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Establishing a Reference Interval for an Estimate of Peripheral Insulin Resistance in a Group of Iraqi People

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Abstract

BACKGROUND: Insulin resistance (IR) is the cornerstone in pathophysiology of T2DM. Identifying people with IR can slow the progress to diabetes. Triglyceride and glucose index (TyG index) is a simple tool to assess IR without insulin measurement.

AIM: This study aims at establishing the reference interval for TyG index in apparently healthy Iraqis.

MATERIALS AND METHODS: This study involved (77) apparently healthy adults (41 men and 36 women) in Mosul, Iraq. Fasting serum lipids, glucose, and insulin were measured and BMI was calculated. The modified TyG index was calculated and compared to other surrogate measures of IR and its reference interval was calculated.

RESULTS: TyG index values were normally distributed and significantly correlated with HOMA-IR, Mc-Auley index, QUICKI, and triglycerides/HDL-c index ($r = 0.322$, $p = 0.004$; $r = -0.68$, $p < 0001$; $r = -0.29$, $p = 0.01$; and $r = 0.84$, $p < 0.0001$ respectively). ANOVA and *post hoc* Duncan's analyses revealed significant differences in mean TyG between (lean people) and (overweight and obese subjects), ($p = 0.02$). BMI-based TyG reference intervals were calculated as (4.11–4.91) and (4.25–5.05), respectively. This is the first study in Iraq to set a reference interval for the TyG index. Values should be interpreted according to BMI.

CONCLUSION: TyG index is a reliable inexpensive tool to assess IR and its reference range determination is linked to BMI.

Introduction

There is no doubt that Type 2 diabetes mellitus (T2DM) is too common and that its incidence is increasing worldwide especially with the continuous urbanization of life [1]. Reduced peripheral responsiveness to the pancreatic hormone "insulin" in the insulin-sensitive tissues (mainly adipose tissue, liver, and muscles) with the relative gradual deterioration in pancreatic β-cells function represents the main pathophysiology of the disease [2].

For a considerable long-time, insulin resistance (IR) is present in pre-diabetic people although hidden, but compensated, until symptoms of diabetes appear [3]. Identifying people with IR before the clinical manifestations flare up can assist slowing down the progress to diabetes and minimize its drawbacks [4].

Overall peripheral insulin sensitivity (IS)/resistance is best assessed through direct (somewhat invasive) methods such as hyperinsulinemic euglycemic clamp (HEC) and intravenous glucose tolerance test and their modifications. However, these investigations sound impractical in routine clinical practice or when large population-based studies are to be conducted [5]. Instead, several surrogate measures have been employed to assess peripheral IS/IR. Homeostasis Model Assessment-IR (HOMA-IR) which was developed in 1985 by Matthews *et al.* is the most widely used right now especially in large population-based studies [6], [7].

However, beside fasting serum insulin, HOMA and insulin/glucose ratio, other estimates are in use including different (random and fasting) blood indexes such as Stumwolls,' Matsudas,' Bennetts,' Mc-Auleys,' fasting insulin resistance index, quantitative insulin sensitivity check index (QUICKI), and others [8]. IR is well known to be associated with dyslipidemia [9], [10], [11]. Increased serum triglycerides (Tgs) levels can be a marker for defective insulin signaling.

In 2008, Simental-Mendía *et al.* developed a new simple estimate of IR as the product of fasting glucose and Tgs [12]. Triglyceride and glucose index (TyG index) can be utilized as a fast, practical, easy to calculate, and inexpensive tool to assess IR/IS in clinical settings. The aim of this study is to find out the reference interval of TyG index in a group of apparently healthy adult Iraqi people.

Materials and Methods

Study design and patients

This is a small cross-sectional study conducted over an eight months period starting from December 10th 2019. Ninety apparently healthy adult (≥ 30 years) subjects living in Mosul city/Northern Iraq with negative family history of diabetes were randomly selected to participate voluntarily. The study was conducted in accordance with the Declaration of Helsinki II. All participants signed a written informed consent and the study was approved by the Medical Research Ethics Committee, College of Medicine, University of Mosul (Ref. no.: UOM/COM/MREC/2019(27)).

Laboratory, anthropometric and clinical data collection

All subjects were interviewed with a brief medical history taking and physical examination. Body weight (with light clothes) and height (upright position without shoes) were recorded for all and body mass index (BMI) was calculated accordingly [13]. Resting blood pressure was measured in sitting position and hypertension was defined as SBP ≥140 and/or DBP ≥ 90 mmHg, according to the newest European guidelines [14].

Those with fasting serum glucose (FG) ≥ 100 mg/dl [15], positive family history of diabetes, having malignancy, hepatic, cardiovascular, or renal diseases and those taking drugs for dyslipidemia or hypertension were excluded from the study. Finally (77) subjects (41 men and 36 non-pregnant women) aged (30–68) years were only enrolled.

A 6-ml venous whole blood sample was aspirated from every subject following 10–12 h fasting, allowed to clot and serum was separated immediately by centrifugation, aliquoted and frozen at −20°C for subsequent measurement of serum glucose, lipids, and insulin. Biochemical analyses were conducted at the Clinical Biochemistry Laboratory, College of Medicine, University of Mosul.

Serum Tgs, total cholesterol, and FG were measured using endpoint enzymatic reaction kits purchased from Randox Ltd, UK. Serum HDL-cholesterol (HDL-c) was estimated by phosphotungstic acid-precipitation method [16] while LDL-c was just calculated mathematically [17]. Hypertriglyceridemia was defined as Tgs ≥ 150 mg/dL [18].

Fasting serum insulin levels were measured using TOSOH AIA-360 System Analyzer and ST AIA- PACK IRI kits from Tosoh Bioscience, Japan as directed by the manufacturer. IR/sensitivity was estimated mathematically. Surrogates included HOMA-IR as (Fasting insulin [μU/mL] × FG [mg/dL]/405) [6], Mc-Auley index (Exp [2.63–0.28X ln [insulin]–0.3X ln [Tgs]) [19], and QUICKI as the reciprocal of the sum of log values of fasting insulin (μU/mL) and glucose (mg/dL) [20]. However, the modified TyG index was calculated as ln (Tgs [mg/dL] × glucose [mg/dL])/2 [12], [21] and this is the form that the online TyG index calculators apply.

Statistical analysis

SPSS (version 20.0) was used for analysis of data. Descriptive statistics were employed to determine mean, range, standard deviation (SD), and skewness as indicated. Normality of data was determined using the "1-sample Kolmogorov–Smirnov test". Data followed Gaussian pattern when $p \geq 0.05$. Linear regression analysis was used to study the relationship between independent and dependent variables (namely TyG and other surrogate measures of IS/IR). Independent Student t-test (two-tailed) was used to compare continuous variables among the two genders, and χ^2 test for categorical variables. One-way ANOVA was used to compare means of TyG index among different age groups and BMI subclasses followed by *post hoc* Duncan's test when significant. Values were expressed as mean ± SD or N% as indicated. Differences were considered statistically significant when $p < 0.05$.

Results

The mean age of subjects enrolled was 46.3 ± 10.2 years (range 30–68). About 18% were hypertensive and dyslipidemic. In general, men were leaner than women with no significant differences in any of the surrogate measures of IR. The basic characteristics of the study subjects are shown in Table 1.

Table 1: The basic characteristics of the study subjects. Data are expressed as mean ± SD or n (%) as indicated

	Men	Women	All	p-value*
N	41	36	77	
Age (years)	45.2 ± 9.4	47.58 ± 11.09	46.3 ± 10.2	0.32
Smoking				
Yes	22 (54)	3 (8)	25 (32)	<00001
No	19 (46)	33 (92)	52 (68)	
Body Weight (Kg)	72.98 ± 16.98	69.25 ± 12.5	71.2 ± 15.1	0.33
BMI (Kg/m^2)	24.80 ± 5.25	28.00 ± 4.95	26.3 ± 5.32	0.008
SBP (mmHg)	120.7 ± 22.96	122.8 ± 15.23	121.7 ± 19.6	0.65
DBP (mmHg)	80 ± 7.3	79.9 ± 9.14	79.9 ± 8.2	0.94
FG (mg/dL)	84.39 ± 8.36	85.06 ± 8.27	84.7 ± 8.27	0.73
Insulin (uU/mL)	6.3 ± 3.8	7.0 ± 3.1	6.65 ± 3.48	0.37
Tgs (mg/dL)	121 ± 49.99	125.4 ± 50	123 ± 49.7	0.70
Total cholesterol (mg/dL)	148.5 ± 38.14	181 ± 43.2	163.6 ± 43.5	0.001
HDL-Cholesterol (mg/dL)	54.30 ± 12.80	57.5 ± 12.5	55.8 ± 12.7	0.27
LDL-Cholesterol (mg/dL)	70.17 ± 35.07	98.68 ± 41.9	83.5 ± 40.76	0.002
HOMA-IR	1.34 ± 0.88	1.47 ± 0.6	1.40 ± 0.0.76	0.48
QUICKI	0.38 ± 0.05	0.37 ± 0.03	0.38 ± 0.04	0.12
Mc-Auley Index	8.3 ± 2.06	7.7 ± 1.47	8.0 ± 1.83	0.13
TyG Index	4.57 ± 0.21	4.60 ± 0.19	4.59 ± 0.20	0.50
Tgs/HDL-C index	2.46 ± 1.45	2.35 ± 1.26	2.41 ± 1.36	0.72
Hypertriglyceridemia	8 (19.5)	6 (16.7)	14 (18.2)	0.75
Hypertension	8 (19.5)	6 (16.7)	14 (18.2)	0.75

*Comparisons using t-test for continuous variables or (χ^2) for non-parametric ones. BMI: Body mass index, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, FG: Fasting glucose, Tgs: Triglycerides, HOMA-IR: Homeostasis model assessment-insulin resistance, QUICKI: Quantitative insulin sensitivity check index, TyG index: Triglycerides glucose index.

Values of the (TyG index) ranged between 4.02 and 5.16 (mean 4.59 ± 0.20). TyG index relationship to some other surrogates of IS/IR was studied. Linear regression analysis revealed a significant positive correlation between TyG index and HOMA-IR (r = 0.32, p = 0.004), Tgs/HDL-c index (r=0.84, p < 0.0001). Meanwhile, It gave significant negative correlations with both Mc-Auley index and QUICKI (r = −0.68, p < 0001 and −0.29, p = 0.01), respectively, (Figures 1-4).

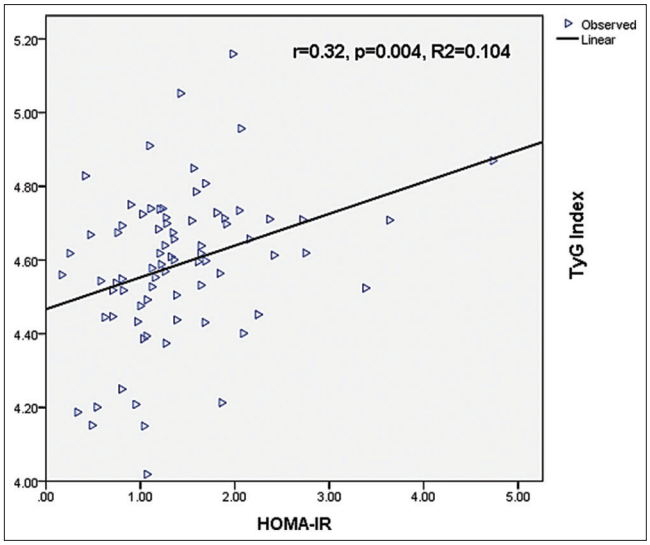

Figure 1: Linear regression analysis of HOMA-IR and TyG index as surrogate markers of insulin resistance. HOMA-IR: Homeostasis model assessment-insulin resistance, TyG index: Triglycerides glucose index

To determine the reference range of the TyG index as a surrogate measure for overall IR in our population representatives, its pattern of distribution was examined first using One-sample Kolmogorov–Smirnov statistics. This test revealed the normal distribution of TyG index where (Mean = 4.59, SD = 0.20, Z = 0.86

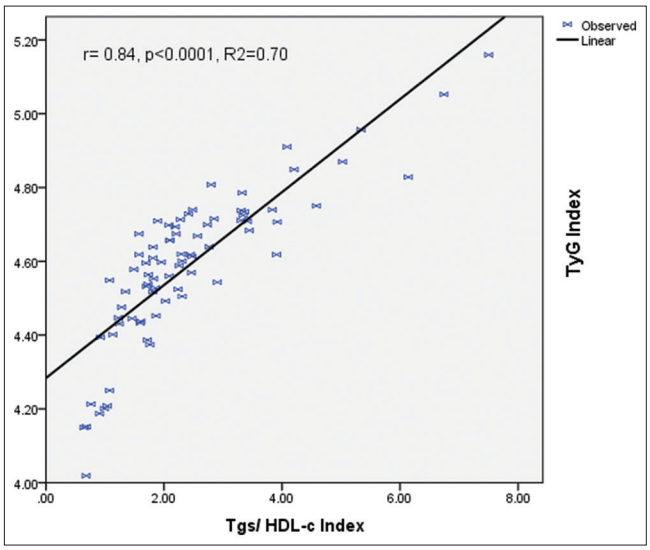

Figure 2: Linear regression analysis of Tgs/HDL-c index and TyG index as surrogate markers of insulin resistance. Tgs: Triglycerides, TyG index: Triglycerides glucose index

and p = 0.45). The frequency distribution of TyG index values in the studied population is exhibited in Figure 5.

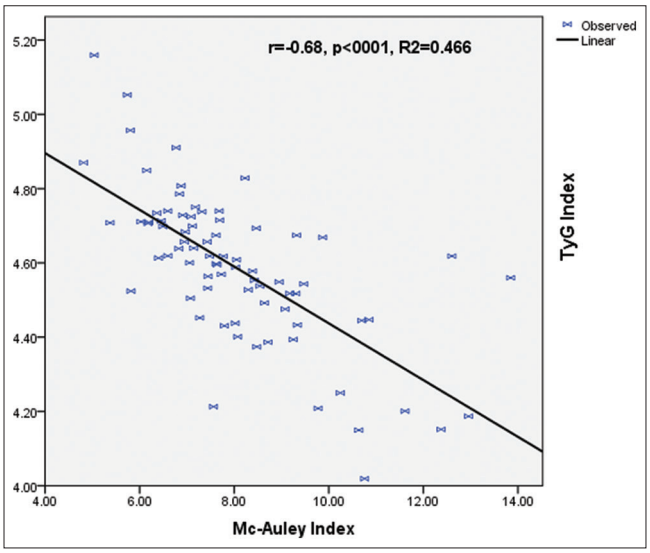

Figure 3: Linear regression analysis of Mc-Auley index and TyG index as surrogate markers of insulin sensitivity/resistance. TyG index: Triglycerides glucose index

There were no statistically significant differences in the mean TyG values comparing both sexes (Table 1). In addition, when subjects were stratified by age (10 years interval), there were no significant differences in mean TyG values as well (using ANOVA test [F = 2.06, p = 0.113]) despite non-significant increments with advancing age, (Table 2).

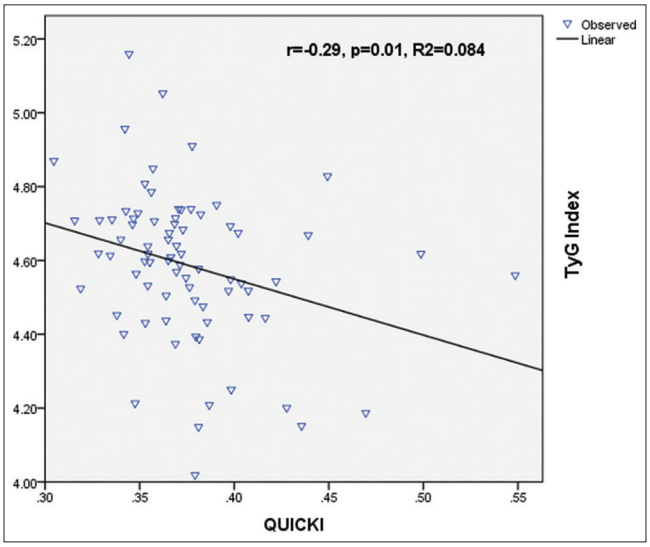

Figure 4: Linear regression analysis of QUICKI and TyG index as surrogate markers of insulin sensitivity/resistance. QUICKI: Quantitative insulin sensitivity check index, TyG index: Triglycerides glucose index

People in this study were categorized into three groups based on their BMI (lean BMI <25, overweight 25–29.9, and obese ≥30 kg/m^2) [22]. Values of TyG index were compared among the BMI subclasses using On-way ANOVA, followed by *post hoc* Duncan's test which revealed significant differences between lean people, on the one hand, and overweight and obese subjects, on the other hand.

Based on the normal pattern of distribution of TyG index values, its reference range as a surrogate

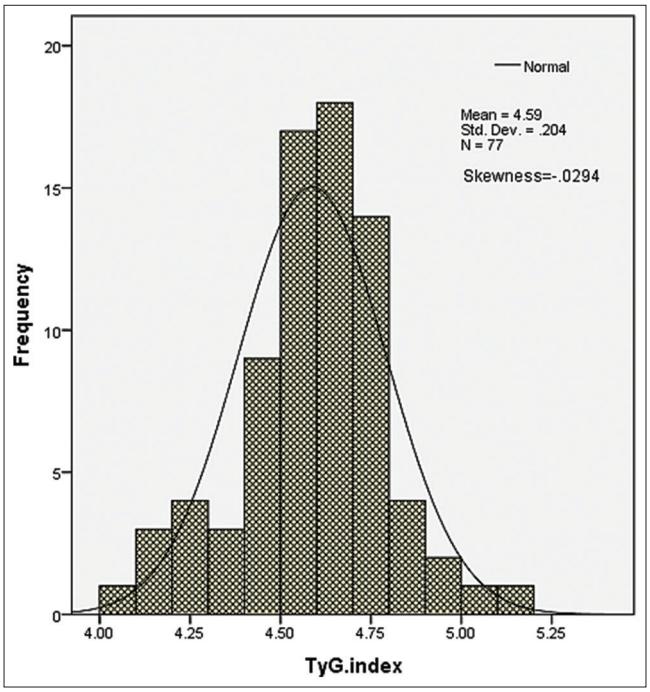

Figure 5: Frequency distribution of TyG index values in the study subjects. TyG index: Triglycerides glucose index

measure for peripheral IR in our subjects (regardless of sex and age) was calculated as mean ± 2SD. Accordingly, BMI-based TyG reference intervals were constructed for lean and (obese and overweight) subjects, respectively. The reference range for the TyG index in lean people is 4.11–4.91 and 4.25–5.05 for overweight and obese, (Table 3).

Table 2: Comparison of TyG index values by age groups

Age (years)	n (%)	TyG Index (mean ± SD)
30–39	23 (29.9)	4.51 ± 0.20
40–49	27 (35.1)	4.597 ± 0.18
50–59	17 (22.1)	4.63 ± 0.26
60–69	10 (12.9)	4.66 ± 0.12
p-value*		0.113

*Using One-Way ANOVA. TyG index: Triglycerides glucose index.

Discussion

IR is the main player in the development of metabolic syndrome and T2DM. Many people would have IR while asymptomatic. These people may be yet euglycemic or have some kind of derangement in glucose metabolism such as impaired fasting or impaired glucose tolerance whose prevalence is increasing worldwide and represent a high risk of developing future diabetes [23].

Identifying people with IR while apparently healthy (with or without abnormal glycemic state) is of high value to slow down their progress toward diabetes through modifying their living habits and/or adding some medicines [24]. The use of techniques like the HEC to diagnose IR in clinical practice is not practical as it is invasive, difficult to do and time consuming [25]. Surrogate measures have been thus developed and alternatively used on a wide basis.

Most of these mathematically calculated surrogates of IR are based on fasting plasma glucose, insulin and Tgs mainly HOMA, QUICKI, Mc-Auely index, Tgs/HDL-c index, and others. Of these, HOMA-IR is considered as the gold standard among these and is still the most widely used. Many studies worldwide-enrolling different ethnic groups and BMI - have established reference intervals for HOMA-IR [26], [27], [28].

Table 3: Reference intervals for TyG index-based on categories of BMI

	n (%)	TyG Index (Mean ± SD)	Reference Interval (Mean ± 2SD)
BMI<25 kg/m^2	36 (46.8)	4.51 ± 0.20^a	4.11–4.91
BMI 25–29.9 kg/m^2	21 (27.3)	4.65 ± 0.21^b	4.25–5.05**
BMI≥30 kg/m^2	20 (25.9)	4.65 ± 0.19^b	
*p-value		0.02	

*Comparisons by One-Way ANOVA. Means with different letters (a, b) indicate significant difference at p 0.05. **Reference intervals were calculated using SD of 0.20. BMI: Body mass index, TyG index: Triglycerides glucose index.

However, the problem of HOMA-IR calculation is its dependence on fasting insulin measurement which may not be freely available in most hospital laboratories of developing countries and expensive privately. For this reason, scientists were so eager to look for some alternative that would be available, reproducible, cheap, reliable, and insulin independent.

Reduced fatty acid oxidation due to decreased action of insulin-sensitive lipoprotein lipase in the presence of IR together with the enhanced flux of free fatty acids to non-adipose tissues (like the liver and muscles) would help build up more Tgs in these tissues and contribute to more metabolic abnormalities including hypertriglyceridemia - the one of IR characteristics [29], [30]. Simental-Mendía *et al.* in 2008 proposed an index that is based on both fasting glucose and Tgs values-the TyG index.

They found that TyG index performed as a highly sensitive (but not fairly specific) tool to diagnose IR in apparently healthy (but at risk) subjects in clinical settings at the cutoff value of Ln 4.65. As the current study shows, they also revealed a very good correlation between the TyG index and HOMA-IR. However, its relative low specificity limits its benefit as a large scale tool for IR screening [12]. Beside its association with IR, TyG index has been found in different studies to be associated with problems such as fatty liver diseases, hypertension, and diabetes [31], [32], [33]. These findings support the need for further focusing on TyG index in clinical association studies.

Referring to normal values is mandatory for appropriately interpreting laboratory tests. To the best of our best knowledge, this is the first study that establishes a reference interval for TyG index among apparently healthy adult people in Iraq. It was established between the (2.5th) and (97.5th) percentiles

of our TyG data which followed Gaussian distribution, as recommended [34]. Obesity is well-known to associate with IR and hypertriglyceridemia and our results showed statistically significant differences in the mean TyG index value by BMI classes - but not by age or sex categories. Thus, we have determined the upper limit of the TyG index as 4.91 in lean people and 5.05 when BMI ≥25 Kg/m^2.

One of our study's limitations is the small sample size. The study was interrupted by the pandemic of COVID-19. In addition, our study compared the TyG index to HOMA-IR and some other surrogates of IR, but not with the real gold-standard test - the HEC. Overall, calculating TyG index is easy, insulin independent requiring FG and Tgs only and can be used in clinical settings.

Conclusions

The TyG index is a reasonable estimate of IR in apparently healthy people keeping in mind the person's BMI. In Iraqi adult people, the upper limit of the TyG index is 4.91 in lean people and 5.05 if BMI ≥25 Kg/m^2. Further studies are needed to validate its performance as a diagnostic test for IR involving people with different glycemic states.

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