Study of Markers for Assessment of Insulin Resistance in Obese Children and Adolescents

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Original Research Article

ABSTRACT

Background: Valid and reliable methods are essential to assess the presence and the extent of insulin resistance, the associated risk factors and the effect of pharmacological and lifestyle interventions. The aim of this work was to evaluate Homeostatic model assessment of insulin resistance (HOMA-IR) for assessment of insulin resistance among obese children and adolescents.
Methods: This case control study included 40 children and adolescent with ages of 6 to 16 years who were classified into: Group I: 20 obese children and adolescents (body mass index (BMI) > 95th percentile on Egyptian growth curves and Group II: 20 healthy children as a control group of matched age and sex to group 1 and who had normal BMI. All subjects underwent 1) Thorough history taking 2) Full clinical examination 3) Laboratory investigations: Fasting blood glucose, Fasting serum insulin level, HOMA-IR, HbA1c.and OGTT.
Results: There is no significant statistical difference as regard age, height, sex and puberty staging in both groups. The mean for weight, BMI, waist circumference, hip circumference, waist/hip ratio and acanthosis nigricans were found to be significantly higher in patient group. FBG, fasting serum insulin, HbA1c and HOMA-IR were significantly higher in patient group than in control group (p <0.001). HOMA-IR was significantly correlated with HbA1c and OGTT in obese patients (p<0.001*).

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Conclusions: HOMA-IR can be used in assessment of insulin resistance among obese children and adolescents.

1. INTRODUCTION

Childhood obesity has become a serious health concern in many countries globally [1,2]. Child and adult obesity accounts for 2–8% of global health care costs [3].

Overweight and obesity in children often leads to adulthood obesity, which is associated with an enhanced risk of type 2 diabetes, metabolic syndrome, cardiovascular diseases, and different cancers. In addition, high insulin resistance is a harbinger of T2DM in obese children [4].

Insulin resistance is a key component of the metabolic syndrome, and its prevalence in the pediatric population is increasing, particularly among obese children and adolescents [5]. Several factors are implicated in the pathogenesis of obesity-related insulin resistance, such as increased free fatty acids and many hormones and cytokines released by adipose tissue [6].

Valid and reliable methods are essential to assess the presence and the extent of insulin resistance, the associated risk factors and the effect of pharmacological and lifestyle interventions. The two most common tests to assess insulin resistance are the hyperinsulinemic euglycemic clamp and the frequently sampled i.v. glucose tolerance test utilizing the minimal model. However, both these tests are not easily accomplished, are time consuming, expensive and invasive [7].

Simple methods to assess insulin resistance based on surrogate markers derived from an oral glucose tolerance test (OGTT) or from fasting insulin and glucose levels have been validated and widely used [8]. The homeostasis model assessment of insulin resistance (HOMA-IR) is the most popular for epidemiological studies. HOMA-IR is a simple and helpful tool in the assessment of insulin resistance in epidemiological studies, including subjects with both glucose intolerance, mild to moderate diabetes, and in other insulin-resistance conditions [9].

The aim of this work was to evaluate HOMA-IR for assessment of insulin resistance among obese children and adolescents.

2. SUBJECTS AND METHODS

This observational study was done Tanta University Hospital, and investigated at Clinical Pathology Department, Tanta University Hospital. They were collected during the period December 2018 to June 2020.
The study included 40 children and adolescent with ages of 6 to 16 years who were classified into:

- **Group I:** including 20 obese children and adolescents (body mass index (BMI) more than 95th percentile on Egyptian growth curves) who had regular follow up in pediatric endocrinology outpatient's clinic.
- **Group II:** including 20 healthy children as a control group of matched age and sex to group 1 and who had normal BMI for age between 10th and 90th percentiles according to Egyptian growth charts.

2.1 Exclusion Criteria

- Patients with conditions that predispose them to being overweight.
- Obese children and adolescents suffering from chronic disease.

All subjects included in the study were subjected to the following:

1. Thorough history taking: age and sex of patients, gestational age and birth weight, developmental history, history suggestive for medications or chronic diseases, dietetic history and family history of obesity or any other diseases.
2. Full clinical examination with special emphasis on:
   I. Anthropometric measurements: Height, weight and BMI, waist circumference, hip circumference and waist hip ratio (WHR).
   II. Acanthosis Nigricans.
   III. Pubertal staging: was assessed and classified according to Tanner. Therefore, individuals were considered prepubertal when they were at stage 1 and pubertal at stages 2, 3, 4 & 5.
3. Laboratory investigations including:
   Fasting blood glucose (FBG) level by using Automatic biochemical analyzer [Normal

FBG: 70 - 100 mg/dl. Impaired Fasting glucose: 100- 125 mg/dl. Provisional diagnosis of diabetes: ≥ 126 mg/dl].

- Fasting serum insulin level by using ELISA method (Normal fasting serum insulin level: < 25 μIU/L).
- Homeostatic model assessment of insulin resistance (HOMA-IR) Online Calculator [The cutoff used was greater than or equal to 3.43 for both genders [10].

$$HOMA\ IR\ =\ \frac{[\text{Fasting Insulin}\left(\frac{\mu IU}{ml}\right)\ x\ \text{Fasting Glocuse}\left(\frac{mg}{dl}\right)]}{405}$$

- HbA1c (Glycated hemoglobin) [Normal: 4% to 5.6%, Prediabetes: HbA1c 5.7% to 6.4% and Diabetes: HbA1c ≥6.5%].
- OGTT [Normal fasting: 70 to 100 mg/dl. After 2 hours: Normal, less than 140 mg/dl. Between 141mg/dL and 200 mg/dl, is considered impaired glucose tolerance. Above 200 mg/dl is diagnostic of diabetes].

In another day, OGTT for obese patients was done as follows: after 8 hours overnight fast, a venous catheter was inserted in an ante-cubital vein; fasting blood sample was withdrawn for estimation of 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 blood glucose.

2.2 Statistical Analysis

Data were analyzed by IBM SPSS version 21. The data were presented as numbers and percentages for the qualitative data, mean, standard deviations and ranges for the quantitative data with parametric distribution. Chi-square test ($\chi2$) was used in the comparison between two groups with qualitative data while Independent t-test was used in the comparison between two groups with quantitative data and parametric distribution. Spearman correlation coefficients were used to assess the significant relation between two quantitative parameters in the same group. Significance was adopted at p < 0.05 for interpretation of results of tests of significance.

3. RESULTS

There is no significant statistical difference as regard age, height and sex in both groups. The mean for weight, BMI, waist circumference, hip circumference and waist/hip ratio were found to be significantly higher in patient group. (P = 0.004, <0.001* respectively) Table 1.

Acanthosis nigricans was present in 70% of obese patient group while it was absent in control group (n=20). (P <0.001). Patient group included 9 prepubertal (Tanner 1) and 11 pubertal (Tanner 2-5) patients while control group included 10 prepubertal (Tanner 1) and 10 pubertal (Tanner 2-5) without significant statistical difference in both groups (p=0.725) Table 2.

FBG, fasting serum insulin, HbA1c and HOMA-IR were significantly higher in patient group than in control group (p <0.001) Table 3.

Blood glucose at 0min ranged from 72-121 mg/dl with a mean of (96.233±12.384) mg/dl, at 30 min ranged from 128-171 mg/dl with a mean of (141.533±11.104) mg/dl, at 60 min ranged from 120 – 175 with a mean of (135.233±13.242) mg/dl, at 90 min ranged from 115- 159 with a mean of (135.233±13.242) mg/dl and at 120 min ranged from 111-152 mg/dl with a mean of (127.867±11.063) in obese patients. Impaired FBG diagnosed in 6 patients (23%), Impaired glucose tolerance diagnosed in 5 patients (17%), while no patient was diagnosed as type 2 DM.

HOMA-IR was significantly correlated with HbA1c and OGTT in obese patients (p<0.001*) Table 4.

4. DISCUSSION

The present study was done to evaluate HOMA-IR for assessment of insulin resistance among obese children and adolescents.

In our study, FBG mean in obese patients was 99 (±11.97) mg/dl while in controls was 78.85 (±5.38) mg/dl which was significantly higher in obese patients than control group, (p <0.001). Fasting serum insulin mean in obese patients was 10.31 (± 2.86) u IU/ml while in controls mean was 7.26 (± 1.51) uIU/ml, which was significantly higher in patient group than in control group, (p <0.001). HOMA-IR in obese patients, mean was 2.55 (± 0.87) while in controls HOMA-IR mean was 1.41 (± 0.27), so it was significantly higher in obese patients than control (p <0.001).

There is still no consensus on the cutoff of HOMA-IR for the assessment of children and adolescents, as it tends to vary during these life stages. In our study, to adjust for the

physiological IR that occurs during adolescence, it was decided to use the HOMA-IR cutoff of 3.4 suggested by García Cuartero et al. [10] who assessed children and adolescents taking into account variations of this index for age and gender.

In concordance with our study, Barseem and Helwa [11] concluded that HOMA-IR is 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.

Serrano et al. [12] observed that overweight adolescents were 4.5-fold more likely to have alterations in HOMA-IR index and that these values were higher in adolescents with higher percentage of body fat. Also, Costa et al. [13] found that being overweight was associated with increased blood pressure, triglycerides, HOMA-IR index, and low HDL-C, comprising a pro-atherosclerotic profile in this population.

HOMA-IR ≥3.4 was present in 4 patients (20%) of obese children and adolescents. In our study, the identified prevalence of insulin resistance is consistent with that found by other authors who confirms the severity of the problem [11,14,15].

In agreement with our study, Mieldazis et al [16] concluded that there is a strong association between hyperinsulinemia and obesity, and that the higher the BMI, the higher the HOMA-IR index. Madeira et al. [17] also found that obese children showed differences in mean HOMA-IR, serum insulin, glucose/insulin ratio, and waist circumference. Also, Lavrador et al. [18] observed that obese patients had higher frequencies of alterations in blood glucose, HOMA-IR, triglycerides and blood pressure.

Table 1. Descriptive data of obese patients and controls

	Patient group (n = 20)		Control group (n = 20)		P-value
Age (Years)	9.975 ± 3.11		10.79 ± 3.15		0.417
Weight (Kg)	64.4 ± 24.22		43.75 ± 18.43		0.004*
Height (cm)	142.725 ± 17.81		143.65 ± 19.23		0.875
BMI (Kg/m2)	30.16 ± 5.24		20.04 ± 4.15		<0.001*
Waist Circumference (cm)	88.4 ± 17.00		60.15 ± 8.32		<0.001*
Hip Circumference(cm)	90.675 ± 18.74		70.65 ± 11.03		<0.001*
W/H ratio	0.98 ± 0.06		0.85 ± 0.04		<0.001*
Sex	N	%	N	%	P-value
Male	10	50%	8	40%	0.525
Female	10	50%	12	60%	

*Data are presented as mean ± SD or number and percent *Significant (P≤0.05), BMI: Body Mass Index, W/H ratio: Waist/hip ratio*

Table 2. Acanthosis Nigricans in the studied groups

		Patient group (n = 20)		Control group (n = 20)		P-value
		N	%	N	%	
Acanthosis	Absent	8	40%	20	100%	<0.001*
Nigricans	Present	12	60%	0	0%	
Puberty	Prepubertal	9	45%	10	50%	0.725
	Pubertal	11	55%	10	50%	

*Significant (P≤0.05)

Table 3. Fasting blood glucose, fasting serum insulin and HOMA-IR in obese patients and controls

	Patient group (n = 20)	Control group (n = 20)	P-value
Fasting Blood Glucose (mg/dl)	99 ± 11.97	78.85 ± 5.38	<0.001*
Fasting Serum Insulin (μIU/ml)	10.31 ± 2.86	7.26 ± 1.51	<0.001*
Hba1c (%)	5.57 ± 0.48	4.98 ± 0.38	<0.001*
HOMA-IR	2.55 ± 0.87	1.41 ± 0.27	<0.001*

*Data are presented as mean ± SD *Significant (P≤0.05), HOMA-IR: Homeostatic Model Assessment for Insulin Resistance*

Table 4. Correlation Coefficient between HOMA-IR and HbA1c and OGTT in obese patients

	HOMA-IR	
	r	P-value
Hba1c (%)	0.791	<0.001*
OGTT (mg/dl) at 0 Minute	0.648	<0.001*
OGTT (mg/dl) at 30 Minutes	0.509	0.004*
OGTT (mg/dl) at 60 Minutes	0.491	0.006*
OGTT (mg/dl) at 90 Minutes	0.470	0.009*
OGTT (mg/dl) at 120 Minutes	0.492	0.006*

*Significant (P≤0.05), HOMA-IR: Homeostatic Model Assessment for Insulin Resistance, OGTT: Oral Glucose Tolerance Test

In agreement with our study, Assunção et al. [19] reported a high prevalence of glucose metabolism and insulin abnormalities in this population of obese and severe obese children and adolescents, similarly to the findings described by D'Adamo and Caprio [20].

As regard, OGTT in obese patients in our study, impaired FBG diagnosed in 4 patients (20%), impaired glucose tolerance diagnosed in 3 patients (15%), while no patient was diagnosed as type 2 DM.

Weiss et al. [21] concluded that the changes of OGTT is associated with the degree of and changes in weight and waist circumference and is an independent predictor of glucose tolerance dynamics, in concordance with our study.

In contrast to Cambuli et al. [22] who reported that OGTT as currently performed in children and adolescents is not adequate as it is currently unknown whether the diagnostic fasting and 2-h cut points used for adults are applicable to children. In particular, no data are available to confirm if the cut-off value of 7.8 mmol/L (140 mg/dl) at 120 min is abnormal or normal in children, or if age and sex percentiles are needed. Despite the high frequency of IFG in their sample, results from the 2-h glucose test were not concordant.

Alberti et al. [23], reported that the validity of OGTT in children and adolescents, as it is currently designed, is a matter of debate.

In our study, HbA1c mean in obese children was 5.57% (± 0.48), while in controls HbA1c mean was 4.98% (± 0.38) which was significantly higher in obese patients than controls, (p <0.001).

Lee et al. [24] concluded that HbA1c was better than fasting glucose in predicting impaired glucose tolerance in obese children and adolescents.

In contrast to, Nowicka et al. [25] who studied the utility of hemoglobin A1c for diagnosing prediabetes and diabetes in obese children and concluded that the American Diabetes Association suggested that an A1C of 6.5% underestimates the prevalence of prediabetes and diabetes in obese children and adolescents. Given the low sensitivity and specificity, the use of A1C by itself represents a poor diagnostic tool for prediabetes and type 2 diabetes in obese children and adolescents.

In our study, there was a strong positive correlation between HOMA-IR and HbA1c, also there was a positive correlation between HOMA-IR and OGTT in obese patients.

In fact, our study confirms the literature data by showing that IR is present in obese children and adolescents, and that this condition is associated with clinical and metabolic alterations. The present findings contribute to a better understanding of the association between IR and metabolic effects frequently observed in obese children and adolescents. It is noteworthy that the observed association between IR and the variables analyzed in this study indicate an increased risk for the development of cardiovascular disease, DM2, and MS in adulthood for this group.

The number of patients in our study was relatively small and data resulting from this study should be considered as preliminary observations. Larger studies with a greater number of patients should be conducted to validate our results.

5. CONCLUSIONS

HOMA-IR can be used in assessment of insulin resistance among obese children and adolescents.

CONSENT AND ETHICAL APPROVAL

The study was approved by Tanta Medical Ethics Committee. Informed consents were taken after an explanation of the study to children and teenagers and to their parents and before the initiation of the research study.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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