Research Article

Novel Index Value of Fibrinogen and Glucose in Risk Assessment with HOMA-IR

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ABSTRACT

In Type 2 diabetes, Insulin resistance leads to microvascular and macrovascular complications. Early diagnosis prevents this complication. Previous studies confirm the association between fibrinogen level and insulin sensitivity but compound effect of glucose and fibrinogen risk levels are not analysed in insulin resistant non-insulin-dependent diabetes. Present study deriving model index with the combination of fibrinogen, glucose value (FiG) and investigating whether linked to HOMA-IR, triglyceride, and glucose (TyG) index also finding alternative index in type 2 diabetes insulin-resistant patients. The study includes 30 Type 2 Diabetic patients and 20 Non-diabetics (control). Fasting serum samples were used to measure Insulin, Triglyceride. A fasting plasma sample was used to measure Glucose and Fibrinogen. The Fasting blood sugar, HOMA-IR, TyG index and the Fibrinogen-Glucose (FiG) novel index between Non-diabetic and Diabetic at a significance of p value < 0.001 level. Serum insulin level shows a significant difference between Non-diabetic and Diabetic at p value < 0.05 level. Also, the receiver operating characteristic curve (ROC) explains the FiG novel index with the good value of are under the curve by 0.877. The FiG index value shows a good correlation with HOMA-IR, and TyG index value also predicts the value of a variable on the value of another variable through linear regression. Hence, it could be suggested for beneficial index value in type 2 diabetes insulin resistant and its complication like cardiovascular diseases.

Key words: Type 2 diabetes, Fibrinogen, Glucose, Triglyceride, Insulin resistant, Index value.

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INTRODUCTION

In insulin-resistant type 2 diabetes, one of the associated complications is cardiovascular disease. Studies show that elevated fibrinogen concentration is a risk factor for cardiovascular disease. The mechanism of fibrinogen interference in the atherogenesis process involves an increased platelet aggregation resulting in the risk of thrombus formation on the atherosclerotic plaque, increasing blood viscosity, infiltration through the arterial wall, and stimulation of cell proliferation.[1] Apart from the cardiovascular risk factor, many studies describe the association of elevated fibrinogen with glucose metabolism. Elevation in fibrinogen level was reported before the onset of type 2 diabetes in nonclinical inflammation.[2,3] Few studies report the significant association between fibrinogen level and glucose metabolism in coronary artery disease.[4] The increased production of fibrinogen observed in acute insulin infusion study by Rocco Barazzoni *et al.* This study suggests that the increased fibrinogen production in hyperinsulinemia or in insulin resistant noninsulin-dependent diabetes mellitus.[5] Moan A *et al.* and Landin K *et al.* study found a significant inverse correlation between fibrinogen and glucose utilization in euglycemic clamp study in young men, the same observation was noted between normal

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and hypertensive patients.[6,7] In the present study, the insulin resistance and its complications were sought to be identified through the novel Fibrinogen-Glucose (FiG) index compared to the HOMA-IR and TyG index.

MATERIALS AND METHODS

Thirty non-insulin-dependent diabetes patients and twenty healthy control were studied. Diabetes criteria were followed according to the Indian Council of Medical Research (ICMR) guidelines. Individual informed consent was received before the study. Age group between 40-60 males excluded with previous cardiovascular problem and parameters studied include plasma fasting blood sugar, plasma fibrinogen, serum insulin, serum triglyceride. Calculated indexes are HOMA-IR, TyG index, and the model proposed index FiG. Blood samples collected after 10-12 hr fasting and 2 ml placed in citrate anticoagulant tube, 2 ml transferred in sodium fluoride/Na_2 EDTA anticoagulant tubes for fasting blood glucose estimation, remaining 6 ml blood was transferred in plain tubes (without anticoagulant) for estimation of serum fasting insulin and triglyceride. ACL TOP.300 Hemostasis testing system used for analyzing the fibrinogen level. Fibrinogen was measured in plasma using the Clauss/chromogenic method, based on the comparison of thrombin clotting times of plasma dilutions against a plasma standard. In the presence of an excess of thrombin, plasma clotting time has a direct bearing on the level of plasma fibrinogen.[8] Beckman Coulter UniCel Dxi 800 biochemistry auto analyzer estimated the serum triglyceride, serum insulin. Serum insulin measured by a chemiluminescent method with access to an ultra-sensitive insulin assay kit. Serum insulin binds to the antibody on the solid phase while the conjugate reacts with a different antigenic site on the insulin molecule. After incubation in reaction vessels, materials attached to the solid phase are held in a magnetic field, and unbound materials are washed away. The chemiluminescent substrate Lumi-phos 530 is added to a vessel and light generated by the reaction is measured with a luminometer, which is directly proportional to the insulin concentration in the sample.[9] Serum triglyceride analyzed through Enzymatic/GPO Trinder method. This Triglyceride procedure is based on a series of coupled enzymatic reactions. The triglycerides in the sample were hydrolyzed with a combination of microbial lipases to give glycerol and fatty acids. The glycerol is phosphorylated by adenosine triphosphate (ATP) in the presence of glycerol kinase (GK) to produce glycerol-3-phosphate. The glycerol-3-phosphate is oxidized by molecular oxygen in the presence of GPO (glycerol phosphate oxidase) to produce hydrogen peroxide (H_2O_2) and dihydroxyacetone phosphate. The formed hydrogen peroxide reacts with 4-aminophenazone and N,N-bis(4-sulfobutyl)-3,5-dimethylaniline, disodium salt (MADB) in the presence of peroxidase (POD) to produce a chromophore, which is read at 660/800 nm. The increase in absorbance at 660/800 nm is proportional to the sample's triglyceride content.[10,11] Estimation of glucose was done by GOD/POD method. Glucose oxidase (GOD) converts glucose to gluconic acid. The hydrogen peroxide formed in this reaction, in the presence of Peroxidase (POD) oxidatively couples with 4-amino antipyrine/phenol to produce red quinonimine dye. This dye has an absorbance maximum at 505 nm. The intensity of the color complex is directly proportional to the glucose in the specimen.[12] Previous studies confirm the accuracy and precision of the homeostasis model assessment (HOMA-IR).[13] The formula for the HOMA-IR index is (Glucose x Insulin) / 405, HOMA-IR calculated according to the formula. Few studies described the TyG index in various conditions.[14-16] The formula for the TyG index is TyG = Ln [Fasting triglyceride (mg/dl) x Fasting glucose (mg/dl)] / 2, as per the formula novel index Fibrinogen-Glucose (FiG) index also calculated (FiG = Ln [Fasting fibrinogen (mg/dl) x Fasting glucose (mg/dl)] / 2).

Statistical Analysis

SPSS (version 20) statistical software was used for analyses. Data were also categorized according to 40 to 60 years in age, patients and control, fasting serum insulin, triglyceride, fasting plasma glucose, HOMA-IR index, TyG index, Novel FiG index and were evaluated using a Pearson's correlation coefficient analysis, Linear regression analysis. Comparisons of patients and control parameters were performed with a significance level of $p < 0.05$.[17,18]

RESULTS

Table 1 shows the significant difference in the Fasting blood sugar, HOMA-IR, TyG index, and the Fibrinogen-Glucose (FiG) novel index between Non-diabetic and Diabetic at p-value < 0.001 level. Serum insulin level shows a significant difference between Non-diabetic and Diabetic at p-value < 0.05 level. Serum triglyceride and Plasma fibrinogen values are higher in Diabetic compared to Non-Diabetic.

In Table 2 the regression analysis between the FiG novel index and HOMA-IR (gold standard) shows

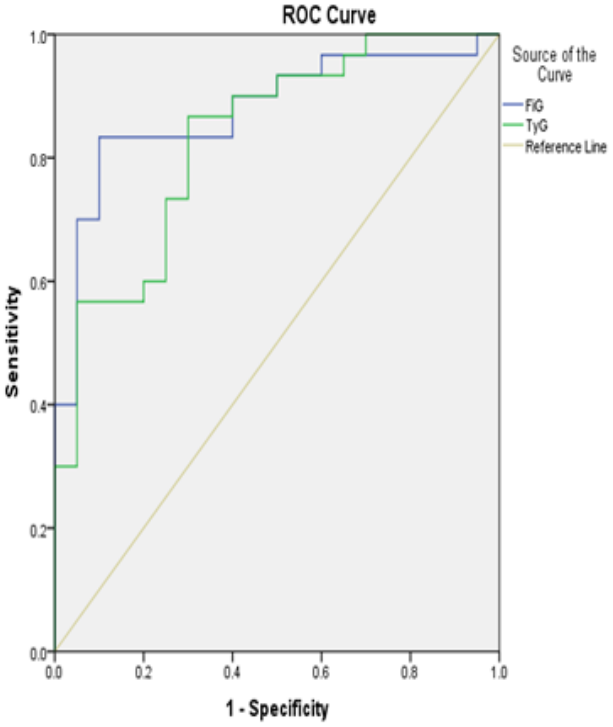

Figure 1: ROC curve analysis for performance of the Novel FiG index and TyG index.

Area Under the Curve	
Test Result Variable(s)	**Area**
FiG (Novel Fibrinogen-Glucose) Index	0.877
TyG (Triglyceride-Glucose) Index	0.832

the significant relationship positively correlated. The regression equation derived as y = -24.91 + 5.76x. The analysis between Fasting blood sugar and FiG novel index shows a significant relationship with positive correlation, and the derived regression equation is y = -649.04 + 157.59x. The TyG index and FiG novel index, regression analysis derive significant relationship with positive correlation, and the regression equation is y = 2.685 + 0.463x.

Figure 1 and the Area under the curve show the model's good performance in distinguishing the positive and negative classes. Both the indexes, Area under curve value, shows the acceptable in using as a diagnostic index.

DISCUSSION

Previous studies conclude fibrinogen increase in insulin-resistant and one of the associated risk, cardiovascular disease. Fibrinogen level studies mention that in non diabetes with impaired glucose tolerance (IGT) and in type 2 diabetes, increased fibrinogen is observed.[19] In our study, the high fibrinogen level was noted in Diabetic persons compared to Non-Diabetic persons. To know the combined effect of sugar and fibrinogen, we designed the novel index fibrinogen-glucose (FiG) index with the TyG index's guidance.[20] The natural log of the fibrinogen-glucose index shows a significant difference between diabetes and non-diabetes. Also, a significant positive correlation was observed

Table 1: The data are presented as mean, ± standard deviation, fasting blood glucose, triglyceride, fibrinogen, insulin, HOMA-IR index, TyG index, FiGnovel index between Non-Diabetic and Diabetic persons. The significance (*p*-value) is estimated through the Independent sample ' t ' test.

Biomarkers	Groups	Mean	Std. Deviation	*P*-value
Fasting blood sugar (mg/dl)	Non-Diabetic	103.35	12.57	< 0.001
	Diabetic	192.06	72.62	
HOMA-IR Index	Non-Diabetic	2.24	0.94	< 0.001
	Diabetic	6.10	4.09	
Insulin (µIU/mL)	Non-Diabetic	8.72	3.23	< 0.05
	Diabetic	13.86	9.66	
Triglyceride (mg/dl)	Non-Diabetic	174.55	75.66	.585
	Diabetic	185.83	67.91	
Fibrinogen (mg/dl)	Non-Diabetic	186.40	70.57	.119
	Diabetic	224.63	90.82	
Fibrinogen-Glucose novel Index (FiG)	Non-Diabetic	4.88	0.23	< 0.001
	Diabetic	5.26	0.29	
Triglyceride-Glucose Index (TyG)	Non-Diabetic	4.85	0.22	< 0.001
	Diabetic	5.18	0.25	

Table 2: Linear regression analysis by considering FiG (Fibrinogen-Glucose) novel index as an independent variable with Fasting blood sugar, HOMA-IR index, TyG index as the dependent variable.

Coefficients							
Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.	R SQUARE
		B	Std. Error	Beta			
1	(Constant)	-24.915	7.290		-3.418	0.001	
	FiG	5.766	1.423	0.505	4.051	0.000	0.255

a. Dependent Variable: HOMA Predictors: (Constant), FiG

Coefficients							
Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.	R SQUARE
		B	Std. Error	Beta			
1	(Constant)	-649.040	112.285		-5.780	0.000	
	FiG	157.591	21.921	0.720	7.189	0.000	0.518

a. Dependent Variable: FBS
Predictors: (Constant), FiG

Coefficients							
Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.	R SQUARE
		B	Std. Error	Beta			
1	(Constant)	2.685	0.543		4.943	0.000	
	FiG	0.463	0.106	0.533	4.361	0.000	0.284

a. Dependent Variable: TyG
Predictors: (Constant), FiG

between the model FiG index and HOMA-IR, which is a gold standard index for insulin resistance in type 2 diabetes. Positive Pearson correlation was observed between FiG and Fasting blood sugar, FiG, and TyG. The regression analysis on the FiG novel index (independent variable) and HOMA-IR (dependent variable) explains the variability in 1 unit rise of FiG model index, 5.76 unit rise of HOMA-IR with the R square 0.255. FiG novel index (independent variable) and Fasting blood glucose (dependent variable) explains the variability in 1 unit rise of FiG rise the fasting value of 157 mg with the R square 0.518. Previous studies explain the TyG index associated with the prevalence of symptomatic coronary artery disease and correlates in ischemic stroke in risk assessment of diabetes.[21-23] In our study, the FiG novel index explains the variable TyG index with the R square 0.284 and 1 unit novel FiG index rise the 0.463 unit in TyG index. The receiver operating characteristic curve also explains the FiG novel index with the good value under the curve by 0.877, which confirms a diagnostic value.

CONCLUSION

In conclusion, the Fibrinogen-Glucose (FiG) novel index correlated well with gold standard HOMA-IR, Fasting blood sugar and HOMA-IR explained significant value variability in regression showing that the FiG novel index can be used as an alternative index to the HOMA-IR in finding insulin resistance. Also, the FiG novel index is well correlated with the TyG index, and in ROC curve shows better performance than TyG. Moreover increase in fibrinogen value has been mentioned in research studies as a risk factor for cardiovascular diseases. Hence, the FiG novel index can be used as an alternative index to the TyG index. It is also emphasized that further studies in more number of

samples are necessary to implement FiG novel index as an alternative to HOMA-IR and TyG index.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

ABBREVIATIONS

FiG: Fibrinogen-Glucose; **TyG:** Triglyceride-Glucose; **HOMA-IR:** Homeostatic Model Assessment of Insulin Resistance; **ROC Curve:** Receiver Operating Characteristic Curve.

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