist circumference; hip, hip circumference.

Table 2 Clinical characteristic differences between studied groups (MS+ vs. MS−).

	MS + No (%) 42(70)			MS − No (%) 18(30)			*t* test	*P*-value
	Mean ± SD	Med	*R*	Mean ± SD	Med	*R*		
Sex No (%)								
M	26(62)			12(66.7)			Chi ^{2} 0.12	0.726
F	16(38)			6(33.3)				
Age (Y)	12.52 ± 2.13	12.5	8–18	11.50 ± 2.89	11	8–18	1.52	0.132
BMI (kg/m^2)	28.97 ± 1.53	28.80	26.4–32.1	26.29 ± 1.08	26.1	25.1–28.7	6.71	<0.001
WC (cm)	92.02 ± 5.87	92	83–102	87.72 ± 6.62	84	80–102	2.50	0.015
HC (cm)	88.04 ± 5.84	88.5	80–99	83.66 ± 4.37	81	79–91	2.84	0.006
WHR	1.04 ± 0.07	1.04	0.94–1.26	1.04 ± 0.08	1.03	0.95–1.28	0.11	0.912
WHtR	0.45 ± 0.09	0.48	0.30–0.60	0.44 ± 0.11	0.40	0.30–0.70	0.30	0.006
SBP	123.74 ± 7.53	125	110–135	111.44 ± 9.93	110	100–125	5.25	<0.001
DBP	78.45 ± 4.99	80	70–85	72.22 ± 4.91	70	65–80	4.44	<0.001
TC (mg/dl)	194.29 ± 10.75	193	165–215	168.89 ± 22.72	180	102–190	4.52	<0.001
TG (mg/dl)	119.05 ± 23.37	128	84–165	101.91 ± 18.28	94.5	80–132	3.20	0.003
HDL (mg/dl)	34.11 ± 1.67	35	31–38	38.38 ± 2.47	38	33–42	7.80	<0.001
LDL (mg/dl)	137.69 ± 4.49	138	130–145	132.67 ± 5.12	133	120–142	3.80	<0.001
FG (mg/dl)	90.15 ± 10.58	92	70–183	95.90 ± 22.04	81	73–108	2.17	0.033
FI (mIU/dl)	23.72 ± 10.38	21.35	11.8–54.2	13.53 ± 2.55	12.5	11.4–19.8	5.95	<0.001
HOMA-IR	5.43 ± 2.02	4.8	2.59–11.01	2.89 ± 0.67	2.48	2.09–4.5	7.04	<0.001
Glucose 120 (mg/dl)	111.48 ± 6.37	110	101–124	106.17 ± 5.74	104.5	98–121	3.04	0.004

MS+: with metabolic syndrome.
MS−: without metabolic syndrome.

Table 3 Correlation between HOMA-IR and the studied parameters in our patients.

Parameters	HOMA-IR	
	r	*P* value
BMI (kg/m^2)	0.78	<0.001
WC (cm)	0.63	<0.001
HC (cm)	0.19	0.625
WHR	0.11	0.741
WHtR	0.07	0.564
SBP	0.45	0.01
DBP	0.61	<0.001
TC (mg/dl)	0.48	0.032
TG (mg/dl)	0.06	0.664
HDL (mg/dl)	−0.22	0.250
LDL (mg/dl)	0.26	0.049

prevalent within the adult population worldwide and is becoming a serious problem in the pediatric population as well. Unfortunately; there is no standard definition of MS for use in pediatric populations. In this study, we used modified WHO criteria with cutoff values for children and adolescents, although small number of obese children and adolescents, it is important to determine MS risk in obese children.[25,26] The prevalence of MS was 70% among our patients, mainly post pubertal. This indicates the severity of the problem among our population. It has been suggested that ethnic differences play a role in the prevalence of obesity related cardio-metabolic complications. Recent reports show that the Middle East and North Africa have the highest obesity and diabetes prevalence among young adults.[27]

There has been debate about the extent to which the metabolic syndrome defines the risk of CVD associated with insulin resistance beyond the risk associated with classic CVD risk factors (obesity, HDL, triglycerides, and blood pressure).[28] Therefore, it would be useful to understand the extent to which the presence of the syndrome is associated with IR. Several studies from different populations were conducted to establish the role of HOMA-IR and abnormal glucose homeostasis to define MS in obese adolescents.[29,30] This present study analyzed abnormal glucose homeostasis, HOMA-IR values and lipid profile in obese children and adolescents in both sexes, also taking into account anthropometric measurements associated with MS.

In our study, MS showed no association with age. This may be influenced by heterogeneity of pubertal status in different chronological ages. In the same way there was no association between gender and MS, conflicting data exist on this subject since there are publications showing higher frequencies of MS in males, others showing a slightly higher prevalence in females or as in the present work, showing no significant difference according to gender.[31] In this study, when considering anthropometric measurements, a significant difference was observed in obese children with MS+ regarding BMI, WC and WHtR. Previous studies have shown that WC and WHtR are good predictors of IR in adolescents. Khoury et al. (2013) reported that WC can be used as a well accepted marker for assessing the cardio metabolic risk and should be included as part of routine screening of obese children and adolescents.[32] Insulin resistance is commonly associated with obesity, and HOMA-IR is a sensitive and specific method for its determination.[33] However, there is no consensus on HOMA-IR cutoff values for identifying MS in children and adolescents, thus dramatically increasing the specificity and usefulness of HOMA-IR for targeting research and intervention. This distinction will be useful in studies of population known to have high genetic predisposition for diabetes in whom the range of

HOMA-IR values is likely to be higher than other populations with lower genetic susceptibility.[34] Among the variable biochemical parameters, there was a significant difference in TG level in those with MS (Table 2). The finding of TG as an associated factor for MS is congruent with the report by Koury et al. in a long follow-up study, where a significant association of high TG retained from childhood to adulthood with young adult CVD was found. Also, the association of high TG from childhood through adulthood with adult CVD could reflect the presence of pediatric MS, a known predictor of adult CVD as speculated by Koury et al. The importance of HOMA-IR index as an adequate tool for determination of IR in obese children was further supported by Makni et al. (2012) who reported that HOMA-IR correlated better with the majority of MS components in both sexes (Table 3). Sharma et al. (2011) found that HOMA-IR is a stronger indicator of MS in children than fasting blood glucose.[35] Our results showed higher rates of insulin resistance and lower rates of glucose intolerance, and none of the patients in the study had FG level $\geqslant$110 mg/dl so, diagnosing MS according to the adapted WHO criteria, considering cutoff values for IFG is 100 mg/dl and abnormal glucose homeostasis, defined in the presence of hyperinsulinemia and/or impaired glucose tolerance is important.[36–40] It takes a long time before abnormal glucose homeostasis progresses to impaired glucose tolerance, for this reason, use of modified WHO criteria for early diagnosis is essential for preventive measures.[41] So, our results based on the adapted WHO criteria, are consistent with the literature in that: insulin resistance parameters, indexed by HOMA-IR as a corner stone for defining IR, should be included among the MS diagnostic criteria for children, to reduce the number of cases with falsely negative diagnosis of metabolic syndrome.[42]

Conclusion

In conclusion, the prevalence of MS among our patients is high. HOMA-IR was identified in 53% of obese children and adolescents, 70% of which were in the group of MS+. HOMA-IR was positively correlated with major MS-related parameters. The correlation was strongest with BMI and WC. Basal insulin, FG and glucose 120 were significantly higher in the MS + group. So, dysregulated glucose homeostasis mainly HOMA-IR plays an important role in early identification and prediction of MS in obese children and adolescents which allows early intervention.

Conflict of interest

We have no conflict of interest to declare.

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