

Surrogate Markers of Insulin Resistance: Search for Simple and Valid Marker in Adult Population Attending Tertiary Level Hospital of Bangladesh

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ABSTRACT

Background: Insulin resistance (IR) is a pathological situation characterized by a lack of physiological response of peripheral tissues to insulin action, leading to the metabolic and hemodynamic disturbances known as the metabolic syndrome. The main features of this condition include dyslipidemia (high triglyceride and low HDL cholesterol levels), hypertension, glucose intolerance or type 2 diabetes, hyperuricemia or gout, abdominal obesity, hypercoagulability and defects in the fibrinolytic system, hyperandrogenism, fatty liver, and an increased incidence of coronary heart disease. **Objective:** To determine a simple and valid surrogate marker of insulin resistance in adult population. **Methods:** Cross sectional analytical study. Apparently nondiabetic healthy adult individual (patient and their attendant) attending BSMMU outpatient department. **Results:** It was a cross sectional analytical study. 1250 adult individuals were selected from Bangabandhu Sheikh Mujib Medical University (BSMMU) outpatient department (OPD). Initially we recruited 1250 adult individuals attending BSMMU OPD. From them (N=1250), finally we enrolled 1203 adult individuals in our study because of 47 individual insulin resistance were not calculated (IR index can be calculated by HOMA calculator when insulin level is between 2.9 -57.6 µU/mL and glucose level is between 3 to 25 mmol/L). The study subjects were divided into two groups (no insulin resistance and insulin resistance). **Conclusion:** TyG related parameters for prediction of IR are cost effective and easily applicable in clinical setting compared to HOMA-IR. These parameters are based on routine laboratory measurements and simple non-invasive anthropometric parameters. On the contrary, HOMA-IR needs measurement of fasting insulin level for estimation of IR which is costly and not available in all laboratories. Therefore, based on simplicity and low-cost, we recommend TyG related parameters are clinically useful predictors of IR in adult individuals of Bangladesh attending tertiary level hospital.

Keywords: Surrogate Marker, Insulin Resistance, Valid Marker.

INTRODUCTION

Insulin is a key regulator of glucose homeostasis. IR is established by genetic and environmental factors. IR leads to impaired glucose tolerance, and plays an important pathophysiological role in the development of diabetes. In addition, IR leads to many of the metabolic abnormalities associated with metabolic syndrome/syndrome X.^[2] The hyperinsulinemic-euglycemic clamp technique (HIEG) is

generally accepted as the best available direct method to assess insulin sensitivity. However, this method has many clinical limitations, including higher cost and the requirement for invasive procedures. Several investigators have therefore proposed various indirect indices of IR (or insulin sensitivity) based on the measurement of biochemical values such as fasting blood glucose, fasting serum insulin, and lipid subtypes. The previously validated homeostasis model assessment insulin resistance index (HOMA-IR) and the quantitative insulin sensitivity check index (QUICKI) are the most widely used surrogate measures of IR. However, these indices only reflect the feedback between fasting serum insulin and glucose. Recently, other studies have shown that insulin sensitivity can additionally be influenced by other factors such as excess adiposity and dyslipidemia. Based on these factors, alternative

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surrogate markers have been developed to measure IR, which better reflect lipid profiles such as triglyceride (TG) (McAuley index) or free fatty acid (FFA) (Disse index). Several recent investigations have provided evidence that these indices better correlate with IR.^[3] Others indices have been proposed to identify IR, although the 'gold standard' method remains the euglycemic hyper-insulinemic clamp, which involves continuous intravenous infusion of insulin and measurement of the glucose disposal rate to calculate the insulin sensitivity index. The clamp procedure is, however, technically demanding and invasive, and is therefore limited to research or clinical applications in a small number of patients. Investigators have therefore sought more practical methods for assessing IR, the simplest of these being measurement of fasting insulin and glucose concentrations, with the results being expressed as either the reciprocal of insulin concentration (1/insulin) or the glucose-to-insulin ratio. Both these indices have a relatively low degree of correlation with euglycemic clamp data and have been superseded by a range of more complex mathematical models that provide more consistent and accurate information. A majority of these models are derived from glucose and insulin levels, either from numerous separate data points, as in the frequently sampled intravenous glucose tolerance test, or as a single fasting sample in the case of the homeostasis model assessment index (HOMA-IR). A similar commonly used model is the quantitative insulin sensitivity check index (QUICKI), calculated as the log transformation of HOMA-IR. More recently, an index incorporating fasting insulin and triglyceride levels, the McAuley index, has also been shown to be a sensitive marker of IR and has attracted increasing use in clinical research. The presence of the metabolic syndrome (MetS) itself is also often used as a surrogate marker of IR, with its characteristic abnormalities of a raised triglyceride (TG) to high density lipoprotein (HDL)-cholesterol ratio (TG:HDL) and low circulating levels of the insulin-sensitizing adipocytokine, adiponectin, 14–16 shown to correlate with the degree of IR.^[4]

The interest of IR and metabolic syndrome lies in their high prevalence in the population and the associated high death rate, fundamentally through coronary heart disease, even in nondiabetic subjects. The connection between IR, hyperinsulinemia, and coronary heart disease has been established by several transverse, prospective, and experimental studies. Difficulties in measuring insulin sensitivity, however, prevent identification of insulin-resistant individuals in the general population. The quantification of IR can be performed by evaluating the peripheral insulin sensitivity in vivo with methods such as the pancreatic suppression test, the hyperinsulinemic-euglycemic clamp technique, and the minimal model approximation of the metabolism of glucose (MMAMG). They are complicated, time-

consuming, and expensive methods suitable only for studies with a small number of subjects.^[1]

Objective:

Determining a clear and accurate indicator for resistance to insulin in adults.

MATERIALS AND METHODS

Type of study: Cross sectional analytical study.

Place of study: Department of Biochemistry & Molecular Biology, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh (BSMMU), Dhaka, Bangladesh.

Period of study: March 2017-February 2018.

Study subjects: Apparently, nondiabetic healthy adult individual (patient and their attendant) attending BSMMU outpatient department.

Grouping of study subjects:

- Group- A (No insulin resistance)
- Group- B (Insulin resistance)

Research instrument: Data collection sheet were prepared for the purpose of the study, which were included all the variables of interest.

Sampling Method: Non-probability sampling

Sample size: 1250 (Twelve hundred fifty)

RESULTS

It was a cross sectional analytical study. 1250 adult individuals were selected from Bangabandhu Sheikh Mujib Medical University (BSMMU) outpatient department (OPD). Initially we recruited 1250 adult individuals attending BSMMU OPD. From them (N=1250), finally we enrolled 1203 adult individuals in our study because of 47 individual insulin resistance were not calculated (IR index can be calculated by HOMA calculator when insulin level is between 2.9 -57.6 $\mu\text{U/mL}$ and glucose level is between 3 to 25 mmol/L). The study subjects were divided into two groups (no insulin resistance and insulin resistance).

All subjects were briefed about the study properly & after taking written consents, their anthropometric measurements & blood pressures (BP) were recorded. Fasting blood samples were collected from each subject with full aseptic precaution. Fasting serum glucose, insulin and lipid profile were measured in the Department of Biochemistry & Molecular Biology, BSMMU. All the variables such as HOMA1-IR, TG to HDL Ratio, VAI, LAP, BAI, TyG index and its related parameters were calculated to find out the predictors of insulin resistance among the adult individuals.

Among 1203 study subjects, Group A: IR <2.5 (No insulin resistance) 539(44.80%) and Group B: IR \geq 2.5 (Insulin resistance) 664(55.20%).

Table 1: Distribution of the study subjects according IR index (N=1203)

IR Index	Number of subjects	Percentage
Group A: < 2.5 (No insulin resistance)	539	44.80
Group B: ≥ 2.5 (Insulin resistance)	664	55.20
Total	1203	100.0

TG/HDL Ratio= Triglyceride High density Lipoprotein ratio, TyG index=Triglyceride glucose index, TyG-BMI=Triglyceride glucose-BMI index, TyG-WC=Triglyceride glucose-waist circumference index, VAI=Visceral adiposity index, LAP=Lipid accumulation product, BAI=Body adiposity index, (N=1203).

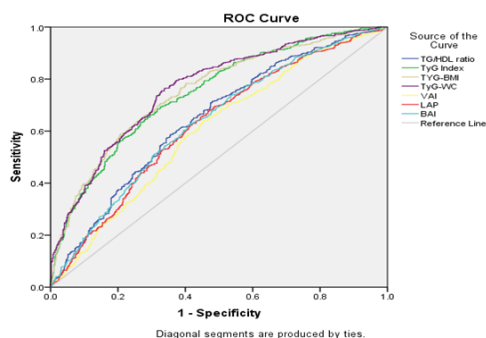


Figure 1: ROC Curves analysis on the basis of TG/HDL ratio, TyG index, TyG- BMI, TyG- WC, VAI, LAP, BAI.

TyG-BMI=Triglyceride glucose-BMI index, TyG-WC=Triglyceride glucose-waist circumference index, LAP=Lipid accumulation product, VAI=Visceral adiposity index, TyG index=Triglyceride glucose index, TG/HDL ratio= Triglyceride to High Density Lipoprotein ratio, BAI=Body adiposity index, showed maximum AUC of TyG- WC.

Table- 2: Area under the ROC curves (AUC) of different predictors of insulin resistance in adult individuals with optimal cutoff point (N=1203)

Predictors	Area Under Curves (AUC)	P Value	Optimal cutoff point (Determined by Youden Index)
TyG- WC	0.763	<0.001	805.98
TyG-BMI	0.753	<0.001	233.42
TyG Index	0.745	<0.001	8.83
TG/HDL ratio	0.645	<0.001	3.18
BAI	0.634	<0.001	32.72
LAP	0.625	<0.001	45.52
VAI	0.602	<0.001	123.43

TG/HDL ratio= Triglyceride to High Density Lipoprotein ratio, TyG index=Triglyceride glucose index, TyG-BMI=Triglyceride glucose-BMI index, TyG-WC=Triglyceride glucose-waist circumference index, BAI=Body adiposity index, VAI=Visceral adiposity index, LAP=Lipid accumulation product.

Table 3: Performance of different predictors of insulin resistance in adult individuals according to optimal cutoff point determined by Youden index (N=1203)

Predictors	Sensitivity	Specificity	PPV	NPV
TG/HDL ratio	71.4%	51.9%	64.67%	59.57%
TyG Index	68.52%	68.27%	72.55%	63.45%
TyG BMI	69.73%	68.27%	72.91%	64.61%
TyG- WC	76.35%	66.23%	73.57%	68.77%
VAI	63.86%	54.73%	63.47%	55.14%
LAP	67.62%	53.25%	64.05%	57.17%
BAI	62.05%	59.18%	65.19%	55.87%

PPV=Positive predictive value, NPV=Negative predictive value. Among them TyG- WC, TG/HDL ratio showed higher sensitivity, TyG index and TyG-BMI found to show higher specificity and high PPV simultaneously.

Table 4: Area under the ROC curves of different predictors of insulin resistance in adult individuals

Test Result Variable(s)	AUC	Std. Error	P value	Asymptotic 95% Confidence Interval	
				Lower Bound	Upper Bound
TG/HDL ratio	0.645	0.016	<0.001	0.614	0.677
TyG Index	0.745	0.014	<0.001	0.717	0.772
TyG BMI	0.753	0.014	<0.001	0.725	0.780
TyG- WC	0.763	0.014	<0.001	0.736	0.790
VAI	0.602	0.016	<0.001	0.570	0.634
LAP	0.625	0.016	<0.001	0.593	0.657
BAI	0.634	0.016	<0.001	0.602	0.665

Bivariate simple logistic regression analysis was done with all predictors in relation to insulin resistance (binary outcome variable) in total adult individuals. All were found statistically significant predictors of IR.

Table 5: Bivariate simple logistic regression analysis was done with all predictors in relation to insulin resistance (binary outcome variable) in total adult individuals. All were found statistically significant predictors of IR.

Predictors	Odds ratio (OR)	95% CI of OR	P value
TG/HDL ratio	1.171	1.118 – 1.227	<0.001
TyG Index	2.022	1.946 – 3.392	<0.001
TyG BMI	1.024	1.021 – 1.028	<0.001
TyG- WC	1.010	1.009 – 1.012	<0.001
VAI	1.002	1.001 – 1.004	<0.001
LAP	1.009	1.006 – 1.013	<0.001
BAI	1.085	1.061 – 1.109	<0.001

DISCUSSION

This cross sectional analytical study was aimed to find out surrogate markers of insulin resistance: search for simple and valid marker in adult

population attending Bangabandhu Sheikh Mujib Medical University (BSMMU) outpatient department (OPD). With this aim, initially we recruited 1250 adult individuals attending BSMMU OPD. From them (N=1250), finally we enrolled 1203 adult individuals in our study because of 47 individual insulin resistance were not calculated.

In our study, the frequency of insulin resistance (IR) was found to be (55.20%) in all adult individuals (N=1203). Du, et al. (2014) conducted a cross sectional study on 7629 Chinese adults and found that the frequency of IR in 36.70%. Another cross sectional study was done by Er, et al. (2016) on 511 Taiwanese adults and found frequency of IR in adults 20.70%.

Our study revealed that among the individuals were no significant difference insulin resistance between males and females. In our study, 119 (51.20%) female individuals & 113 (48.70%) male individuals were insulin resistance. Guerrero-Romero, et al. (2016) conducted a cross sectional study on healthy young adults (mean age 19.2 years) and found IR more in female (15.90%) than male (9.10%). This finding was not in agreement with our result because our study mean age were 40.99 ± 10.99 .

Our study revealed that frequency of IR was significantly high at younger age group. We have found the frequency of IR 18.70% in 31-40 age group and 15.70% in 36-40 age group respectively. This finding was in agreement with Zhu, et al. (2012). They explored the aging-related changes of insulin secretion and insulin sensitivity among normal glucose tolerant (NGT) individuals in China. They found HOMA-IR negatively correlated with age among men and women even after adjusted for BMI and waist circumference in both univariate & multivariate linear regression. They concluded that the basal postchallenge insulin secretion and postchallenge islet compensatory function decreases with aging, while insulin sensitivity does not deteriorate with aging and its related change of body composition and weight gain.

Insulin resistance in young adults is often accompanied by a dyslipidemic profile.^[5] Prevailing theories for the pathogenesis of insulin resistance focus on lipid-mediated mechanisms; however,^[6] the etiology also involves obesity-induced metabolic by-products and inflammatory signaling.^[7]

Our finding was not supported by Short, et al. (2005). According to them, insulin resistance and impaired glucose tolerance are commonly observed phenomena among elderly adults. Aging is associated with detrimental changes in body composition, which persists even when elderly adults are matched to younger adults for BMI.^[8] It remains contentious whether chronological age is a primary determinant of insulin resistance or age-related elevations in adiposity and/or physical inactivity are the primary causes of age-related insulin resistance.^[9,10] So, there is a debate whether

IR is higher in younger age or in older age which is yet to be resolved.

In our study TG/HDL ratio was found sensitivity and specificity 71.40% and 51.90% respectively with cutoff point 3.18 and P value <0.001. An elevation in the TG/HDL-C ratio could be a novel marker for hyperinsulinaemia among people with normal weight in routine clinical practice (Ray et al. 2015). In a study in an East African population, the TG/HDL-C ratio was found to be significantly associated with insulin. McLaughlin et al. in 2005 proposed TG/HDL-C ratio ≥ 3.5 as a cut-off value to predict the presence of insulin resistance. They found that this cut-off had high sensitivity (79%) and specificity (85%) in their study population and concluded that a plasma TG/HDL-C concentration ratio might provide a simple means of identifying insulin resistance.

According to Guerrero-Romero et al.2010 and Simental-Mendia et al.2008, TyG index has been recently recommended as a simple and inexpensive index to evaluate IR. Because of the variability of TG levels according to ethnicity, it is necessary to assess the utility of TyG in predicting IR in a Chinese population. Du et al. 2014 found that the TyG index was a good discriminator in predicting IR and was a better correlate of IR than TG/HDL-C, a finding consistent with results from other studies. Moreover their study extends previous studies by directly comparing the utility of TyG with visceral adiposity indicators and other lipid parameters in assessing IR risk. In this study TyG index was found 68.52% sensitivity and 68.27% specificity with cutoff value 8.83 and AUC 0.745 which is statistically significant. Our study support the study of Du et al. 2014

In our study we found TyG- BMI 69.73% sensitivity and 68.27% specificity with cutoff value 233.42 and AUC 0.753. According to Er et al. 2016, TyG-BMI, Leptin and adiponectin ratio (LAR) had the largest AUC (0.801). The TyG-BMI AUC in detecting IR was significantly higher than that of TyG, TG/ HDL-C, and leptin (P = 0.004, 0.004 and < 0.001, respectively). Their data showed that TyG-BMI is a simple and clinically useful surrogate marker for IR in nondiabetic individuals. In addition, the ROC curve investigation affirmed that TyG-BMI is the most favorable surrogate marker of IR. Our result support with this study.

In our Study TyG-WC showed 76.40% sensitivity (highest) and 66.20% specificity with optimal cut off point 805.98 and AUC 0.763. Zheng, et al. (2016) conducted a cross sectional and prospective cohort study on first degree relatives (FDRs) of T2DM patients (635 men and 909 women). Logistic regression analysis and receiver operating characteristic (ROC) curve were used to compare and identify the associations of the six parameters (BMI, WC, VAI, TyG, TyG-BMI and TyG-WC) with the prevalence of prediabetes and diabetes.

Subsequently, 452 of them were followed-up for an average of 5 years. Among the indices, TyG-WC was more strongly associated with the prevalence of prediabetes and diabetes. They proposed TyG-WC as a novel and clinically effective marker for early identifying the risks of prediabetes and diabetes in FDRs of T2DM patients. Our findings also support TyG-WC in this regard.

Different predictors TG/HDL ratio, TyG index, TyG-BMI, TyG-WC, Visceral adiposity index (VAI), Lipid accumulation product (LAP) and Body adiposity index (BAI) of IR were evaluated by ROC analysis in total adult study subjects. In our study highest AUC was found in TyG- WC (0.763) then TyG-BMI (0.753), TyG index (0.745), TG/HDL Ratio (0.645), BAI (0.634), LAP (0.625), VAI (0.602), respectively. All predictors found to be significant. Among them TyG-BMI and TyG-WC found to be better with higher AUC compared to others. This is in agreement with other previous studies (Er et al. 2016; Du et al. 2014). Er et al. (2016) found TyG-BMI with largest AUC (0.801), followed by TyG-WC (0.772), LAP (0.761), VAI (0.743), TyG index (0.708). They did not evaluate body adiposity index (BAI) as a predictor of IR. According to them, although LAR (Leptin and adiponectin ratio) had a comparable effect on IR, it is clinically less useful because it is not routinely measured in clinical practice, we did not calculate it. It is concluded that TyG-BMI is a simple and clinically useful surrogate marker for early identification IR in Taiwanese individuals. Guerrero-Romero et al. (2016) concluded TyG index as a useful diagnostic test for screening IR in young adults (mean age 19.2 years).

To find out the predictors associated with insulin resistance, bivariate logistic regression analysis was done in adult individuals. All predictors of IR found statistically significant though their unadjusted odds ratio (OR) found close to 1.0 but except TyG index, it was 2.022 which is top of the list. Others like, TG/HDL ratio (1.171), BAI (1.085), TyG-BMI (1.024), TyG- WC (1.010) and VAI (1.002) were topping the list. These findings were nearly consistent to the findings of Er, et al. (2016). They conducted a cross sectional study on 511 Taiwanese adults and found all visceral adiposity indicators, TyG related parameters, adipokines to be strongly associated with IR ($P < 0.001$). Of them, LAR & TyG-BMI were topping the list of OR. Du, et al. (2014) also found association of TyG index, VAI, LAP with insulin resistance.

We calculated optimal cutoff point (OCP) of different predictors for detection of IR in adult individuals on the basis of Youden Index. We found OCP for TG/HDL ratio – 3.18, TyG index—8.83, TyG-BMI—233.42, TyG-WC—805.98, LAP—45.52, BAI—37.72, VAI—123.43. Lee, et al. (2016) evaluated the OCP of TyG index—8.8 for identifying

the development of diabetes in first degree relatives of T2DM which was in agreement with our study.

A diagnostic test with high sensitivity and high NPV is useful for screening disease, whereas a diagnostic test with high specificity and high NPV is useful to confirm diagnosis (Altman and Bland, 1994). Therefore, we evaluated different predictors of IR by comparing their performances with a validated and clinically most widely used method for measurement of IR, homeostatic model assessment of insulin resistance (HOMA-IR).

In this regard, our study showed high sensitivity with TyG- WC (76.35%), TG/HDL ratio (71.40%), TyG-BMI (69.73%), TyG index (68.52%), LAP (67.62%), VAI (63.86%) and BAI (62.05%). All of them could be used as an alternative test for screening IR in adult individuals. Regarding the specificity and NPV; TyG-WC found to be on the top to be used as a diagnostic test for confirming IR in adult individuals. From the view point of sensitivity and PPV; TyG-WC and TyG-BMI found to be satisfactory predictors to be used both for screening and confirmation of IR. Er, et al. (2016) conducted a study on non-diabetic adult individuals and concluded that TyG- BMI is a simple powerful and clinically useful surrogate marker for identification of IR.

Finally our study recommended TyG-WC, TyG-BMI and TyG index as better predictors of IR in adult individuals.

CONCLUSION

Our study concludes that TyG related parameters for prediction of IR are cost effective and easily applicable in clinical setting compared to HOMA-IR; because TyG related parameters are based on routine laboratory measurements (fasting triglyceride, fasting glucose levels) and simple non-invasive anthropometric (height, BMI, WC, HC) parameters. On the contrary, HOMA-IR needs measurement of fasting insulin level for estimation of IR which is costly and not available in all laboratories. Therefore, based on simplicity and low-cost, we recommend TyG related parameters are clinically useful predictors of IR in adult individuals of Bangladesh attending tertiary level hospital.

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