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ORIGINAL ARTICLE

# TyG index and insulin resistance in beta-thalassemia

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**Abstract** Insulin resistance (IR) underlies some glucose metabolism abnormalities in thalassemia major. Recently, triglyceride glucose index (TyG) has been proposed for evaluating insulin resistance as a simple, low cost, and accessible tool. In this study, the TyG index were studied for IR monitoring in beta-thalassemia major (βTM) patients. The participants were 90 βTM patients on chronic regular transfusion therapy. The TyG index was computed based on fasting plasma glucose (FPG) and triglyceride (TG). The time gap between the first and the second TyG index survey (TyG.1 and TyG.2) was 2 years. The agreement between TyG and HOMA-IR were studied with the extension of limit of agreement (LOA). We included 90 patients 53.3 % men ($n$=48). Among them, 14.4 % (14.6 % male, 14.3 % female) had impaired fasting glucose level (e.g., 100–125 mg/dl) at first test. It rose to 37.8 % (27.1 % male, 50 % female) during 2 years. Based on TyG.1, the 34.4 % of patients was detected as IR cases. After 2 years, the percent of IR based on TyG.2 was 82.2 %. The mean differences between TyG.1 and TyG.2 and their differences from the considered cutoff values were significant ($P$<0.001). The prediction limits between TyG and HOMA-IR had good agreement. These data may suggest the use of TyG index for detection/monitoring of IR in βTM patients.

**Keywords** Insulin resistance · Beta-thalassemia major (βTM) · Triglyceride glucose (TyG) index

## Introduction

Diabetes mellitus is an important and a prevalent endocrine complication in beta-thalassemia major patients [βTM] [1]. Insulin resistance (IR) is known as a causative or predisposing factor for development of diabetes mellitus and as an independent cardiovascular risk factor [2–4]. The IR as a long lasting subclinical state can also be detected in other disorders, and its early detection is generally recommended. Both the improved life expectancy and the high prevalence of diabetes mellitus in secondary hemosiderosis highlight IR screening in βTM [5, 6].

Different methods have been introduced for IR assessment. The gold standard method is euglycemic clamp, but it is invasive, requires expert staff, and has very limited clinical indications. Thus, other alternative non-invasive indirect indices for IR risk assessment are introduced. The homeostasis model assessment of insulin resistance (HOMA) and the quantitative insulin sensitivity check index (QUICKI) are among the more commonly used IR surrogate. The HOMA and QUICKI index calculations are based on fasting plasma glucose and insulin level [7]. A recently introduced IR indicator is the triglyceride glucose (TyG) index which shows good correlations with euglycemic clamp, and unlike the HOMA index, its calculation is based on fasting plasma glucose (FPG) and triglyceride [8–14]. TyG index is initially reported for estimation of IR in healthy subjects. But this simple, low cost, and accessible index is also used for patients in a different clinical setting

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[15, 16]. Base on our limited knowledge, there is not any data regarding the application of TyG index for screening IR in βTM. Therefore, the TyG index values and its changes over time were taken into attention in these patients.

## Materials and methods

### Setting and eligibility criteria

This observational longitudinal study started in 2012 with more than 200 cases according to the considered criteria including: negative drug history for exogenous insulin and other anti-diabetic agents, no history of diagnosed diabetes at the beginning of study, negative drug and clinical history of hyperlipidemia and other co-morbid disease such as hyper- or hypothyroidism. Thereafter, only 90 subjects were remained that fully fit above conditions. The study was carried out in Taleghani Pediatrics hospital in Gorgan (north of Iran); approved by the Research and Ethics committees of Golestan University of Medical Sciences (No. 2001). All participants were well informed by the authors and signed individually an informed consent form. All data obtained were kept confidential. No intervention was performed on the patients, and they paid no additional charge.

All blood samples were obtained after an overnight 10–12 h of fasting. The FPG and triglyceride were measured by Prestige 24i fully automatic clinical chemistry analyzer (Japan). The plasma insulin level was determined using human insulin enzyme-linked immunosorbent assay kit.

### Agreement assessment

As shown in Fig. 1, 26 patients were randomly selected and calculated their TyG index, Ln [fasting triglyceride (mg/dl) × fasting glucose (mg/dl)/2], and HOMA-IR, [fasting glucose (mg/dl) × insulin (mU/L)]/405, simultaneously. The agreement between TyG and HOMA-IR were studied with the extension of limit of agreement (LOA) [17] which produced

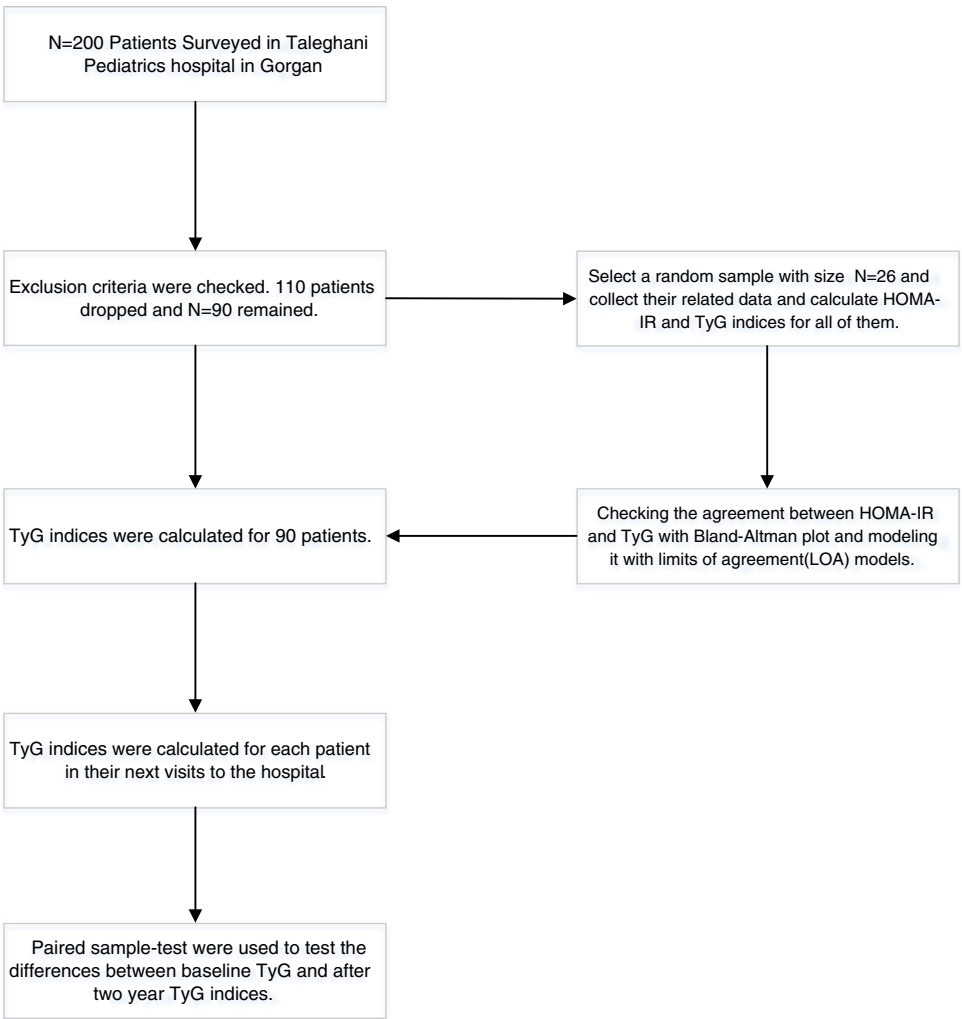


**Fig. 1** Work flow diagram of the study

prediction limits between two indices with MethCamp package in R [18, 19].

### Comparing two TyG

Then, TyG index for whole 90 patients were calculated. During 2 years follow-up of these patients and in each visit to the Taleghiani hospital, their TyG indices were recorded. The paired *t* test was used for comparing TyG indices. The power of the test was conducted with PASS 11 [20].

### Simulation study

Monte Carlo simulations with 1000 replicates were conducted to figure out the possible range of TyG indexes based on these 90 patients. For this purpose, the distributions of fasting triglyceride and FPG in base line and after 2 years were fitted. The fitted distributions were used to simulate TyG index. All statistical analysis conducted with IBM SPSS version 22.

### Diagnosis of IR

Two cutoff values including 4.515 and 4.68 were considered for IR detection. In support of the first threshold (e.g., 4.515), the reported sensitivity and specificity for IR detection was 70 and 85 %, respectively, and for the second threshold (e.g., 4.68), the reported sensitivity and specificity was 60 and 95.5 %, respectively [9, 13]. The relations of TyG index with some proposed markers of IR in βTM including ferritin and AST were also investigated.

## Results

The demographic characteristics of $n=90$ patients were shown in Table 1. The mean and standard deviation of participant's age and height was 19.87±8.15 years and 146.77±28.16 cm simultaneously. The ratio of sex is very close for male and female with 53.3 % male. The reported weight and ferritin were included the measured values at first visit and after 2 years later. Among the participants, 25.6 % had done splenectomy. Most patients had $O^+$ (43.8 %) or $A^+$ (22.5 %) blood group. The systolic and diastolic blood pressures were 101.68±18.00 and 65.15±10.90 mmHg, respectively. According to the number of missing values for these characteristics, only age, sex, height, splenectomy, and blood group were given good estimates.

A random sample with size $n=26$ were chosen to assess the agreement between HOMA-IR and TyG indexes. Table 2 were summarized the descriptive statistics of these two methods. The minimum value of HOMA-IR was 0.1999, but for TyG, it was 4.302, and the maximum value of HOMA-IR was 3.298, but for TyG, it was 5.272. Also, the median of these two methods were far from each other, 1.52 for HOMA-IR and 4.854 for TyG. Therefore, regular limit of agreement methods such as Bland-Altman plot were produced misleading result. Instead the extension to LOA by regression were used which were relaxed to some assumptions. According to Fig. 2, all dots are in the prediction limits except one which was an outlier. The agreement between HOMA-IR and TyG were assessed for this sample.

A paired sample *t* test was conducted to compare TyG score between the first and the 2-year later visit. There was a significant difference in the TyG scores for the first visit (mean=4.610, SD=0.212) and 2-year later visit (mean=4.854, SD=0.204); $t(89)=-14.244$, $P<0.001$. The power of this test were calculated >0.99. Sex difference was not observed for TyG in both sessions. An increasing trend of TyG index with age was existed but it was not statistically significant.

**Table 1** Demographic characteristics of $N=90$ patients

| | *N* of missing | *N*=90 patients |
|---|---|---|
| Age (years)[a] | | 19.87±8.15 |
| Sex (% male) | | 53.3 % (*n*=48) |
| Height (centimeter) | | 146.77±28.16 |
| Weight (kilogram) | | |
| First visit | 22 | 38.68±16.65 |
| Two year later visit | 64 | 49.13±16.40 |
| Ferritin (ng/ml) | | |
| First visit | 40 | 7111.38±15422.15 |
| Two year later visit | 20 | 4259.41±2630.893 |
| Splenectomy (% +) | | 25.6 % (*n*=23) |
| Blood group (%) | 1 | |
| A+ | | 22.5 % (*n*=20) |
| A− | | 6.7 % (*n*=6) |
| AB | | 7.9 % (*n*=7) |
| O+ | | 43.8 % (*n*=39) |
| O− | | 1.1 % (*n*=1) |
| B+ | | 11.2 % (*n*=10) |
| B− | | 3.4 % (*n*=3) |
| AB− | | 3.4 % (*n*=3) |
| Blood pressure (mm Hg) | | |
| Systolic | 44 | 101.68±18.00 |
| Diastolic | 44 | 65.15±10.90 |

Data presented as unadjusted means with standard deviations or percentages (*n*)

[a] At baseline

**Table 2** Descriptive statistics of two methods of HOMA-IR and TyG based on a random sample with size 26

| Method | Number | Min | Median | Max |
|---|---|---|---|---|
| HOMA-IR | 26 | 0.199 | 1.520 | 3.298 |
| TyG | 26 | 4.302 | 4.854 | 5.272 |

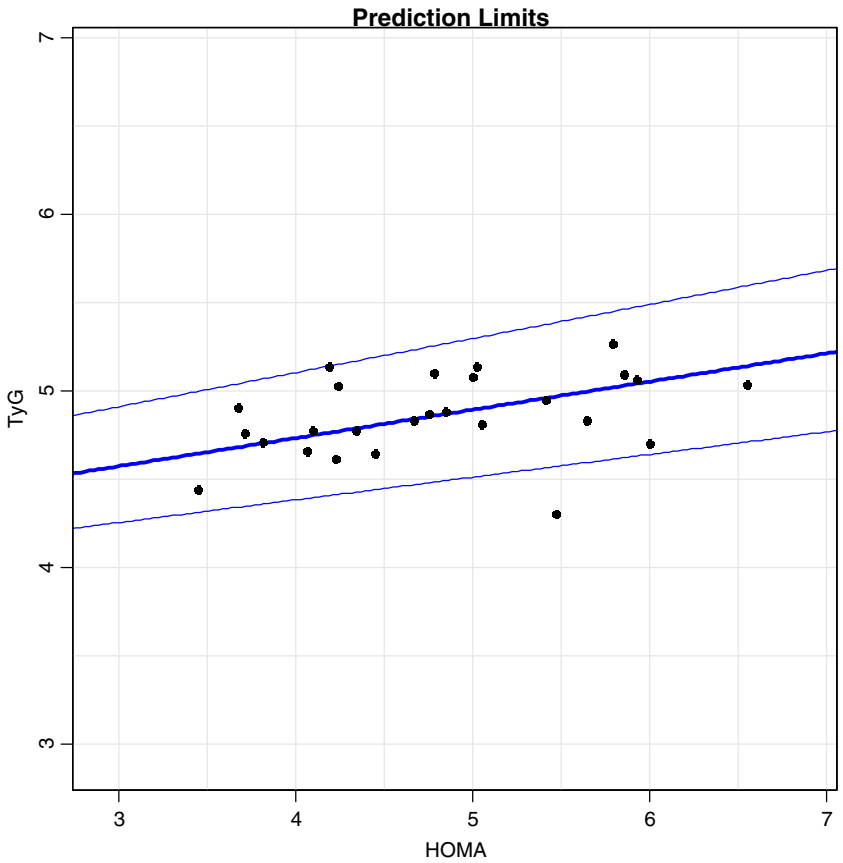


**Fig. 2** Prediction limits between two methods TyG and HOMA-IR

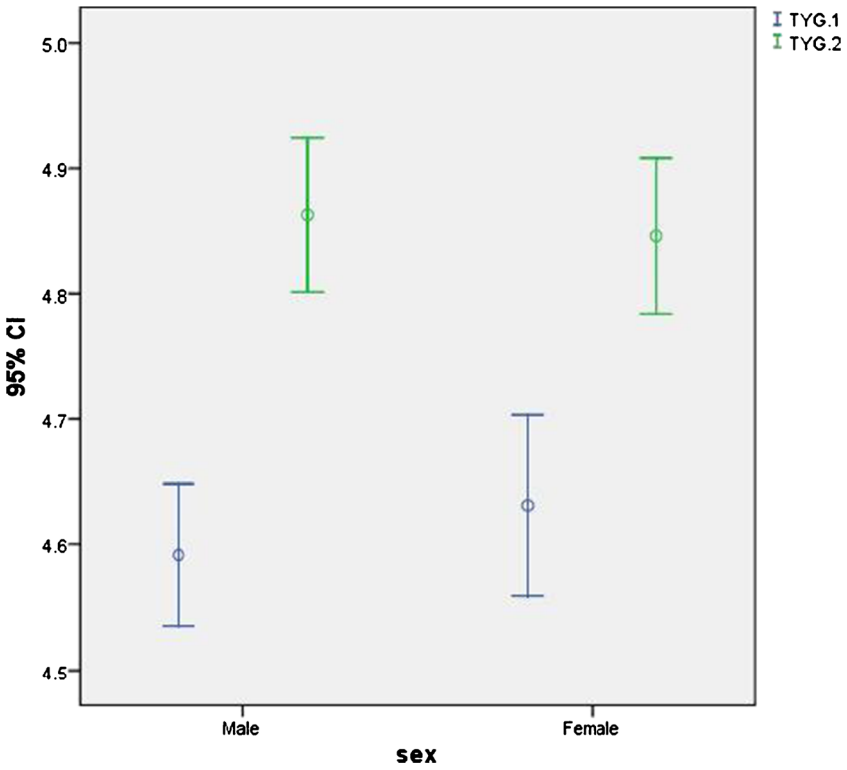


**Fig. 3** The first and the second TyG index for male and female patients

The distributions of fasting triglyceride and FPG were fitted to log-normal and normal distributions simultaneously. The Monte Carlo simulation with $n=1000$ replicates were conducted using these distributions. The results for the first and the 2-year later visit were as follows. The mean, median, and standard deviation values of simulated study (first visit 4.632, 4.613, and 0.226; 2-year later visit 4.850, 4.838, and 0.201, respectively) had negligible difference with actual values (first visit 4.610, 4.604, and 0.212; 2-year later visit 4.854, 4.829, and 0.204, respectively). But the standard errors of simulated data in the first and 2-year later visit (0.007 and 0.006) were dramatically lower than actual values (0.022 and 0.021). The minimum values of TyG in actual data were 4.08 and 4.30, which in simulated data were 3.98 and 4.17 for the first and 2-year later visit, simultaneously. Also, the maximum values of TyG in actual data were 5.08 and 5.38, which in simulated data were 5.44 and 5.56 for the first and 2-year later visit, simultaneously. These results were expressed that TyG indexes can vary from 3.98 to 5.56.

According to the value of FPG in the first and in the 2-year later visit, 14.4 % (14.6 % male, 14.3 % female) and 37.8 % (27.1 % male, 50 % female) had impaired fasting glucose level (100–125 mg/dl), respectively. The means and 95 % confidence intervals of the TyG indices are differentially shown for the male and female patients during 2 years interval in Fig. 3. Based on TyG.1, %34.4 (%25 of males and %45.2 of females) and based on TyG.2, %82.2 (83.3 % of males and 81 % of females) of patients were detected as IR cases (e.g., had values greater than 4.68). The correlation of TyG index with ferritin ($P=0.018$, $R=0.282$) and AST ($P=0.039$, $R=0.226$) was considerable.

## Discussion

We observed that the TyG index increased significantly in βTM patients in the 2 years interval. This index was used for the early detection of IR and offered as a screening tool for prediabetic state [9–11]. The gold standard test for IR is insulin clamp which is an invasive technique and needs well-trained staff [21]. The HOMA-IR and QUICKI indices are well-known estimators for IR too. They are calculated from fasting plasma insulin and glucose level. Different HOMA-IR values were reported as normal in thalassemia major. In 2014, Li reported the IR in 71 Taiwanese patients with thalassemia major (32 male, 39 female; mean age±SD 21.7±6.3 years) and defined HOMA-IR <1.6 as normal [22]. In our study based on TyG.1 with considering 4.515 and 4.68 as IR cutoffs, 67.8 and 34.4 % of patients had IR respectively. Also, based on TyG.2 with the same cut offs, 96.7 and 82.2 % of patients had IR, respectively. These findings were consistent with other reports about high prevalence of IR among βTM patients [23].

It is reported that iron overload in βTM is associated with IR. This overload is accounted as the main cause of diabetes in βTM [24]. In some studies, serum level of ferritin is presented as a risk factor for developing glucose tolerance abnormalities in βTM patients [25, 26].

The increased serum level of aminotransferases in βTM patients mainly attributes to iron overload and is also linked to IR in them [23]. A similar outline was observed in this study because the TyG.2 index had significant correlation with AST ($P<0.05$, $R=0.226$).

Both the IR and the deficiency of insulin are reported in βTM [27]. However, there are some controversies regarding the order of their occurrences or their causative role for different glucose abnormalities in βTM [28–30]. Despite these disagreements, the early detection of IR per se is a well-known recommendation [22]. There are different estimates about the prevalence of insulin resistance in thalassemia major. There are also different estimates about the prevalence of diabetes in βTM patients that ranges from less than 10 % to more than 30 % [6, 31–33] at most; this variation might be due to ethnicity or genetic factors [34]. We did not enroll diabetics in this study, but our finding about the impaired fasting glucose in the first and second session was similar to other reports [34, 35].

The prediction limits between TyG and HOMA-IR show good agreement. Our data also match with Monte Carlo simulation results and may suggest the application of TyG as an IR marker for βTM patients. The simplicity of TyG index has practical outcomes such as accessibility and less cost. These properties may be very important in low-income populations at risk for metabolic syndrome and diabetes as well as for offering it as screening test [12–14]. However, the age and sex dependent cutoff values for TyG are not well established and more studies need to do.

## Conclusion

TyG index may be suggested as a helpful marker for revealing the insulin resistance in βTM patients especially when repeated in regular intervals.

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**Conflict of interest** The authors declare that they have no competing interests.

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