The Product of Triglycerides and Glucose, a Simple Measure of Insulin Sensitivity. Comparison with the Euglycemic-Hyperinsulinemic Clamp

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Context: To meet the worldwide challenge of emerging diabetes, accessible and inexpensive tests to identify insulin resistance are needed.

Objective: To evaluate the sensitivity and specificity of the product of fasting, we compared the triglycerides and glucose (TyG) index, a simple measure of insulin resistance, with the euglycemic-hyperinsulinemic clamp test.

Design and Setting: We conducted a cross-sectional study of the general population and outpatients of the Internal Medicine Department at the Medical Unit of High Specialty of the Specialty Hospital at the West National Medical Center in Guadalajara, Mexico.

Patients: Eleven nonobese healthy subjects, 34 obese normal glucose tolerance individuals, 22 subjects with prediabetes, and 32 diabetic patients participated in the study.

Intervention: We performed a euglycemic-hyperinsulinemic clamp test.

Main Outcome Measures: Sensitivity and specificity of the TyG index [Ln(fasting triglycerides) (mg/dl) $\times$ fasting glucose (mg/dl)/2] were measured, as well as the area under the curve of the receiver operating characteristic scatter plot and the correlation between the TyG index and the total glucose metabolism (M) rates.

Results: Pearson's correlation coefficient between the TyG index and M rates was -0.681 ($P < 0.005$). Correlation between the TyG index and M rates was similar between men (-0.740) and women (-0.730), nonobese (-0.705) and obese (-0.710), and nondiabetic (-0.670) and diabetic (-0.690) individuals. The best value of the TyG index for diagnosis of insulin resistance was 4.68, which showed the highest sensitivity (96.5%) and specificity (85.0%; area under the curve + 0.858).

Conclusions: The TyG index has high sensitivity and specificity, suggesting that it could be useful for identification of subjects with decreased insulin sensitivity. **(*J Clin Endocrinol Metab* 95: 3347–3351, 2010)**

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Abbreviations: AUC, Area under the curve; HOMA-IR, homeostasis model assessment of insulin resistance; M rate, metabolism rate; ROC, receiver operating characteristic; TyG, triglyceride and glucose.

Obese individuals and some normal-weight subjects, those named metabolically obese normal-weight individuals, commonly exhibit insulin resistance, disturbances in lipoprotein metabolism, and increased serum triglyceride levels (1–3). Although there is no explanation for the correlation between hypertriglyceridemia and insulin resistance, it has been reported that an increase of triglycerides interferes with muscle-glucose metabolism (4), a finding consistent with the hypothesis that elevation of triglycerides in serum and tissues is related to a decrease in insulin sensitivity (5).

Recently, we reported that the product of fasting triglyceride and glucose (TyG) levels has high sensitivity for recognizing insulin resistance in apparently healthy subjects, compared with the homeostasis model assessment of insulin resistance (HOMA-IR) index (6).

In this study, we evaluate the sensitivity and specificity of the TyG index, compared with the euglycemic-hyperinsulinemic clamp test, as a surrogate measure for identifying insulin resistance.

Subjects and Methods

With the approval of protocol by the Mexican Social Security Institute Research and Ethics Committee, and after obtaining signed informed consent from subjects, a cross-sectional study was carried out in accordance with the principles of the Declaration of Helsinki as revised in 2000.

Sixty-seven apparently healthy subjects from the general population of Guadalajara, a city in western Mexico, and 32 subjects with type 2 diabetes were enrolled; the mean age of the Mexican population in Guadalajara is 26 yr (7).

The sampling strategy was based on randomized procedures. In brief, a random sample of households within the same neighborhood and similar economic and cultural conditions was obtained, and households were visited to invite apparently healthy subjects to participate in the study. In addition, a random list of outpatients who receive medical care in the Internal Medicine Department at the Medical Unit of High Specialty of the Specialty Hospital at the West National Medical Center at Guadalajara, Mexico, was obtained to invite diabetic patients to participate in the study.

All volunteers maintained stable body weight during the 3 months before the study, consumed an isocaloric diet containing approximately 250 g/d of carbohydrates 3 d before the test, and were required to avoid exercise at least 72 h before the study; none of them received medication that affects lipid metabolism. Medical treatment of diabetic patients was based on the use of oral hypoglycemic agents such as sulfonylureas and/or biguanides; subjects receiving insulin were not included in the study. In women, the test was carried out during the follicular phase (d 3–5) of their menstrual cycle.

All participants underwent anthropometric measurements and routine blood chemistry.

For the euglycemic-hyperinsulinemic clamp technique (8), two points of venous access were established. The first was placed in a retrograde position into any vein in the subject's hand through a 23-gauge catheter to obtain blood samples. The hand was wrapped with a thermal pillow until reaching a temperature above 40 C to improve the amount of oxygen in venous blood. The second point of venous access was established in the contralateral arm with a 20-gauge catheter for infusion. Insulin (Humulin R; Eli Lilly Co., Mexico City, Mexico) was given as a primed continuous infusion calculated to raise the plasma insulin concentration to 100 $\mu U/m^2$, followed by an insulin infusion rate fixed at 40 $\mu U/min/m^2$. A constant blood glucose level was maintained (with a coefficient of variation $<5\%$) throughout the 120-min study by infusing 10% glucose at various rates according to blood glucose measurements performed at 5-min intervals. At the end of the clamp procedure, the 10% glucose infusion was maintained for 30 min to avoid hypoglycemia. Total glucose metabolism (M) rate was calculated to evaluate insulin sensitivity (9). All of the studies began at 0800 h after a 10- to 12-h overnight fast. M rates of at least 2.8 defined insulin resistance.

The TyG index was calculated as the Ln[fasting triglycerides (mg/dl) $\times$ fasting glucose (mg/dl)/2] (6).

According to the American Diabetes Association criteria (10), diagnosis of prediabetes was established by the presence of impaired fasting glucose and/or impaired glucose tolerance. Obesity was defined by body mass index of at least 30 kg/m^2. Individuals in the obese group had normal glucose tolerance; thus, they were categorized as obese normal glucose tolerance individuals.

Assays

On the same day, previous to the euglycemic-hyperinsulinemic clamp technique and after a 10- to 12-h overnight fast, a venous whole blood sample was collected for measuring glucose, triglycerides, and insulin levels.

Triglycerides were enzymatically measured using spectrophotometric methods. The intra- and interassay coefficients of variation were 1.9 and 3.7%, respectively.

Insulin levels were measured by microparticle enzyme immunoassay (Abbott Axsym System; Abbott Laboratories, Abbott Park, IL), with intra- and interassay coefficients of variation of 4.5 and 6.9%, respectively.

Plasma glucose concentrations were determined using the glucose-oxidase method (Sigma Diagnostics, St. Louis, MO), with intra- and interassay coefficients of variation of 2.4 and 3.8%, respectively.

All measurements were performed in a Data Pro Plus random access clinical analyzer (Data Pro, Arlington, TX).

Statistical analysis

Differences between more than two groups were estimated using one-way ANOVA with Bonferroni *post hoc* test. Pearson's simple correlations between M rates and TyG index were computed. For these analyses, serum triglyceride levels and M rates were log-transformed to approximate a normal distribution.

TyG indexes and M rates were stratified into tertiles, and degree of agreement was computed using weighted *k* test. Weights for agreement were set from 0.00 (no agreement) to 1.0 (full agreement).

Sensitivity and specificity of the TyG index were estimated as a function of the threshold used to define insulin resistance by the gold standard test (11). The optimal value of the TyG index for diagnosis of insulin resistance was established on a receiver operating characteristic (ROC) scatter plot. The area under the

TABLE 1. Clinical characteristics of the study population

	Healthy	Obese	Prediabetes	Diabetes	F	*P* value
n	11	34	22	32		
Age (yr)	30.5 ± 8.3	35.6 ± 8.3	44.4 ± 7.1	44.4 ± 7.7	7.5	<0.0001
Body mass index (kg/m^2)	27.8 ± 1.1	33.4 ± 2.1	30.7 ± 3.1	29.3 ± 3.3	73.5	<0.0001
Waist circumference (cm)	94.3 ± 5.0	105.8 ± 8.2	97.7 ± 7.5	98.6 ± 9.0	17.2	<0.0001
Fasting plasma glucose (mg/dl)	88.3 ± 7.2	95.5 ± 10.8	113.5 ± 9.0	136.9 ± 25.2	8.9	<0.0001
Triglycerides (mg/dl)	168.3 ± 53.1	194.9 ± 70.9	230.3 ± 79.7	292.3 ± 70.9	9.1	<0.0001[b]
Insulin (U/ml)[a]	12 (9.1, 14.1)	17.7 (15.8, 20.9)	21.4 (18.0, 24.9)	19.8 (17.0, 27.3)	3.4	0.02[b]
HOMA-IR index[a]	2.5 (2.1, 2.8)	4.7 (3.8, 6.3)	5.6 (4.5, 6.7)	6.8 (5.3, 8.6)	5.4	0.002[b]
Total glucose metabolism (mg/min/kg)[a]	3.3 (2.8, 4.6)	2.6 (2.0, 3.8)	2.5 (2.1, 3.4)	2.2 (1.8, 3.5)	3.8	0.01
TyG index[a]	3.7 (3.5, 3.9)	5.3 (4.9, 5.6)	5.5 (5.0, 5.7)	5.6 (5.1, 5.8)	4.3	0.01[b]

Values are expressed as mean ± SD, unless otherwise is indicated. TyG index: Ln[triglyceride (mg/dl) × glucose (mg/dl)/2].

[a] Values are median (25th, 75th percentile).

[b] For estimation of *P* value, values were log-transformed to approximate a normal distribution.

ROC curve (AUC), as a summary of the overall diagnostic accuracy of the test, was estimated (11). The best markers have ROC curves that are shifted to the left with AUCs near 1.

Results

A total of 99 subjects (52 women and 47 men; average age, 39.9 ± 9.3 yr) were enrolled, including 11 nonobese healthy subjects, 34 obese normal glucose tolerance individuals, 22 subjects with prediabetes, and 32 diabetic patients.

The average body mass index, waist circumference, fasting glucose level, and triglyceride level were: 30.8 ± 3.3 kg/m^2, 100.4 ± 8.9 cm, 109.9 ± 25.2 mg/dl (6.1 ± 1.4 mmol/liter), and 177.1 ± 70.9 mg/dl (2.0 ± 0.8 mmol/liter), respectively. The median (25th and 75th percentiles) of M rates and TyG index were 2.8 (2.03, 3.54) mg/min/kg of body weight and 5.4 (5.1, 5.7).

Anthropometric and biochemical characteristics of the target population are shown in Table 1. Diabetic patients were older and had higher fasting plasma glucose and triglycerides levels and lower M rates than subjects in the other groups.

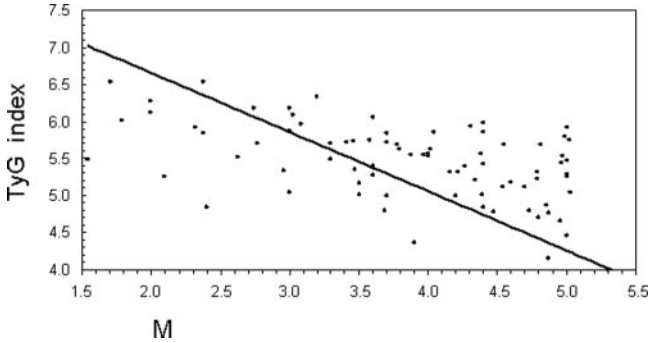

FIG. 1. Pearson's correlation between TyG index and total glucose M rates estimated using the euglycemic-hyperinsulinemic 2-h clamp test. n + 99 subjects. TyG + Ln[fasting triglycerides (mg/dl) × fasting glucose (mg/dl)/2].

Pearson's correlation coefficient between the TyG index and M rates was −0.681 (*P* + 0.01) (Fig. 1). On the other hand, correlation between HOMA-IR index and M rates was −0.765 (*P* + 0.001), and between TyG and HOMA-IR index was 0.391 (*P* + 0.01). Correlation between the TyG index and M rates was similar between men (−0.740) and women (−0.730), between nonobese (−0.705) and obese (−0.710) subjects, and between nondiabetic (−0.670) and diabetic (−0.690) individuals.

Subjects were categorized by tertiles of TyG index and M rates; on the assumption that the maximum insulin sensitivity corresponds to tertile I of the TyG index and tertile III of M rates, and minimum insulin sensitivity to tertile III of TyG index and tertile I of M rates, the weighted *k* test (*k* + 0.806) showed a good agreement (Table 2).

The ROC scatter plot revealed that the best value of the TyG index for diagnosis of insulin resistance corresponded to 4.68, which showed the highest sensitivity (96.5%) and specificity (85.0%; AUC + 0.858) (Fig. 2).

The TyG index failed to detect 2.0% of the subjects with insulin resistance; on the other hand, 3.0% of the participants who were classified as normal by the euglycemic clamp had insulin resistance by the TyG index criterion.

TABLE 2. Agreement in the categorization of subjects according insulin sensitivity measured by euglycemic-glucose clamp (M) and TyG index

		TyG tertiles		
M tertiles	Cutpoint values	III 4.87–6.53	II 3.62–4.86	I 1.90–3.61
I	1.81–2.20	31	3	2
II	2.21–3.30	1	25	0
III	3.31–5.46	0	7	30

Subjects were stratified into tertiles of TyG indexes and M rates showing a high degree of agreement (weighted *k* coefficient of agreement = 0.806). Maximum and minimum insulin sensitivity corresponded to tertile III and I, respectively, of both parameters.

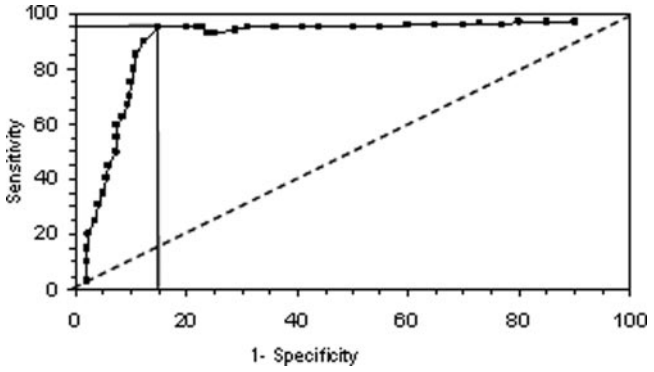

FIG. 2. ROC curve. Sensitivity represents true-positive results and 1-specificity, the false-positive results. The best TyG value for diagnosis of insulin resistance was 4.68, which showed the highest sensitivity (96.5%) and specificity (85.0%) (*black lines*) (AUC + 0.858).

Discussion

Our results show that TyG index closely mirrors the glucose clamp technique in the assessment of insulin sensitivity, suggesting that it could be useful to recognize insulin resistance among subjects with various degrees of glucose tolerance and body weight.

The main strength of this study is that TyG index was evaluated *vs.* the gold standard test in a sample of individuals with various degrees of body weight and glucose tolerance. In addition to its high sensitivity and specificity, the main advantages of the TyG index are that it is derived from the fasting state, it is less costly, measurements of glucose and triglycerides are available in all clinical laboratories, and quantification of serum insulin levels (an expensive test that is not available in most laboratories of cities in undeveloped countries) is not required. Thus, TyG index could be an accessible and reliable test for estimating insulin resistance of low-income individuals in high-risk groups in undeveloped countries.

The main limitation of the study is that TyG index does not mirror the physiological condition of constant changes in glucose and insulin; however, no method will ever be capable of truly measuring insulin sensitivity (12). Although euglycemic hyperinsulinemic clamp is the method with the fewest drawbacks and is closest to the real measure of insulin sensitivity (12), it is not available in a clinical setting and is time consuming and costly. Finally, given the variability of triglyceride levels according to ethnicity, further research is needed to evaluate the TyG index in different populations.

Increases in obesity and diabetes affect all ages, all races, and all educational levels (13). A recent report by Cowie *et al.* (14) found that over 40% of people aged 20 yr or more have hyperglycemic conditions and that diagnosis of diabetes has significantly risen over the last 10–15 yr. Given that the prevalence of diabetes is rapidly increasing worldwide, among policies needed to face the challenge of emerging diabetes are accessible and inexpensive laboratory tests to identify insulin resistance; in this regard, the TyG index could be an attractive approach to estimate insulin resistance.

The HOMA-IR (15) is the most frequently used index to evaluate insulin resistance using measures derived from the fasting state. Recently, Bonora *et al.* (12) reported a strong inverse correlation between clamp-measured glucose disposal and HOMA-estimated insulin sensitivity (Pearson's correlation coefficient of −0.820), concluding that HOMA-IR can be reliably used in large-scale or epidemiological studies. In this study, the correlation coefficient of TyG (−0.681) and HOMA-IR (−0.765) with the M rates was similar, supporting the statement that TyG index can also be reliably used to recognize insulin resistance. In addition, the low rate of false-negative tests (high sensitivity) of TyG index indicates that diseased individuals can be accurately identified. This finding suggests that TyG index also could be useful for identifying insulin resistance in large-scale studies or for examining populations at high risk of developing diabetes. In this regard, TyG index is not better than HOMA-IR index but is an alternative test for recognizing insulin resistance in the framework where measurement of insulin is not available.

The availability of simple and inexpensive tools such as the hypertriglyceridemic waist (16) and TyG index contributes to a better identification of individuals at high risk, expanding the benefits of screening. In the target population of this study, the Pearson′s correlation coefficient between hypertriglyceridemic waist and M rates was lower than the coefficient between TyG indexes and M rates (−0.110 and −0.681). However, taking into account that the hypertriglyceridemic waist is focused on the identification of subjects at high risk for cardiovascular disease (as a marker of the atherogenic metabolic triad of hyperinsulinemia, hyperapolipoprotein B, and small, dense low-density lipoprotein in men) and TyG index in the identification of subjects with decreased insulin sensitivity, the use of both indexes could be useful for a better characterization of subjects at risk. Furthermore, the correlation between TyG and HOMA-IR index (0.391) was slightly higher than that previously reported in healthy subjects (0.322) (6), a difference that could be attributable to the target population that, in this study, included diabetic patients.

Whether variability of fasting triglyceride levels influences the values of TyG index and establishes the role that postprandial triglycerides exert on insulin sensitivity remains to be clarified.

In conclusion, our results show that TyG index has high sensitivity and specificity to recognize insulin resistance,

suggesting that it could be useful for identification of subjects with decreased insulin sensitivity.

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