Association Between Triglyceride-Glucose Index and Homeostasis Model Assessment for Insulin Resistance with Estimated Glucose Disposal Rate

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ABSTRACT

This cross-sectional study was aimed to compare insulin resistance, Triglyceride- Glucose (TyG) index, fatty liver index (FLI) and hepatic steatosis index (HSI), glycaemic and lipids among groups/quartiles based upon estimated Glucose Disposal Rate (eGDR) from August 2022 to December 2022 among 249 male participants. The eGDR results in (mg/kg/min) were divided into four quartiles as: Group-I: {<6.88, n = 62}, Group-II: {<6.88-9.45, n = 63}, Group-III: {9.46-10.39, n = 62}, and Group-IV: {>10.39, n = 62}. Fasting plasma glucose (FPG), HbA1c, low density lipoprotein (LDL), homeostasis model assessment for insulin-resistance (HOMAIR), and TyG index demonstrated significant worsening increase from high to low eGDR groups. Receiver operating curve (ROC) analysis to calculate area under curve (AUC) for diagnostic efficiency candidate indices for eGDR demonstrated highest AUC for FLI as AUC: 0.736 (95% CI: 0.669-0.803), p < 0.001, followed by FPG: AUC: 0.682 (95% CI: 0.606-0.757), HOMAIR: AUC: 0.670 (95% CI: 0.602-0.739), HSI: AUC: 0.660 (95% CI: 0.589-0.731), TyG index: 0.658 (95% CI: 0.583-0.732), and HbA1c: 0.639 (95% CI: 0.583-0.732). Glycaemic measures, lipid indices, insulin resistance and TyG index deteriorated with declining eGDR. Diagnostic performance as evaluated by AUC for eGDR was highest for FLI, followed by FPG, HOMAIR, HSI, TyG index, HbA1c, and triglycerides.

Key Words: *Triglyceride, Insulin, Glucose, Diabetes*.

How to cite this article: Khan SH, Hafeez A, Khan Y, Khalid UB, Shah S, Ghauri AA. Association Between Triglyceride-Glucose Index and Homeostasis Model Assessment for Insulin Resistance with Estimated Glucose Disposal Rate. *J Coll Physicians Surg Pak* 2024; **34(05)**:617-619.

Insulin resistance, type-2 diabetes mellitus, obesity and hyperlipidemia are directly responsible for the increasing atherosclerotic cardiovascular diseases (ASCVD). There remains an unmet need for devising newer but simpler biomarkers and equations to define the progressive decline among patients to better predict the metabolic disease process for optimal management. Williams *et al.* have suggested a mathematical formula to measure estimated Glucose Disposal Rate (eGDR) which has been shown to relate with insulin resistance.[1]

Earlier documented studies highlighted the use of eGDR which has been developed mainly for type-1 diabetes. However, the equation was later also utilised for the measurement of insulin resistance. Zabala *et al*. conducted a study funded by the European Association for study of Diabetes (EASD), utilising the same equation as used by William *et al.* in participants with type-2 diabetes mellitus demonstrated eGDR to be associated with stroke and incidence of death.[2]

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Received: March 10, 2023; Revised: October 09, 2023; Accepted: November 13, 2023
DOI: https://doi.org/10.29271/jcpsp.2024.05.617

The use of eGDR has been differing in literature both for diagnostic targets and variabilities in formula. In addition, majority of the researches have been carried out in the Caucasian population. Obesity has been termed as a paradox with regards to Asian communities and thus it remains relevant to the study and validate the equation in the Pakistani population.[3] There are very few studies from the Asian continent dealing with type 1 diabetes or insulin resistance with eGDR but none to date in Pakistan. Furthermore, eGDR equation incorporates basic measures like blood pressure, anthropometric measures, and glycated haemoglobin which can provide simple and cost-effective information for general medical practitioners for measuring insulin resistance. Thus, it was aimed to measure insulin resistance and triglyceride-glucose (TyG) index among subjects with various levels of eGDR for clinical use.

This cross-sectional study was conducted between August 2022 to December 2022 at the National University of Medical Sciences, Pakistan after formal approval by Ethical Review Committee (ID:42, dated: 23 Aug 2022). The study incorporated non-probability convenience sampling where sample size was calculated by online calculator: (http://www.calculator.net/sample-size-calculator.html. Accessed on 9 July 2022). Target population were males aged between 20-55 years who reported in medical fasting status between 08:00-09:00 hours at the pathology department. Participants with known chronic diseases were excluded. Finally, selected individuals formally consented and

finally enrolled for the study after providing written consent. History and examination were conducted as per standard protocol. Blood was collected in tubes for measurement of biochemical parameters. All analyses were conducted on Cobas-501 and Cobas-401 instruments as per standard protocols. eGDR measurement: eDGR (mg/kg/min) = 21.158+(-0.09 x WC in cm) + (-3.407 x Hypertension) + (- 0.551 x HbA1c), where 0 = No hypertension, and 1 = diagnosis of hypertension.[2] Results of eDGR were divided into quartiles as: Group-I: eGDR <6.88, Group-II: eGDR= 6.88-9.45, Group-III: eGDR = 9.46-10.39, and Group-IV: eGDR = >10.39. HOMAIR [Fasting plasma glucose (mmol/L) × fasting insulin (µmol/L)/22.5] and TyG index [TyG index = ln [fasting TG (mg/dL) x fasting glucose (mg/dL)/2] were calculated as per original formula of Mathew's *et al.* and Selvi *et al.*

The data were analysed using SPSS version-22. Differences between FPG, HbA1c (%), lipids, insulin, HOMAIR and TyG index between four groups based upon eGDR by using one-way ANOVA. ROC analysis was utilised to measure the area under curve (AUC) for evaluated parameters including fatty liver index (FLI), hepatic steatosis index (HSI), Homeostasis model assessment for insulin resistance (HOMAIR), Fasting plasma glucose (FPG), TyG index, HbA1c, and triglyceride. Categorical variables were presented as counts and percentages and continuous variables were expressed as mean ± SD. A p-value < 0.005 was considered as significant.

Mean age of the study population was 36.38 ± 7.47 years. Main outcome measures included eGDR, glycaemic and lipid indices, insulin resistance, TyG index, FLI, and HSI. The differences between four groups based upon eGDR for FPG, HbA1c, lipid indices, insulin, HOMAIR, and TyG index are demonstrated in Table I. ROC curve analysis identified eGDR from highest AUC for FLI as AUC: 0.736 (95% CI: 0.669-0.803) followed by other parameters as demonstrated in Figure 1.

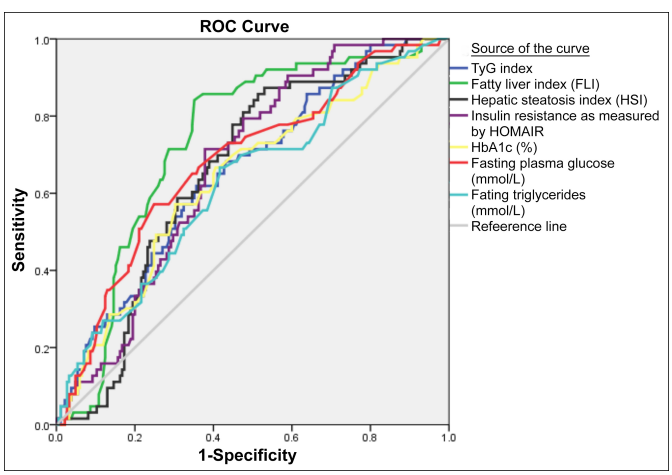

Figure 1: ROC curve analysis depicting top seven parameters for diagnosing eGDR depicted with AUC from highest to lowest as: FLI, AUC: 0.736 (95% CI: 0.669 - 0.803) p < 0.001; FPG, AUC: 0.682 (95% CI: 0.606 - 0.757) p < 0.001; HOMAIR, AUC: 0.670 (95% CI: 0.602 - 0.739); HSI, AUC:0.660 (95% CI: 0.589 - 0.731) p < 0.001; TyG index, AUC: 0.658 (95% CI: 0.583 - 0.732) p < 0.001; HbA1c, AUC: 0.639 (95% CI: 0.583 - 0.732) p = 0.001, and triglyceride, AUC: 0.628 (95% CI: 549 - 0.707) p = 0.040.

Table I: Differences between glycaemia, lipid indices, insulin resistance and TyG index between groups based upon estimated Glucose Disposal Rate (eGDR).

Parameter	Groups based upon eGDR [mg/kg/min]	Mean	Std. Dev	Sig.
Fasting plasma glucose (mmol/L)	eGDR < 6.88 (n = 62)	5.61	2.17	<0.001
	eGDR = 6.88-9.45 (n = 63)	5.29	0.89	
	eGDR = 9.46-10.39 (n = 62)	4.79	0.43	
	eGDR = >10.39 (n = 62)	4.58	0.60	
Total cholesterol (mmol/L)	eGDR < 6.88 (n = 62)	4.70	1.10	<0.001
	eGDR= 6.88-9.45 (n = 63)	4.68	0.98	
	eGDR = 9.46-10.39 (n = 62)	4.49	0.77	
	eGDR = >10.39 (n = 62)	3.91	0.84	
Fasting triglycerides (mmol/L)	eGDR < 6.88 (n = 62)	2.54	2.89	0.002
	eGDR = 6.88-9.45 (n = 63)	2.53	1.83	
	eGDR = 9.46-10.39 (n = 62)	1.93	0.99	
	eGDR = >10.39 (n = 62)	1.48	0.66	
LDL cholesterol (mmol/L)	eGDR < 6.88 (n = 62)	2.89	0.78	0.001
	eGDR = 6.88-9.45 (n = 63)	2.85	0.74	
	eGDR = 9.46-10.39 (n = 62)	2.78	0.64	
	eGDR = >10.39 (n = 62)	2.42	0.67	
HDL cholesterol (mmol/L)	eGDR < 6.88 (n = 62)	0.98	0.23	0.092
	eGDR = 6.88-9.45 (n = 63)	0.95	0.16	
	eGDR = 9.46-10.39 (n = 62)	1.04	0.21	
	eGDR = >10.39 (n = 62)	0.97	0.20	
HbA1c (%)	eGDR < 6.88 (n = 62)	6.45	2.08	<0.001
	eGDR = 6.88-9.45 (n = 63)	5.92	0.84	
	eGDR = 9.46-10.39 (n = 62)	5.49	0.36	
	eGDR = >10.39 (n = 62)	5.28	0.66	
Insulin (uIU/ml)	eGDR < 6.88 (n = 62)	18.40	9.75	<0.001
	eGDR = 6.88-9.45 (n = 63)	15.32	9.58	
	eGDR = 9.46-10.39 (n = 62)	10.61	5.58	
	eGDR = >10.39 (n = 62)	6.53	3.99	
Insulin resistance (HOMAIR)	eGDR < 6.88 (n = 62)	4.48	2.56	<0.001
	eGDR = 6.88-9.45 (n = 63)	3.65	2.48	
	eGDR = 9.46-10.39 (n = 62)	2.27	1.25	
	eGDR = >10.39 (n = 62)	1.39	1.05	
TyG index	eGDR < 6.88 (n = 62)	9.07	0.68	<0.001
	eGDR = 6.88-9.45 (n = 63)	9.09	0.56	
	eGDR = 9.46-10.39 (n = 62)	8.79	0.47	
	eGDR = >10.39 (n = 62)	8.49	0.49	

**Analysis conducted by One way ANOVA*

To the authors' knowledge, this is the first regional study which has explored the association between eGDR and various conventional metabolic risk factors. eGDR usage as a surrogate biomarker for metabolic risk indicator has been there for some time, especially for type-1 diabetes mellitus having slight insulin resistance i.e., double diabetes and ASCVD.[1,4,5] There was an overall metabolic functional decline to be associated with increase in eGDR. The research has targeted eGDR as a surrogate marker for metabolic decline and insulin resistance as has been highlighted in literature.[4,5]

The end outcome of complete insulin release to receptor action pathway is optimal glucose disposal. Depicting successful glucose disposal rate seems to be the end point of whole pathway thereby highlighting the importance of eGDR as a marker for identifying insulin resistance.[2,4,5] The eGDR equation can be more valuable for depicting underlying metabolic risk as the insulin release-to-disposal mechanics is affected by multiple genetic and epigenetic factors which can cause variation in glucose disposal rate which together define the contribution towards insulin resistance.[6] Furthermore, Nystrom *et al.* also identified low eGDR results were independently associated with all-cause mortality thus, further potentiating the association with insulin resistance and the present findings.[7] Furthermore, this study has provided a preliminary platform for deciphering insulin resistance and associated ASCVD risk evaluation for local data which can help both healthcare workers and researchers to make its utility within their working domains.

Few limitations associated with this study need to be acknowledged. It was a cross-sectional research which needs to be repli-

cated at a wider scale in a community setup separately among male and female participants to define and further streamline the reference ranges for clinical use.

This study can have strong clinical implications. This research stands the primary effort for evaluating the use of eGDR index with quartile-based cut-offs; eGDR can be a surrogate insulin resistance index and may be extremely useful in smaller, distant, and minimally resourced hospital setups. Finally, the authors also believe the eGDR equation can augment clinical use as a therapeutic gauge for therapy monitoring patients.

In conclusion, glycaemic and lipid indices, insulin resistance and TyG index deteriorated with increasing eGDR. Higher AUCs for depicting eGDR were observed for FLI, FPG, HOMAIR, HSI, TyG index, HbA1c, and triglycerides.

ETHICAL APPROVAL:
This study was approved by the hospital's ethical review committee (ERC no. 42/2022, dated: 23 Aug 2022).

PATIENTS' CONSENT:
Written informed consents were obtained from all participants.

COMPETING INTEREST:
The authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:
SHK: Idea conception, sampling, manuscript preparation, and laboratory analysis.
AH: Patient history, examination, SPSS analysis of data, and contribution towards manuscript preparation.
YK: Radiological analysis and contribution towards manuscript writing.
UBK: Patient history and examination, manuscript writing, and contribution to lab analysis.
SS: Patient history and examination, SPSS analysis, and manuscript writing.
AAG: Contribution to laboratory analysis and manuscript writing.
All authors approved the final version of the manuscript to be published.

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