Original Article

Association of HOMA-IR and TyG Index with some acute phase reactants in obese and lean subjects

Tahrir Etihad Kadium, Abdulhadi Alrubaie, Ahmed Abed Marzook

Departments of Clinical Biochemistry and Community Medicine and Obesity Research and Therapy Unit, Alkindy College of Medicine, University of Baghdad, Iraq

Objective: To evaluate biomarkers of insulin resistance and acute phase reactants in obese, overweight and lean subjects and investigate the associations among those biomarkers.

Methodology: This cross sectional study included 158 subjects who were stratified into three groups. Group1 comprised 53 obese patients (BMI≥ 30 kg/m^2); group 2 were 54 overweight subjects, and group 3 had 51 healthy lean (BMI <25 kg/m^2). Insulin resistance biomarker was assessed by Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) and Triglyceride to Glucose (TyG) index. High-sensitivity C-reactive protein (hsCRP), ceruloplasmin (CP), haptoglobin (HP) and albumin were also evaluated as acute phase reactants (APRs).

Results: HOMA-IR and TyG index, hs-CRP, CP, HP and BMI were significantly increased in both group1 and 2 as compared to lean Subjects ($p<0.01$). Albumin levels were lower in group1versus group 2 and group 3, respectively ($p>0.05$). The TyG index and HOMA-IR showed significant positive correlations with waist circumference (WC), waist to hip ratio (WHR), BMI, HP, CP, ($p<0.001$), and negative correlation with albumin ($p<0.01$). Multiple regression analysis showed that hsCRP and CP were the most powerful predictors of insulin resistance in obese and overweight subject as compared to other APRs in this study. Additionally, WHR and BMI are strong independent risk factors for insulin resistance in these subjects.

Conclusion: Insulin resistance biomarkers HOMA-IR and TyG index were linked with acute phase reactants and obesity indices. (Rawal Med J 202;45:513-518).

Keywords: Obesity, insulin resistance, inflammation, acute phase reactants.

INTRODUCTION

Obesity is considered a critical public health concern, since these patients are more predisposed to the risks of diabetes, cardiovascular diseases and cancer.[1] In obesity, there is secretion of inflammatory proteins including adipokines like leptin, adiponectin, and serum amyloid and acute phase proteins or reactants (APRs). These proteins change their serum concentration in response to inflammatory cytokines like (IL-1, IL-6, TNFα), which may contribute to low-grade chronic systemic inflammation.[2,3] There is relation between BMI and visceral obesity and their complications, such as metabolic syndrome (MS), with high levels of C-reactive protein (CRP) and inflammatory acute phase proteins. Some of the APRs have been linked with impaired glucose tolerance.[4] Muhammed et al showed a strong association of APRs like fibrinogen, orosomucoid, haptoglobin (HP), and alpha-1-antitrypsin in patients with diabetes.[5] Low-grade systemic inflammation is often related to insulin resistance (IR) and impaired insulin secretion or action, the corner-stone mechanisms underlying type 2 diabetes.[6]

Serum fasting Triglyceride to Glucose index (TyG index) presents a sensible powerful substitute marker for estimating the Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) index in healthy subjects and for identifying IR with a high sensitivity and specificity compared with the euglycemic hyperinsulinemic clamp test.[7-9] However, there is a lack of evidence about the relationship between TyG index as a biomarker of IR and these acute phase proteins in obese subjects. The aim this study was to evaluate insulin resistance biomarkers (HOMA-IR; TyG index) and APRs such as CRP, HP, ceruloplasmin (CP) and albumin in obese, overweight and lean subjects and investigate the associations among those biomarkers.

METHODOLOGY

This cross-sectional study was conducted at Obesity Research and Therapy Unit (ORTU), Alkindy College of Medicine, Baghdad from October 2018 to May 2019. After ethical approval for the study protocol by Alkindy College of Medicine, all participants gave their informed consents to be included in the study. Inclusion criteria for study participants were age 20-60 years by convenience sampling. Exclusion criteria were history of hypothyroidism, diabetes, hypertension, pregnancy, alcohols, smoking or current use of antibiotics and/or anti-inflammatory drugs, cancer, and infectious diseases. A total of 158 subjects were included (68 male and 90 females); and stratified into three groups according to BMI; Group 1 obese patients (BMI $\geq$30 kg/m^2); Group 2 overweight subjects (30>BMI $\geq$ 25 kg/m^2); and group 3 included healthy lean volunteers (BMI <25 kg/m^2).

The anthropometric measurements included body height, weight (Wt.), hip, waist circumference (WC) and waist to hip ratio (WHR) were measured according to the standardized methods.

BMI was estimated based on equation: BMI= weight (kg)/height (m^2).[10]

Blood samples were drawn for serum total proteins, albumin, fasting serum glucose (FSG), and triglycerides (TG) (Diagnostic kits; Human, Germany). Serum fasting insulin levels were measured by enzyme-linked immunosorbent assay (ELISA) (Demeditec Diagnostics, Germany).

Serum APRs levels were measured using diagnostic ELISA kits according to the instructions of the manufacturers (hs-CRP; Demeditec Diagnostics GmbH, Germany; HP and CP; Shanghai Yehua Biological Co. Ltd, China).

Estimation of Insulin Resistance Biomarkers like FSG and insulin levels were used to calculate the HOMA-IR with (HOMA2) version calculator available at: http: //www.dtu.ox.ac.uk/homacalculator/index.php.[11] The TyG index was calculated by the equation: TyG index = Ln [Fasting TG (mg/mdl) * Fasting Glucose (mg/dl) /2].[8,9]

Statistical Analysis: The SPSS version 24 was used for statistical analysis. The data were analyzed for significance among the selected groups by one-way analysis of variance (ANOVA). The least significant difference (LSD) method was used to compare the individual studied groups. Correlations among the study analytes assessed by Pearson's correlation coefficients. Multiple regression analysis was determined in the population using HOMA-IR and TyG index as dependent variables. $p<0.05$ was considered statistically significant.

RESULTS

The basic anthropometric and biochemical variables of the participants enrolled in the present study are summarized in Table.1. Significant differences were observed in mean levels of BMI, WC, WHR, FSG, Insulin, TG, total proteins, HOMA-IR and TyG index among the studied groups. These markers tended to increase significantly in obese group1 as compared to lean subjects. The acute phase reactants (APRs) including (high sensitivity C-reactive proteins) hsCRP, ceruloplasmin (CP), and haptoglobin (HP) were significantly increased in both group 1 and 2 when compared to group 3.

Both TyG index and HOMA-IR showed a significant and positive correlations with WC, Hip, WHR, Wt., BMI, FSG, insulin, TG, total proteins, HP, CP, and a negative correlation with albumin (Table 2). Multiple linear regression analysis was performed using HOMA-IR and TyG index as the dependent variables and the other biochemical, anthropometric and APRs as the independent variables (Table 3).

DISCUSSION

In this study, the levels of HOMA-IR and TyG index were significantly increased; as well as the levels of hs-CRP, CP and HP (as positive acute phase reactants) in group 1 (obese) and group 2 (overweight) as compared to the levels of these analytes in group 3 (healthy lean). Furthermore, significant associations were found between HOMA-IR, TyG index with anthropometric and biochemical parameters. These results are consistent with previous studies that linked obesity, IR, and inflammation.[2,3,12,13,14] Accumulation of advanced glycation end products and oxidative stress are suggested causes for the impairments in endothelial cell function as a consequence of obesity and IR.[15]

Table 1. The anthropometric, biochemical variables and Acute phase reactants of participants.

Parameters	Group1 (Obese)	Group2 (Overweight)	Group3 (Lean)	*P* value
n (%)	53 /158 (33.6%)	54 /158 (34.1)	51/158 (32.3)	
Male/Female Ratio	23/30	24/30	21/30	
Age (year)	34.49 ± 10.42	36.78 ± 13.12	34.28 ± 11.19	0.760
Systolic blood pressure (mmHg)	117.3 ± 2.1	109.5±1.9	102.4± 2.3	0.002**
Diastolic blood pressure (mmHg)	69.3±1.6	65.1±2.2	63.3±1.5	0.041*
Waist Circumference (cm)	113.91±11.65	90.35 ± 5.33	76.78±4.39	0.001**
Hip (cm)	123.12 ± 10.01	105.58 ± 3.68	95.37 ± 5.11	*P* <0.001***
Waist to Hip Ratio (WHR)	0.93 ± 0.05	0.87±0.06	0.74± 0.04	*P* <0.001***
Weight (k)	105.9 ± 21.45	79.40 ± 8.19	62.9 ± 5.26	*P* <0.001**
Height (m)	1.62± 0.97	1.68±0.95	1.64±0.84	0.145
BMI (kg/m^2)	39.81 ± 7.2	27.02 ± 1.12	23.16 ± 1.4	0.001**
Fasting Serum Glucose (mg/dl)	105.22±20.13	96.4±12.46	83.78±4.28	0.001**
Fasting Serum Insulin (µIU/ml)	32.25±7.43	16.01±5.59	12.67±2.75	0.001**
Fasting Triglyceride (mg/dl)	152.25±46.29	121.65±40.44	75.21±20.44	0.001**
Total Proteins (mg/dl)	9.85±1.56	9.27±0.63	8.76±0.87	0.001**
Acute phase reactants:				
hsCRP (µg/ml)	7.70± 4.25	1.29 ± 0.24	0.97±0.15	0.001**
Haptoglobin (ng/ml)	67.4 ± 17.12	61.06 ± 12.56	56.08±10.43	0.016*
Ceruloplasmin (mg/dl)	62.32±18.81	49.67±11.8	30.76±8.6	0.01*
Albumin (mg/dl)	4.93±0.33	4.98±0.39	5.02±0.65	0.622
Insulin Resistance Biomarkers:				
HOMA-IR	3.86±1.87	2.08±1.02	1.66±0.51	0.001**
TyG index	4.77±0.29	4.51±0.31	4.25±0.13	0.001**

Data are represented as (mean ± SD). hsCRP, high Sensitivity C-reactive protein. HOMA-IR, homeostasis model assessment of insulin resistance; TyG index, Triglyceride to glucose index; BMI, body mass index. Statistical significance considered at * p <0.05, ** p <0.01, ***p <0.001.

Table 2. Correlations of Study Analytes with HOMA-IR and TyG Index.

Parameters	HOMA-IR	TyG index
Age (year)	(r = 0.079, *P* =0.167)	(r = 0.353, *P*< 0.001)***
Waist Circumference (cm)	(r = 0.602 ,*P* < 0.001)***	(r = 0.464, *P*< 0.001)***
Hip (cm)	(r =0.478 , *P*< 0.001)***	(r =0.423 , *P*< 0.001)***
Waist to Hip Ratio (WHR)	(r =0.539 , *P*< 0.001)***	(r =0.418 , *P*< 0.001)***
Weight (kg)	(r = 0.66 , *P*< 0.001)***	(r =0.439 , *P*< 0.001)***
Height (m)	(r =0.062 , *P*= 0.440)	(r = 0.045 , *P* =0.584)
BMI (kg/m^2)	(r = 0.581 , *P*< 0.001)***	(r = 0.29 , *P*< 0.001)***
Fasting Serum Glucose (mg/dl)	(r =0.588 , *P*< 0.001)***	(r = 0.735 , *P*< 0.001)***
Fasting Serum Insulin (µIU/ml)	(r =0.949 , *P*< 0.001)***	(r = 0.505 , *P*< 0.001)***
Fasting Triglyceride (mg/dl)	(r = 0.520 , *P*< 0.001)***	(r =0.933 , *P*< 0.001)***
Total proteins (mg/dl)	(r = 0.357 , *P*< 0.001)***	(r =0.356 , *P*< 0.001)***
hsCRP (µg/ml)	(r = 0.588 , *P*< 0.001)***	(r = 0.445 , *P*< 0.001)***
Haptoglobin (ng/ml)	(r = 0.320 , *P*= 0.044)*	(r =0.373 , *P*< 0.001)***
Ceruloplasmin (mg/dl)	(r = 0.390 , *P*= 0.01)*	(r = 0.411 , *P*< 0.001)***
Albumin (mg/dl)	(r = -386 , *P*= 0.003)**	(r = - 0.401 , *P*< 0.001)***
HOMA-IR *vs*. TyG index	(r =0.557, *P*< 0.001)	

HOMA-IR, homeostasis model assessment of insulin resistance; TyG index, Triglyceride to glucose index; BMI, body mass index; hsCRP, high Sensitivity C-reactive protein. Values with statistical significance considered at * p <0.05, ** p <0.01, ***p <0.001.

Table 3. Multiple Regression Analysis of Study.

Parameters	HOMA-IR [a]		TyG index [b]	
	β-coefficient	Sig.	β-coefficient	Sig.
Age (year)	0.027	0.314	0.05	0.045 *
Waist Circumference (cm)	0.018	0.06	0.004	0.091
Hip (cm)	0.219	0.13	0.203	0.12
Waist to Hip Ratio (WHR)	0.078	0.036*	0.532	0.022*
Weight (k)	0.144	0.053	0.301	0.07
Height (m)	0.032	0.081	0.143	0.10
BMI (kg/m^2)	0.307	0.01**	0.149	0.023*
Fasting Serum Glucose (mg/dl)	0.151	*P*< 0.001***	0.281	*P*< 0.001***
Fasting serum Insulin (µIU/ml)	0.863	*P*< 0.001***	0.003	0.930
Fasting Triglyceride (mg/dl)	0.446	0.028	0.799	*P*< 0.001***
Total Proteins (mg/dl)	0.008	0.791	0.108	*P*< 0.001***
hsCRP (µg/ml)	0.270	0.046*	0.115	*P*< 0.001***
Haptoglobin (ng/ml)	0.001	0.381	0.018	0.453
Ceruloplasmin (mg/dl)	0.18	0.042*	0.087	0.210
Albumin (mg/dl)	- 0.044	0.333	-0.004	-0.898

a. Dependent variables HOMA-IR
b. Dependent variables TyG index
Values with statistical significance considered at * p <0.05, ** p <0.01, ***p <0.001.

Many researchers spent their efforts to detect IR biomarker at a simpler technique and inexpensive cost to replace the high-price method required for insulin and HOMA-IR estimation in laboratories. One of these, the TyG index that was regarded to be a highly sensitive and specific reliable biomarker to detect IR.[7,8,9,13] Hypertriglyceridemia may be associated with increased transport of free fatty acids to the liver, and subsequent cause of increased glucose output.[16] Therefore, evaluation of TyG index and obesity indices can be better predicters of IR.[13]

The important findings from the present study were the associations of HOMA-IR and TyG index levels with increments in FSG, WC, WHR, BMI, hsCRP, HP, and CP in the study groups. CRP was associated with HOMA-IR, TG, and to markers of endothelial dysfunction, suggesting that adipose tissue is a significant factor to explain the elevation in CRP levels and subsequently indicate a chronic inflammatory condition.[17] High levels of CRP speculated a cause of infection or inflammation that can result, with low grade inflammation and IR.[18] WHR, BMI, age, smoking habits, and TG were important predictors of elevated CRP that associated with chronic inflammation.[19,20]

In the present study CP levels was found to be increased in both obese and overweight subjects. Sharma et al.[21] suggested that serum TG and TG/HDL-C ratio are surrogate biomarker of IR that could be marked by CP evaluation. Additionally, to its role as acute phase reactant; CP could be used as substitute to reflect IR and considered a biomarker of inflammation in obesity. High levels of HP may be caused by hyperinsulinemia and is considered part of the intersection between obesity and inflammation.[22]

In addition to results of the present study, albumin levels tend to decline in obese and overweight as compared to lean subjects (as a negative acute phase reactant). Even though these results were not statistically significant. Relatively small sample size may contribute to these outcomes. A study suggested that obesity can be considered as independent predictors of low serum albumin and the increment of BMI was linked to hypoalbuminemia.[23] This explains the negative correlations between albumin with BMI (r= -0.333,

P<0.05; not shown in Tables). In addition to the negative correlations of albumin versus HOMA-IR and TyG index that were found in our study. Albumin act as an antioxidant and protecting protein versus chronic inflammation; although this antioxidant property is reduced in chronic diseases like diabetes.[24]

CONCLUSION

Our findings suggest that APRs such as hs-CRP, CP, HP are associated to IR biomarkers (HOMA-IR and TyG index). Moreover, hs-CRP, CP were the most powerful predictor of IR in obese and overweight subjects as compared to other APRs which were evaluated. Additionally, WHR and BMI are considered strong independent risk factors for IR in these subjects.

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Conception and Study Design: Tahrir Etihad Kadium, Abdulhadi Alrubaie.
Collection and assembly of Data: Abdulhadi Alrubaie, Tahrir Etihad Kadium,
Analysis and interpretation of data: Ahmed A. Marzook, Tahrir Etihad Kadium.
Drafting of the article: Tahrir Etihad Kadium.
Statistical expertise: Ahmed A. Marzook.
Final approval and guarantor of the article: Tahrir Etihad Kadium, Abdulhadi Alrubaie, and Ahmed A. Marzook.
Corresponding Author: Dr. Tahrir Etihad Kadium: tahriretihad@kmc.uobaghdad.edu.iq
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