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The Cut-off Values of Triglycerides - Glucose Index for Metabolic Syndrome Associated with Type 2 Diabetes Mellitus

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Abstract:

The co-occurrence of metabolic syndrome with type 2 diabetes mellitus (T2DM) will potentiate the morbidity and mortality that may be associated with each case. Fasting triglycerides-glucose index (TyG index) has been recommended as a useful marker to predict metabolic syndrome. Our study aimed to introduce gender-specific cut-off values of triglycerides- glucose index for diagnosing metabolic syndrome associated with type 2 diabetes mellitus. The data were collected from Baghdad hospitals between May - December 2019. The number of eligible participants was 424. National cholesterol education program, Adult Treatment Panel III criteria were used to define metabolic syndrome. Measurement of fasting blood glucose, lipid profile, HbA1c level, blood pressure, and anthropometric were done and the triglyceride-glucose index was calculated. Ethical approval and informed consent were obtained. SPSS was used to analyze the data. Diabetic patients with metabolic syndrome showed an increased level of TyG Index. The prevalence of metabolic syndrome increased with increased TyG index quartiles. The TyG-Index showed significant correlations with all components of metabolic syndrome. The optimal cut-off value revealed 9.14, 9.28 for males and females respectively. In conclusion, TyG index is a good predictor of the presence of MetS in T2DM the TyG index, just measured in one laboratory test, is simple, informative and more suitable for the detection of metabolic syndrome in Iraqi type 2 diabetes mellitus.

Keywords: Hyperglycemia, Lipid profile, Metabolic syndrome, Triglyceride-glucose index, Type 2 Diabetes Mellitus

Introduction:

The co-occurrence of metabolic syndrome (MetS) with (T2DM) will potentiate the cardiovascular diseases risk associated with each of these two conditions. Recognizing MetS in patients with T2DM patients is therefore valuable for the aiming of cardiovascular disease prevention^{1,2}.

Metabolic syndrome is a cluster of cardiovascular disease risk factors, including hypertension, central obesity, hyperglycemia, and dyslipidemia. Insulin resistance is recognized as the main underlying mechanism. MetS is a common disorder and its incidence has been rising during diabetic

complications. It is associated with a higher risk of mortality from coronary artery diseases, vascular dysfunction, stroke, polycystic ovarian syndrome, certain types of cancer and all-cause mortality. MetS is diagnosed by the co-occurrence of the three of the five for mentioned metabolic defects^{3,4}.

Many shreds of evidence have suggested that TyG index can be useful as a reliable marker for insulin resistance that has an excellent correlation with the gold standard method (the hyperinsulinaemic-euglycaemic clamp test) and the homeostatic model assessment of insulin

resistance (HOMA-IR) ⁵. TyG index has the privilege of incorporating simple, inexpensive, readily available laboratory parameters (glucose and triglycerides). Moreover, TyG index was also been advised as a marker for categorizing the metabolic health rating ⁶.

Many studies found a link between TyG Index and the MetS ⁷. However few established a cut-off point for MetS. A previous study established gender and ethnic- -specific cut-off values of TyG index for MetS in Korean children and Adolescents ⁸.

Definition of Type 2 Diabetes Mellitus ⁹

Diabetes was initially diagnosed in pursuant to the American Diabetes Association (ADA) through individual symptoms of diabetes with random plasma glucose concentration equal or more than 200 mg/dL (11.1 mmol/L), or FPG equal or more than 126 mg/dL, or 2-h post load glucose \geq 200 mg/dL ,or the levels of HbA1c equal or more than 6.5%.

Definition of Metabolic Syndrome ¹⁰

"The National Cholesterol Education Program, Adult Treatment Panel III (NCEP ATP III)" initially defines the Metabolic Syndrome with a more precise categorization, it requires three of below listed points to be diagnosed

1. waist circumference (>102 cm in men and >88 cm in women),
2. high triglyceride ≥ 150 mg/dl (1.7 mmol/l),
3. low high density lipoprotein cholesterol (HDL-c) <40 mg/dl (1.03 mmol/l) in men and <50 mg/dl (1.29 mmol/l) in women,
4. blood pressure ($\geq 130/85$ mmHg or current antihypertensive medication),
5. fasting plasma glucose ≥ 100 mg/dl (≥ 5.6 mmol/l).

This study aims to evaluate TyG index as a marker that predicts the presence of MetS in T2DM and to conclude a cut-off value of TyG Index for MetS in Iraqi T2DM subjects .

Materials and Methods:

Sample Selection and Study Design

The study is a cross-sectional study that was carried out in Baghdad- Iraq at the time from April 2019 to November 2019. The inclusion criteria were individuals with type 2 diabetes mellitus 18 years and older on oral hypoglycemic drugs). The initial samples were 500 individuals, after the exclusion of individuals with Triglyceride ≥ 500 mg/dl., type 1 diabetes mellitus, pregnant women, patients with missing data patients with other endocrine diseases or patients with major micro or macro vascular complications medications as (lipid lowering drugs)

that affect the results of the tested parameters. The remaining were 424 participants.

Individual Evaluation

The data were collected by full medical assessments with proper evaluation of past medical history related to endocrine-metabolic and cardiovascular events.

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Anthropometric and Blood Pressure Measurement:

The measurement of blood pressure, using calibrated sphygmomanometers, was carried out with each participant at rest (for 15 minutes or more), with two measurements observed with 15 minutes apart.

Weight was obtained through an electric balance; height was determined using a vertical tape with centimeters calibration. Throughout the assessment, participants were wearing light clothing and standing barefooted, Body Mass Index was calculated by dividing the weight in kilogram/height squared in meter ¹¹. The measurement of the waist circumference was done with a metric tape at equidistant positions between the lower margin of the costal rib and the iliac crest.

Biochemical Analysis:

Blood samples were collected in the morning after an overnight fast (about 12 hours). Determination of, total cholesterol (TC), triglycerides (TG), High density lipoprotein (HDL-C.) and glucose was done with an automated analyzer.

High performance liquid chromatography (supplied by Variant Company, USA) was used to estimate the glycated hemoglobin (HbA1C)

Calculation of TyG Index:

The TyG Index was calculated done using the following equation ¹².

TyG Index =Ln [Fasting TAG (mg/dl) x FG (mg/dl)]/2

Ethical Approval

Ethical approval was obtained from the Ethical Unit in Al-Kindy College of Medicine –University of Baghdad. All participants were required to sign a written consent prior to their enrollment in the

study. “All the procedures carried out in the research with participation of humans were in compliance with the ethical standards of the National Research Ethics Committee and with the Helsinki Declaration of 1964 and its subsequent changes or with comparable ethics standards. Informed voluntary consent was obtained from every participant of the study”

-“From all participants whose personal information is contained in this manuscript the additional written voluntary consent was obtained”.

Statistical Analysis

SPSS version 21 for Windows (IBM Chicago, IL) was used to analyze data, results with p value less than 0.05 was considered statistically significant. The quantitative variables were expressed as mean \pm SD, while the qualitative variables were expressed in frequencies. Student's t -test was used to assess differences between groups, while an ANOVA was applied to compare three or more groups.

Chi square test was used to assess the categorical variables. Linear regression or multinomial logistic regression was used to achieve the associations between TyG index and the tested variables. The TyG quartiles were stratified into quartiles Q1 (less than 8.92), Q2 (8.93-9.32), Q3 (9.33-9.74), Q4 more than 9.74. ROC curves were plotted to investigate the predictive capacity and to determine an optimal cutoff point for the TyG Index

Results:

A 424 type 2 diabetes mellitus participated in this study; the mean age was (55.55 \pm 9.3years). According to the ATP III definition, the prevalence of MetS was 55.66 % (a 236, 47.88% of them were male and 52.11 % female).

The clinical, biochemical and anthropometric features of the studied individuals are shown in Table 1 and stratified according to the presence or

absence of MetS by gender (Table 2). The mean TyG Index in type DM with the MetS was higher than its mean in diabetic patients without MetS ($P=0.000$). The prevalence of diabetic patients associated with MetS increased across the TyG index quartiles ($p=0.000$) (Table 3). In addition, the glycemic control and lipid profile got worse across the TyG index quartile (Table 3). TyG index showed a significant positive correlation with FBG, Triglycerides, WC, and DBP while it correlated negatively with the HDL-C (Table 4).

The ROC curves of TyG index for metabolic syndrome revealed an AUC of 0. **0.826** (95% CI: **0.784-0.868**) with a proposed TyG index cut-off of value for MetS was **9.20** (80.1 % specificity and 70.2.1 % sensitivity) while the AUC for TyG index in males was **0.873** (95% CI: **0.823- 0.923**) and for females was **0.798** (95% CI: 0.740-0.856) with a cut-off value for MetS were **9.14, 9.28** for male and female respectively as shown in (Table 5).

Table 1. Baseline characteristics of the participants

Characters	Mean \pm SD
Number	424
Age (years)	55.55 \pm 9.3
DM .Duration (years)	7.93 \pm 0.33
Fasting Blood Glucose (mg/dl)	187.18 \pm 3.4
Hemoglobin A1c (%)	8.77 \pm 2.12
Systolic Blood Pressure (mm Hg)	137.25 \pm 21.1
Diastolic Blood Pressure (mm Hg)	85.75 \pm 10.3
Serum Triglyceride (mg/dl)	147.9 \pm 3.74
Serum Cholesterol (mg/dl)	176.93 \pm 43.1
High Density Lipoprotein (mg/dl)	44.66 \pm 3.1
Low Density Lipoprotein (mg/dl)	102.46 \pm 43.7
Waist Circumference (cm)	100.59 \pm 10.8
Weight(kg)	78.41 \pm 14.3
Height(m)	162.41 \pm 9.2
Body Mass Index(kg/m ²)	29.77 \pm 5.2
TyG index	9.37 \pm 0.59
Number	424

Data were expressed as mean \pm SD

Table 2. clinical, biochemical and anthropometric characteristics of the participants stratified by the presence of metabolic syndrome

	Type 2 DM without metabolic syndrome			Type 2 DM with metabolic syndrome		
	Total	Male	female	Total	male	female
Number (%)	188 (44.33%)	90	98	236 (55.66 %)	113(47.88%)	123(52.11 %)
Age (years)	54.63±10.15	53.72±10.1	55.4±10.1	56.39±8.53	56.1± 9. 1	56.6±8
DM .Duration (years)	8.15±0.5	7.52 ± 0.7	8.72 ±0.8	7.84±.547	8.01±0.7	7.68 ±0.5
Fasting Blood Glucose (mg/dl)	169.74±5.23	163.17±8.2	175.78±6.6	200.5 ± 4.7 **	201.64 ±6.6**	199.2 ±6.7**
Hemoglobin A1c (%)	8.38±2.2	8.26 ± 2.4	8.49±1.9	9.10 ±2.1 **	8.86±1.9*	9.32 ±1.9**
Systolic Blood Pressure (mm Hg)	131.03±17.2	129.3±16.	132 ± 17.7	143.76 ±22.6**	142.3±25**	145.02±2 **
Diastolic Blood Pressure (mm Hg)	82.66±8.3	83.27 ±8.7	82.10±7.8	88.52± 9.4**	89.11± 9.9**	87.98±1 **
Serum Cholesterol (mg/dl)	166.46± 39	160.22±37	172 ± 40	185.68 ±45.3**	178.42±43**	192.4 ±46**
Serum Triglyceride (mg/dl)	104.87±19.6	103.5 ±19	106. ± 19	182.52± 21**	190.30±20**	175.3 ±28**
High Density Lipoprotein -C (mg/dl)	46.01±2.46	46.17 ±2.5	45.87 ±2.3	43.64± 3.20**	43.42 ± 2.7**	43.84 ± 3.6**
Low Density Lipoprotein-C (mg/dl)	97.27±11.1	92.33±5.3	101 ± 5	103.4 ± 9.5	98.84±5.29	114± 5
Waist Circumference (cm)	97.43 ± 11	96.27 ±9.7	98.29 ±12	103.46 ± 9.1 **	102.6±9.5**	104±9.7**
Weight (kg)	75.34 ± 14.6	78.11±12	72.8 ±15	81. 36 ± 13.8**	84.8± 13. **	78.2 ±13**
Height (cm)	162. ± 0.9	170.4 ±5	1 55±5	162±0.8	1.69 .4±6	156 ±5
Body mass index (kg/m2)	28.60±5.4	26.8 ±3.9	30.1 ±6.1	30.80 ± 4.95**	29.5±4.0**	31.97±5.4**
TyG index	9.00 ±0.4	8.93±0.4	9.06 ±0.4	9.66±0.55**	9.71±0.5 **	9.62±0.5 **
Number (%)	188 (44.33%)	90	98	236 (55.66 %)	113(47.88%)	123(52.11 %)

Data were expressed as mean ± SD or SEM as appropriate

*P value lower than 0.05 is considered statistically significant

** P value lower than 0.01 is considered statistically significant

Table 3.The characteristics of the studied population according to the TyG Index quartiles

	First quartile	Second quartile	Third quartile	Fourth quartile	P
TyG index	less than 8.92	(8.93-9. 32)	(9.33 -9.74)	more than 9.74	
Age (years)	56.44± 9.6	55.84 ± 9.5	54.90 ±10	55.43 ± 8.4	0.643
DM Duration (years)	7.19± 0.7	9.1 ±0.8	8.02 ± 0.5	7.94 ± 0.6	0.367
Fasting Blood Sugar (mg/dl)	123.38± 25.5	165.44 ± 39.3	202.9 ± 58.3	245.1 ±50**	0.000
Haemoglobin A1c 1 (%)	7.57 ±1.6	8.5± 1.9	9.04 ± 2.2	9.81 ±1.9**	0.000
Systolic Blood Pressure	138.5 ± 19	139.1 ± 22.8	136.4 ± 19.5	138.5 ±23.6	0.801
Diastolic Blood Pressure	85.55 ± 9.4	84.69 ± 9.4	85.58 ± 9.1	87.64 ±11.9	0.671
Serum Cholesterol (mg/dl)	162.19 ± 37	171.42 ± 36	177 ± 41	196.85 ± 50**	0.000
Serum Triglyceride (mg/dl)	99.35±12.8	116.82± 27.2	140.49 ± 45.2	231.75 ± 83.8**	0.000
High Density Lipoprotein-C (mg/dl)	46.33 ±2.3	45.64 ± 2.2	44.64 ± 2.7	42.26 ± 3.5**	0.000
Low Density Lipoprotein -C (mg/dl)	92.58± 4.4	101.87±4.99	104.9 ± 4.62	111.2 ±6.5	0.080
Waist Circumference (cm)	99.82 ±11	100.98± 10.1	99.93± 10.34	102.10±11.11	0.331
Weight(kg)	79.29 ±15.8	77.00±13.5	77.58±13.6	79.37±14.5	0.551
Height(cm)	163± 0.09	160±0.09	162±0.1	161± 0.1	0.136
Body mass index(kg/m2)	29.59 ± 5.66	29.79±4.41	29.34± 4.7	30.41 ± 5.8	0.437
Prevalence of MetS	20(8.47%)	33(13.9%)	85(23.6%)	98(41.52 %)	0.000

Data were expressed as mean ± SD

* P value lower than 0.05 is considered statistically significant

** P value lower than 0.01 is considered statistically significant

Table 4. correlations between TyG Index and components of metabolic syndrome

	R value	P value
Fasting Blood glucose (mg/dl)	0.719	0.000**
Waist Circumference (cm)	0.097	0.048 *
Systolic Blood Pressure(mmHg)	0.012	0.813
Diastolic Blood Pressure(mmHg)	0.120	0.014*
High Density Lipoprotein -C (mg/dl)	-0.524	0.000**
Serum Triglyceride (mg/dl)	0.766	0.000**

* P value lower than 0.05 is considered statistically significant

** P value lower than 0.01 is considered statistically significant

Table 5. Cut off point for TyG index according to area under the curve

	AUC	95 % Confidence Interval	specificity	Sensitivity	*TyG Index Cut off
Total	0.826	0.784 0.868	0.801	0.702	9.20
male	0.873	0.823 0.923	0.850	0.780	9.14
Female	0.798	0.740 0.856	0.764	0.673	9.28

*Cut off point selected according to the best combination

Discussion:

As type 2 DM has been recognized as a global epidemic, the detection of metabolic syndrome in type 2 TDM is very important in initiating the proper preventive and therapeutic measures¹². TyG index is a marker which has been proposed as a valuable diagnostic tool to anticipate the presence of metabolic syndrome. Nevertheless, inadequate data is available on the issue with no researches from our area on this subject¹³. In the present study, diabetic patients with metabolic syndrome showed increased level of TyG Index, the prevalence of MetS increased with increased TyG index quartiles. In addition, the TyG-Index showed significant correlations with all components of MetS. This study highlights TyG Index as an effective marker to diagnose MetS in type 2 diabetic patients. This finding is in agreement with the work of Simental-Mendía et al. and Abbasi et al. had who demonstrated TyG index as an efficient marker to detect metabolic syndrome but the populations in their study were apparently healthy non diabetic subjects^{14,15}.

TyG index is recognized as an alternative index for insulin resistance. Insulin resistance is the hallmark of both MetS and type 2 DM, insulin resistance and the subsequent glycemic dysregulation lead to suppression of lipoprotein lipases mediated lipolysis in adipose tissue and a consequent high free fatty acid influx, increase hepatic very low density lipoprotein secretion and impairment of HDL-C particles maturation causing hyper triglyceridemia and low HDL-C, both are components of the MetS. In addition, insulin resistance is associated with compensatory hyperinsulinemia that induces carotid body over activation, increase in sympathetic nervous system activity, increase peripheral vascular resistance and subsequent hypertension^{16,17}.

The ROC figure of TyG index for metabolic syndrome revealed an excellent AUC of **0.826** and TyG index cut-off value of **9.20** for the total participants, after gender stratification, the AUC for TyG index were very good (**0.873, 0.798** and cut-off value of **9.14, 9.28** for male and female respectively) . Previous studies showed that the optimal TyG index cutoff for MetS in non-diabetic healthy middle aged individuals was 8.81, and the AUC was 0.894, display that it is a valuable

predictor of MetS. Moon et al. (18) reported a TyG index cut-off values ranged from 8.35 to 8.55 in Korean adolescents from 8.45 to 8.65 in Mexican American, on-Hispanic White, and from 8.15 to 8.35 in Non-Hispanic Black adolescents. These findings show that "the cutoff for TyG index is higher for middle-aged adults than for adolescents and higher in type 2 DM subjects than in non-diabetic populations".¹⁶ So TyG index cut-off value should be age, race, gender and metabolic status specific.

The prevalence of MetS in the study was 55.66 % (52.11% female and 47.88% male). In previous works of Titty et al. among type 2 diabetics at Komfo Anokye Teaching Hospital¹⁹ and Tamale Teaching Hospital²⁰ with subjects of similar characteristics, the prevalence of MetS in their study was 55.9% and 60.3%, respectively.

This study has certain limitation, first the relatively small sample size, makes it less representative of the diabetic population of the country. Second, the cross-sectional nature would not permit the cause-effect relationship to be established.

Conclusion:

TyG index is a good predictor of the presence of MetS in T2DM. Keeping in sight the cost-effectiveness of the marker, simplicity, and practicability and being reflective of other health risks it is recommended to integrate this index in clinical practice and to be included as a routine part of the laboratory report, in addition to highlighting its role in predicting MetS in diabetic population depending on its cut-off value.

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Authors' declaration:

- Conflicts of Interest: None.
- We hereby confirm that all the Figures and Tables in the manuscript are mine ours. Besides, the Figures and images, which are not mine ours, have been given the permission for re-publication attached with the manuscript.
- The author has signed an animal welfare statement.

- Ethical Clearance: The project was approved by the local ethical committee in University of Baghdad.

Authors' contributions statement:

E. K. Hameed: Conception, design, supervision, acquisition of data, analysis, interpretation, critical review, revision and proofreading

L. T. Al-Ameri: Conception, design, acquisition of data, analysis, interpretation, revision and proofreading

H. S. Hasan: Acquisition of data, revision and proofreading

Z. H. Abdulqahar: Drafting the MS, revision and proofreading

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استخدام مؤشر (الدهون الثلاثية - الجلوكوز) المستعملة لتشخيص متلازمة الايض لدى المرضى المصابين بداء السكري من النوع الثاني

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الخلاصة:

يؤدي حدوث متلازمة الأيض مع داء السكري من النوع 2 الى زيادة شدة المرض والوفيات المرتبطة بكل منهما. يوصى باستخدام مؤشر الجلوكوز الصائم للدهون الثلاثية (مؤشر TyG) كعلامة مفيدة للتنبؤ بمتلازمة التمثيل الغذائي. كان الهدف من هذه الدراسة هو تحديد القيم الحدية لنوع Triglyceride-Glucose لتشخيص متلازمة الأيض في داء السكري من النوع الثاني. تم جمع البيانات من مستشفيات بغداد في الفترة ما بين مايو وديسمبر 2019. وكان عدد المشاركين المؤهلين 424 حيث تم قياس الجلوكوز في الدم في وضع الصيام، مستوى الدهون، مستوى HbA1c. فضلا عن قياس ضغط الدم وتم حساب مؤشر Triglyceride-Glucose. تم الحصول على الموافقة الأخلاقية والموافقة المستنيرة. استخدم برنامج SPSS لمعالجة البيانات. أظهر مرضى السكري الذين يعانون من متلازمة الأيض زيادة مستوى مؤشر TyG. ازداد انتشار متلازمة الأيض مع زيادة مؤشر TyG. أظهر مؤشر TyG ارتباطاً كبيراً مع جميع مكونات متلازمة الأيض. حيث ارتبط طردياً مع مستوى الكاوكوز في الدم ومحيط الخصر، مستوى الدهون وضغط الدم الانبساطي بينما تناسب عكسياً مع مستوى الكولسترول النافع. مقدار قيمة القطع الأمثل للمؤشر كانت 9.14، 9.28 للذكور والإناث على التوالي. نستنتج من الدراسة ان مؤشر TyG ملائم للكشف عن متلازمة الأيض في داء السكري من النوع الثاني

الكلمات مفتاحية: ارتفاع سكر الدم، مستوى الدهون، متلازمة الأيض، مؤشر الجلوكوز الصائم للدهون الثلاثية، داء السكري من النوع الثاني