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Homeostasis Model Assessment of Insulin Resistance in Obese Children as A Predictor for Metabolic Syndrome

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ABSTRACT
Background: Obesity has emerged as one of the most serious public health concerns in the 21st century. HOMA-IR scores are useful indicators of insulin resistance for research purposes.
Objectives: This study was aimed to evaluate HOMA-IR for insulin resistance in obese children, to correlate between HOMA-IR and metabolic syndrome in obese children and also to assess relation between insulin resistance and morbidity. **Subjects and Methods:** This cross-sectional study included a total of ninety overweight and obese children, aged 4-8 years, attending at El-Zahraa University Hospital and National Institute of Nutrition. This study was conducted between from January 2018 to January 2019. All studied children were subjected to anthropometric measurement, blood pressure measuring, skin finding as acanthosis nigricans. Lab investigations including measurement of HB_{A1C}, fasting serum glucose, total cholesterol, HDL-C, LDL-C, triglycerides and insulin were done. **Results:** Mean and median values of HOMA-IR were significantly higher among patients with large birth weight than low and average birth weight and among patients with positive family history of obesity than negative ones. Participants illustrated a significant positive correlations between HOMA-IR and weight and BMI, SBP, DBP and serum cholesterol **Conclusion:** It could be concluded that homeostasis model assessment of insulin resistance index HOMA-IR in obese children is increased with increased body mass index, waist circumference systolic, diastolic blood pressure, serum cholesterol, LDL-C, large birth weight, patients with positive family history of obesity and among patients with acanthosis nigricans.
Keywords: HOMA -Insulin Resistance - Overweight and Obese children.

INTRODUCTION
Obesity has emerged as one of the most serious public health concerns in the 21st century. The worldwide prevalence of childhood obesity has increased strikingly over the past 3 decades [(1)]. Obesity is a proinflammatory state that increases the risk of several chronic diseases encompassing diabetes, hypertension, dyslipidemia, cardiovascular disease, asthma, sleep apnea, osteoarthritis and several cancers in adults [(2)].
Measuring insulin resistance (IR), is therefore a useful tool to allow early intervention to prevent or delay the development of the disease. The gold standard method to measure IR is by hyperinsulinemic euglycemic clamp. However, the complexity and high cost of the test has prevented its use in daily clinical practice and in epidemiological studies [(3)].
Homeostasis model assessment for insulin resistance (HOMA-IR) index is widely used as a measure of insulin resistance in adults and has also been validated in children and adolescents. However, the HOMA calculations require measurement of plasma fasting insulin and glucose. Due to the instability of insulin, blood collected for insulin measurement has to be kept cold, immediately processed and plasma frozen as soon as possible [(3)].
HOMA-IR scores are useful indicators of insulin resistance for research purposes [(4)].
This study was aimed to evaluate HOMA-IR for insulin resistance in obese children, to correlate between HOMA-IR and metabolic syndrome in obese children and also to assess relation between insulin resistance and morbidity.

SUBJECTS AND METHODS
This cross-sectional study included a total of ninety overweight and obese children, aged 4-8 years, attending at El-Zahraa University Hospital and National Institute of Nutrition. Written informed consent from all the parents of the subjects were obtained. This study was conducted between from January 2018 to January 2019.

Ethical consideration:
Approval of Research Ethics Committee of Pediatric Department and Al-Azhar Faculty of Medicine for girls was obtained.

Inclusion criteria
- Both sexes were included.
- Body mass index (BMI) z- score exceeded 2 or 3 standard deviation according to WHO BMI chart recruited for the study [(5)].

Exclusion criteria
- Age less than 4 year and more than 8 years.
- obese children with:

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1. Medications causing weight gain as (sulfonylureas, cortisol, tricyclic antidepressant and monoamine oxidase inhibitors).
2. Hormonal disorders as (growth hormone deficiency or resistance, hypothyroidism, leptin deficiency or glucocorticoid excess).
3. Any infectious disease
4. Genetic disorders as (prader willi syndrome, down syndrome, turner
5. syndrome, laurance Moon Biedel syndrome)
6. Children with skeletal abnormalities and congenital malformation
7. Children with chronic disease.
8. Children with known co-morbidities such as Type 2 Diabetes mellitus , hypertension and cardiovascular disease.

Standardized data sheet appendices were utilized to record patient's history, clinical examination and investigations that were performed as follows:

1- ***Full history taking:*** *a*ge and sex, past medical history, family history, drug history and early onset of obesity.

2- ***Full clinical examination:*** Anthropometric measurement (weight, height, waist circumference)

Weight, was measured in light clothing without shoes and socks to the nearest 0.1 kg using a pre-calibrated body impedance analyzer (BODY COMPOSITION ANALYZER, model TBF-300).

Height: was measured without shoes to the nearest 0.1 cm using calibrated stadiometer (RAVEN EQUIPMENT LIMITED , ENGLAND).

Body Mass Index (BMI): BMI z- score According to WHO BMI chart [5].

Overweight: Defined as BMI z-score ≥ 2 SD.

Obesity: Defined as BMI z-score ≥3 SD.

Waist Circumference: was measured at the minimum circumference between the iliac crest and the rib cage using a tape measure [6].

Blood pressure (systolic and diastolic blood pressure) measurement. Two readings of blood pressure was measured after 5 minutes of resting in sitting position using a mercury sphygmomanometer (ALPK2 , JAPAN) [7].

Examination of Acanthosis Nigricans (AN) (Acanthosis nigricans was a brown to black, poorly, velvety hyperpigmentation of the skin. It is usually found in body folds such as the posterior and lateral folds of the neck, the armpits, groin, navel, forehead, and other areas. It's most common in those who are overweight, have darker skin, and have diabetes or prediabetic conditions) [8].

3-Laboratory investigations: **Fasting serum glucose, insulin, total cholesterol, HDL-C, LDL-C and triglycerides were measured.**

Sampling: Fasting venous blood samples were obtained and distributed between EDTA containing tube for measuring HB_{A1C} and plain tubes for separation of serum to measure glucose, total cholesterol, HDL-C, LDL-C, triglycerides and insulin.

- HOMA will be calculated by multiplying the value of fasting insulin and fasting glucose and divided by 22.5. The score of ≥3.5 was classified as insulin resistance, while a score of less than 3.5 was considered as insulin sensitive [7].

$$\text{HOMA-IR} = \frac{\text{Glucose} \times \text{Insulin}}{\text{(Glucose in molar unit mmol/l)}} \quad 22.5$$

Metabolic syndrome will be considered present if the waist circumference measurement was ≥ 90thcentile of the waist circumference chart .with the presence of at least two of the following criteria; triglycerides ≥ 1.7 mmol/L, HDL cholesterol < 1.03 mmol/L, systolic blood pressure ≥ 130 mmHg and/or diastolic blood pressure ≥ 85 mmHg, or fasting plasma glucose ≥ 5.6 mmol/L [9].

Statistical analysis

The collected data were tabulated and analyzed using SPSS version 18 soft ware (Spss Inc, Chicago, ILL Company). Categorical data were presented as number and percentages. Chi square test (X^2), or Fisher's exact test (FET) were used to analyze categorical variables. Quantitative data were tested for normality using Shapiro-Wilks test, assuming normality at P>0.05, they were expressed as mean ± standard deviation if normally distributed or median and IQR if not. Student "t" test was used to analyze normally distributed variables among 2 independent groups. While non parametric variables were analyzed using Man Whitney U test. Spearman's correlation coefficient (rho) was used to assess liner associations between variables. The accepted level of significance in this work was stated at 0.05 (P <0.05 was considered significant). *P value >0.05 is non significant (NS) P<0.05 is significant (S) .P≤0.001 is highly significant (HS).*

RESULTS

Table **(1)** shows that there was no statistically significant difference regarding sex or educational level (P>0.05 for both), while it was significant to birth weight (P<0.05).

Table **(2)** shows that there was no statistically significant difference regarding history of asthma, physical activity or easily fatigability (P>0.05 for all).

while it was significant among patients with positive family history of obesity (P<0.05).

Table **(3)** shows that there was no statistically significant difference in the level of HOMA-IR regarding sleep disorders (P>0.05) while it was significant among patients with acanthosis nigricans (P<0.05).

Table **(4)** shows that there were significant positive correlations between HOMA-IR and weight and BMI (p=0.002 and <0.001 respectively). On the other hand, its correlations with age and length were non significant (P>0.05 for both).

Table **(5)** illustrates that there was significant positive correlations between HOMA-IR and waist circumference and W/H ratio (P<0.05 for both). On the other hand, its correlations with hip circumference and triceps skin fold thickness were non significant (P>0.05 for both).

Table **(6)** illustrates that there were significant positive correlations between HOMA-IR and S cholesterol and LDL (P<0.05 for both).While, its correlations with S triglycerides and HDL were non-significant (P>0.05 for both).

Table **(7)** shows Prevalence of HOMA IR among the studied sample was (14.4%) , prevalence of WC centiles >90 centiles was (71.1%), prevalence of BP centile >90 centiles was (68.9%), prevalence of dyslipidemia was (53.3%).

Regarding WC, it was found that they were statistically significantly higher among insulin resistance group than non-insulin resistance group. BP centile was significantly higher among insulin resistance group than non insulin resistance group.Dyslipidemia was significantly higher among insulin resistance group than non insulin resistance group Table **(8)**.

Table (1): Relation between socio demographic characters and HOMA IR level

		HOMA IR					Z_{MWU}	P value
		Mean	Standard Deviation	Median	Minimum	Maximum		
Sex	**M**	2.02	1.52	1.58	.70	9.76	0.569	0.569
	F	2.12	1.38	1.55	.70	7.34		
education of mother	**low**	2.05	1.41	1.58	.70	9.76	0.044	0.965
	high	2.12	1.57	1.56	.79	7.34		
birth weight	**low**	1.37	.57	1.08	.76	2.33	KW =8.31	0.016
	average	1.94	1.36	1.50	.70	9.76		
	large	2.78	1.74	2.28	.70	7.34		

Z_{MWU} → Z value of Mann Whitney U test KW= Kruskal Wallis test

Table (2): Relation between history, lifestyle and HOMA IR level

		HOMA IR					Z_{MWU}	P value
		Mean	Standard Deviation	Median	Minimum	Maximum		
family history of obesity	**yes**	2.59	1.80	2.27	0.70	9.76	3.162	0.002
	no	1.60	.78	1.39	0.76	4.53		
history of asthma	**yes**	2.35	1.66	1.90	0.76	7.34	0.748	0.455
	no	1.96	1.35	1.56	0.70	9.76		
physical activity	**yes**	2.01	1.16	1.64	0.79	5.56	0.246	0.806
	no	2.10	1.58	1.52	0.70	9.76		
easily fatigability	**yes**	**2.14**	1.75	1.51	.70	9.76	0.585	0.558
	no	**2.00**	1.06	1.74	.70	5.56		

Table (3): Relation between sleeping disorder, acanthosis nigra and HOMA IR level

		HOMA IR					Z_{MWU}	P value
		Mean	Standard Deviation	Median	Minimum	Maximum		
sleep disorder	**yes**	2.30	1.85	1.57	.76	9.76	0.506	0.613
	no	1.90	1.06	1.57	.70	5.56		
acanthosis nigercans	**yes**	2.45	1.70	1.76	0.98	9.76	3.128	0.02 (S)
	no	1.53	0.71	1.44	0.70	4.01		

Table (4): Correlation between HOMA IR and anthropometric measures

		HOMA IR
Age (years)	**Correlation Coefficient**	-.006-
	P value	.959
	N	90
Weight (kg)	**Correlation Coefficient**	0.323
	P value	0.002
	N	90
Hight (cm)	**Correlation Coefficient**	-.006-
	P value	.954
	N	90
BMI (kg/m^2)	**Correlation Coefficient**	0.440
	P value	< 0.001
	N	90

Table (5): Correlation between HOMA IR and anthropometric measurement

		HOMA IR
waist circumference	**Correlation Coefficient**	0.371
	P value	<0.001 (HS)
	N	90
hip circumference	**Correlation Coefficient**	.072
	P value	.498
	N	90
W/H ratio	**Correlation Coefficient**	0.279
	P value	0.009
	N	76
triceps skin fold	**Correlation Coefficient**	.091
	P value	.392
	N	90

Table (6): Correlation between HOMA IR and lipid profile among cases

		HOMA IR
Cholesterol	**Correlation Coefficient**	.256
	P value	0.015
	N	90
Triglycerides	**Correlation Coefficient**	.053
	P value	.622
	N	90
HDL-C	**Correlation Coefficient**	-.132-
	P value	.215
	N	90
LDL-C	**Correlation Coefficient**	.314
	P value	.003
	N	90

Table (7): Description (count and % in the study group)

		Count	%
HOMA IR	**>3.5**	13	14.4%
	<3.5	77	85.6%
F sugar >100	**Yes**	18	20.0%
	No	72	80.0%
waist circumference centile	**>90 percentile**	64	71.1%
	<90 percentile	26	28.9%
BP centile	**>90 percentile**	62	68.9%
	<90 percentile	28	31.1%
dyslipidemia	**Yes**	48	53.3%
	No	42	46.7%

Table (8): Relation between HOMA IR and other components of metabolic syndrome

		HOMA IR				
		>3.5		<3.5		P value
		Count	N %	Count	%	
F Sugar >100	**Yes**	11	84.6%	7	9.1%	<0.001
	No	2	15.4%	70	90.9%	
waist circumference centile	**>90 percentile**	13	100.0%	51	66.2%	0.017
	<90 percentile	0	0.0%	26	33.8%	
BP centile	**>90 percentile**	13	100.0%	49	63.6%	0.008
	<90 percentile	0	0.0%	28	36.4%	
dyslipidemia	**Yes**	12	92.3%	36	46.8%	0.002
	No	1	7.7%	41	53.2%	

DISCUSSION

This study showed that, there was no statistically significant difference in the level of HOMA-IR regarding sex (P>0.05). This agreed with the result of the study done by [10] who found that, there was no statistically significant difference between sex and level of HOMA-IR.

Lentferink *et al.* [11] reported that in children, girls were significantly more diagnosed with IR. This is in concordance with recent literature; in addition, a higher prevalence of IR in girls without obesity is described [12]. This result can be explained by the fact that pubertal development starts earlier in girls. In adolescents, no difference in gender was observed, possibly because the degree of obesity blurred the effect of puberty as described earlier.

This study showed that, mean and median values of HOMA-IR were significantly higher among patients with large birth weight. **These results was nearly agreed with Lentferink *et al.*** [11]**.** As regard family history of obesity the study showed that, mean and median values of HOMA-IR were significantly higher among patients with positive family history of obesity than negative ones This is similar to the results of the study done by **Corica *et al.*** [13] who **reported** that a family history for obesity is an important risk factor for precocious obesity onset in childhood and influences the severity of obesity; and metabolic profile, especially HOMA-IR, is altered even among the youngest obese children at first evaluation.

When we studied the mean value of HOMA-IR among patients with acanthosis nigricans it was significantly higher when compared to those without than without acanthosis nigricans (2.45 and 1.53 respectively) P<0.05.This agreed with **Koh *et al.*** [14] who found that, the With acanthosis nigricans group had higher HOMA-IR score (5.74±4.71 vs. 2.14±0.86, p<0.001) than Without acanthosis nigricans group. HOMA-IR scores increased with acanthosis nigricans severity, from the without acanthosis nigricans group. Insulin resistance worsens with increasing acanthosis nigricans severity, and patients with Severe acanthosis nigricans (acanthosis nigricans score ≥3) are at increased risk of insulin resistance.

Acanthosis nigricans is known to occur when the concentration of insulin-like growth factor receptors in the skin is too low relative to the amount of insulin present, causing accumulation of insulin in the skin, proliferation of epidermal cells, and thickening of keratocytes acanthosis nigricans is associated with obesity and endocrine diseases caused by severe insulin resistance, and may rarely be seen in patients with genetic diseases or malignant tumors [15].

The development of insulin resistance in obese patients can cause several metabolic abnormalities to occur simultaneously. This phenomenon was first named "syndrome X" by **Reaven** [16]. Since then, various studies have demonstrated that insulin resistance can cause dyslipidemia, fatty liver disease, hypertension, and type 2 diabetes, and this phenomenon is now more commonly referred to as "metabolic syndrome" [17].

Kahn *et al.* [18] first suggested an association between acanthosis nigricans and insulin resistance in obese children in 1976. Since then, many studies have been conducted with the aim of utilizing acanthosis nigricans as an indicator for insulin resistance [19]**.**

In our studied participants illustrated that there were significant positive correlations between HOMA-IR and weight and BMI (p=0.002 and <0.001 respectively).

Vrablík *et al.* [20] demonstrated the correlation of AIP with BMI and HOMA-IR in children.

This similar to the result of the study done by **Iwani *et al.*** [1] who found that, BMI was statistically significantly higher among insulin resistance group.

This agreed also with **Romualdo *et al.*** [21] who found, there were significant positive correlations between HOMA-IR and weight and BMI.

As regard systolic and diastolic blood pressure there were significant positive correlations between HOMA-IR and SBP and DBP (P<0.001for both).

This agreed with **Barseem and Helwa** [22] who found that, the correlation was strongest with body mass index, systolic and diastolic blood pressure.

Our study results revealed significant positive correlations between HOMA-IR and waist circumference and W/H ratio (P<0.05 for both). This agreed with **Bacopoulou *et al.*** [23] who found that, central obesity is one of the strongest indicators of insulin resistance. He stated that WC, WHR and WHtR are the useful measurements for central obesity, and WC is the most sensitive index. This could be explained by that individuals with higher WC have more visceral fat and are more susceptible to chronic diseases caused by insulin resistance than those with lower WC and the same BMI [24].

Korean studies **Kim *et al*** [25] **and Kang *et al.*** [26] adopted the stratification of WC to dispel its effect on insulin resistance as well. One also had exceptional conditions which were analogous to ours.

Insulin resistance influences the link between obesity and dyslipidemia. **Vukovic *et al.*** [27]

demonstrated that HOMA-IR was strictly related to lipid profile in their pediatric population.

As regard lipid profile among studied group there were no significant correlations between HOMA-IR and S triglycerides and HDL.

This agreed with **Barseem and Helwa** [22] who found that, there were no significant correlations between HOMA-IR and S triglycerides and HDL (P>0.05 for both).

In this study there were significant positive correlations between HOMA-IR and S cholesterol and LDL (P<0.05 for both).

This agreed with **Barseem and Helwa** [22] who found that, study there were significant positive correlations between HOMA-IR and S cholesterol and LDL.

Our study result revealed that, prevalence of HOMA IR among the studied sample was (14.4%). This is lower than study done by **Iwani *et al.*** [1] who found a total of 271 blood samples of obese and overweight children aged 9–16 years of whom 49% children were found to have IR.

Our study result showed that, prevalence of BP centile >90 centiles was (68.9%).

Obesity influences BP in children. In a large cohort study of more than 100,000 children and adolescents followed for several years, those with obesity and severe obesity had higher BP at baseline and a greater odd of developing hypertension years later than those of lower BMI categories [28].

Our study result showed that, prevalence of dyslipidemia was (53.3%).This agreed with **Elmaoğulları *et al.*** [29] who found that, among 823 obese patients, 353 (42.9%) had dyslipidemia.

Regarding WC, it was found that they were statistically significantly higher among insulin resistance group than non-insulin resistance group.

Bacopoulou *et al.* [23] found that, central obesity is one of the strongest indicators of insulin resistance. He stated that WC, WHR and WHtR are the useful measurements for central obesity, and WC is the most sensitive index.

It has been reported that individuals with higher WC have more visceral fat and are more susceptible to chronic diseases caused by insulin resistance than those with lower WC and the same BMI [1].

In this study BP centile was significantly higher among insulin resistance group than non insulin resistance group.

The same observation was reported by **Armato *et al.*** [30] who revealed that individuals with insulin resistance had significantly higher BP.

This study showed that, dyslipidemia was significantly higher among insulin resistance group than non-insulin resistance group.

This is similar to the results of the study done by **Kim-Dorner *et al.*** [3] who found that, IR was associated with dyslipidemia.

As shown in many studies, hypertriglyceridemia and decreased HDL-C are the hallmarks of dyslipidemia which is a characteristic of insulin resistance and T2D. The Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY) study showed that 79.8% of T2D youth had a low HDL-C and 10.2% had high triglycerides within a few months of diagnosis and the SEARCH for Diabetes in Youth study found that 73% of 2096 US youth with T2D of longer duration had lower HDL and 60–65% had hypertriglyceridemia [31].

Therefore, the clinical utility of measuring TG and HDL-C extended beyond identifying patients with IR [21].

CONCLUSION

It could be concluded that homeostasis model assessment of insulin resistance index HOMA-IR in obese children were increased with increased body mass index, waist circumference systolic, diastolic blood pressure, serum cholesterol, LDL, large birth weight, patients with positive family history of obesity and among patients with acanthosis nigricans.

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