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Original Article

Triglycerides and glucose index as an insulin resistance marker in a sample of healthy adults

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ABSTRACT

Aim: To assess the association between elevated triglycerides/glucose index (TGI) and insulin resistance (IR) or hyperinsulinemia after oral glucose tolerance test (OGTT) in a sample of healthy adults.
Methods: We conducted an analytical cross-sectional study in euthyroid non-diabetic adults, who attended the outpatient service of a private clinic in Lima-Peru during the 2012–2016 period. Participants were categorized in two groups according to the presence or absence of elevated TGI, IR or hyperinsulinemia after OGTT. A TGI value ≥ 8.65 was considered as elevated. We defined IR as a Homeostasis Model Assessment (HOMA-IR) value ≥ 2.28 and hyperinsulinemia after OGTT as a serum insulin value $\geq 80\mu U/mL$ after 120 min of 75-g glucose intake. We elaborated crude and adjusted Poisson regression models to assess the association between elevated TGI and IR or hyperinsulinemia after OGTT. The reported association measure was the prevalence ratio (PR) with their respective 95% confidence intervals (95%CI).
Results: We analyzed 118 individuals, the average age was 37.5 ± 11.3 years, 21 (17.8%) were males and the median BMI was $22.7 \pm 1.6\ kg/m^2$. The prevalence of elevated TGI was 25.4% (n=30) while the prevalence of IR and hyperinsulinemia after OGTT was 24.6% (n=29) and 17.0% (n=20) respectively. In the adjusted model, elevated TGI was associated with both IR (aPR=6.36; 95%CI: 3.41–11.86) and hyperinsulinemia after OGTT (aPR=4.19; 95%CI: 1.81–9.70).
Conclusions: We found that elevated TGI was associated with both IR markers in a sample of euthyroid adults without T2DM and with a normal BMI. The simplicity of the TGI calculation makes it the first-choice alternative when the hyperinsulinemic-euglycemic clamp or HOMA-IR are not available.

1. Introduction

Insulin resistance (IR) is defined as a metabolic condition in which there is an impaired sensitivity to insulin-mediated glucose disposal [1]. This condition has been previously linked with obesity, type 2 diabetes mellitus (T2DM) and metabolic syndrome [2–5]. However, recent studies have also found that IR plays a key role in the development of other non-communicable diseases. Thus, IR has been closely associated with hypertension [6], cancer [7,8], polycystic ovary syndrome [9], chronic kidney disease [10] and even brain disorders [11,12].

Given its clinical relevance, accurate measurements of IR are essential and the hyperinsulinemic-euglycemic clamp is currently considered the gold standard [13,14]. However, this technique is considered very expensive, labour-intensive and time-consuming [14]. Therefore, it is important to develop easier and less expensive methods that we can use as surrogate markers. In this sense,

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the Homeostatic Model Assessment (HOMA-IR) has been the mathematical model most widely used in studies, since first described in 1985 [15,16]. However, since this method requires insulin determination, an important limitation is the lack of accessibility to people with low incomes [17].

The triglycerides/glucose index (TGI) was first proposed and validated by Simental-Mendía LE et al. (2008) in a sample of Mexican adults [18]. This index has proven to be an accurate diagnostic tool for IR, in some cases even better than HOMA-IR [19]. In recent years, different studies have compared the TGI with the hyperinsulinemic-euglycemic clamp [20] and other surrogate markers [19,21–24]. In Latin America, validation studies have been conducted in Mexico [17,25], Brazil [19], Argentina [22] and Venezuela [26]. However, to date there are no studies conducted in Peru, which is a country with high rates of overweight, obesity and metabolic syndrome [27,28].

For the above mentioned, the objective of the present study was to assess the association between elevated TGI and IR or hyperinsulinemia after oral glucose tolerance test in a sample of healthy adults.

2. Methods

2.1. Study design and population

We carried out an analytical cross-sectional study in euthyroid adults of both sexes with a normal body mass index (BMI) and no medical history of T2DM, who attended the outpatient service of a private clinic in Lima-Peru through 2012–2016.

2.2. Sample type and analysis unit

We performed a non-probabilistic sampling. The sample consisted of all patients who attended the outpatient service of the private clinic between January 2012 and December 2016 and met the eligibility criteria of the study.

2.3. Procedures

We reviewed all the medical records of the patients treated during the study length and collected all the data of interest. The laboratory values were only collected if the patient laboratory tests were performed with a maximum of 30 days after they were attended in the outpatient service of the private clinic. All participants had a minimum fasting period of 8 h for laboratory tests, according to the protocols established by the medical centre.

2.4. Eligibility criteria

We included participants aged ≥18 with a BMI between 18.50 and 24.99 kg/m^2 and no medical background of T2DM, hypothyroidism, subclinical hypothyroidism, hyperthyroidism, polycystic ovary syndrome or metabolic syndrome. Besides, we excluded patients aged ≥60, with fasting glucose values ≥ 126 mg/dL, oral glucose tolerance test (OGTT) ≥200 mg/dL, thyroid hormones values outside the following ranges: free triiodothyronine (FT3): 2.3–4.2 pg/mL, free thyroxine (FT4): 0.89–1.76 ng/dL, thyroid stimulating hormone (TSH): 0.40–5.0 μU/mL [29]; and pregnant women.

2.5. Variables definition

2.5.1. Exposure: TGI

We defined the TGI using the following calculation: ln[triglycerides (mg/dL) x fasting glucose (mg/dL)/2]. Then, participants were categorized in two groups according to the 75-percentile value of the TGI: normal TGI group (TGI values < 8.65) and elevated TGI group (TGI values ≥ 8.65). In addition, this cut-off point was similar to the 75-percentile value described in a previous article [30].

2.5.2. Outcomes: IR and hyperinsulinemia after OGTT

IR was defined as a HOMA-IR value ≥ 2.28, that correlates with the 75-percentile. We used this cut-off point based in a previous study [31]. Mathews et al. (1985) proposed HOMA-IR in a mathematical model to assess hyperinsulinemia. The gold standard to assess IR is the hyperinsulinemic euglycemic clamp, however, HOMA-IR is well correlated with it. HOMA-IR was calculated using the formula: fasting glucose (mg/dL) x fasting insulin (μU/mL)/405 [32].

Hyperinsulinemia after OGTT was defined as a serum insulin value ≥ 80 μU/mL after 120 min of 75-g glucose intake [33]. Participants were divided in two groups according to these criteria.

2.5.3. Other variables

The following variables were also included in the analysis: age (years), sex, body mass index (BMI), fasting glucose, postprandial blood glucose, glycated haemoglobin A1c, fasting insulin, triglycerides, FT3, FT4 and TSH.

2.6. Statistical analysis

We used STATA v14.0 (StataCorp, TX, USA) for our analysis. Descriptive results for numeric variables were presented as means with standard deviation (SD) or medians with interquartile range (IQR), depending on their distributions; otherwise, we expressed the qualitative variables as numbers with percentages. The study population characteristics according to the TGI groups, IR or hyperinsulinemia after OGTT were compared using the student T-test or the Wilcoxon rank sum test as appropriate for continuous variables and using the Chi-square test for categorical variables.

Two generalized linear models (1 crude and 1 adjusted) from Poisson family with robust standard errors were constructed to evaluate the association between elevated TGI and IR or hyperinsulinemia after OGTT. The reported association measure was the prevalence ratio (PR) with their respective 95% confidence intervals (95%CI). The adjusted model included the following confounding variables: age, sex, FT3 (pg/mL) and TSH (μU/mL) [29,30]; and the reported association measure was the adjusted prevalence ratio (aPR) with their respective 95%CI.

2.7. Ethical considerations

The data was collected by two researchers from the private clinic to study epidemiological surveillance. For this study, participant information was delivered in a Microsoft Excel 2010 file without biological identifiers, maintaining the confidentiality of the information.

3. Results

In total, we enrolled 1817 patients during the study period; we excluded 222 participants because they were 60 or older. Besides, 625 patients were withdrawn due to hyperthyroidism, hypothyroidism, subclinical hypothyroidism or T2DM, 695 because their BMI was not between 18.50 and 24.99 kg/m^2 and 157 because they did not have the variables of interest. Finally, 118 participants were analyzed.

Table 1
Characteristics of the study population by triglycerides/glucose index groups (N=118).

Variables	N=118	Normal (n=88)	Elevated (n=30)	P value
Age (years)	37.2 ± 11.3	35.4 ± 10.9	42.4 ± 11.1	0.003
Male	21 (17.8)	15 (17.1)	6 (20.0)	0.715
BMI (kg/m^2)	22.7 ± 1.6	22.5 ± 1.6	23.3 ± 1.5	0.023
Fasting glucose (mg/dL)	86.6 ± 8.1	84.4 ± 6.5	93.1 ± 9.2	<0.001
Postprandial glucose (mg/dL)	92.6 ± 26.5	86.8 ± 22.0	109.6 ± 31.3	<0.001
Fasting insulin (μU/mL)	7.7 (5.1–10.7)	7.0 (4.8–9.4)	11.3 (8.4–16.2)	<0.001
Serum insulin after OGTT (μU/mL)	37.5 (22.5–68.4)	31.1 (21.6–53.3)	70.2 (41.7–109.5)	<0.001
Glycated haemoglobin A1c (%)	5.4 ± 0.4	5.3 ± 0.3	5.6 ± 0.4	0.061
HOMA-IR	1.6 (1.1–2.3)	1.5 (1.0–2.0)	2.5 (1.7–3.7)	<0.001
Triglycerides (mg/dL)	84 (62–130)	74 (55.5–91.5)	153.5 (135–213)	<0.001
Triglycerides/glucose index	8.3 ± 0.5	8.0 ± 0.3	9.0 ± 0.4	<0.001
FT3 (pg/mL)	3.1 ± 0.4	3.1 ± 0.4	3.1 ± 0.4	0.935
FT4 (ng/dL)	1.2 ± 0.2	1.3 ± 0.2	1.2 ± 0.2	0.044
TSH (μU/mL)	2.3 (1.4–3.1)	2.2 (1.4–3.0)	2.6 (1.6–3.6)	0.220

Data expressed as mean ± standard deviation, median (interquartile range) or number (percentage).

3.1. Characteristics of the study population

The average age of the participants was 37.2 ± 11.3 (SD) years, 21 (17.8%) were males and the median BMI was 22.7 ± 1.6 (SD) kg/m^2. The prevalence of elevated TGI was 25.4% (n=30) while the prevalence of IR and hyperinsulinemia after OGTT was 24.6% (n=29) and 17.0% (n=20) respectively.

Furthermore, the FT3, FT4 and TSH, mean or median levels were 3.1 ± 0.4 pg/mL, 1.2 ± 0.2 ng/dL and 2.3 (IQR: 1.4–3.1) μU/mL, respectively. In addition, the fasting glucose, postprandial glucose and HOMA-IR, mean or median levels were 86.6 ± 8.1 mg/dL, 92.6 ± 26.5 mg/dL and 1.6 (IQR: 1.1–2.3), respectively. The group with normal TGI values had a mean of 8.0 ± 0.3, while the elevated TGI group had a mean of 9.0 ± 0.4, with statistically significant differences (Table 1).

3.2. Characteristics of the study population by TGI groups

We observed higher means of age (42.4 vs. 35.4; p=0.003), BMI (23.3 vs. 22.5; p=0.023), fasting glucose (93.1 vs. 84.4; p < 0.001) and postprandial glucose (109.6 vs. 86.8; p < 0.001) in participants with elevated TGI compared with the normal TGI group. Additionally, we found higher means of fasting insulin (11.3 vs. 7.0; p < 0.001), serum insulin after OGTT (70.2 vs. 31.1; p < 0.001), HOMA-IR (2.5 vs. 1.5; p < 0.001) and triglycerides (153.5 vs. 74; p < 0.001) in patients with elevated TGI compared with the group without this condition (Table 1).

3.3. Characteristics of the study population based on IR

We found higher means of BMI (23.4 vs. 22.5; p=0.004), fasting glucose (94.0 vs. 84.2; p < 0.001), postprandial glucose (115.4 vs. 85.1; p < 0.001) and glycated haemoglobin A1c (5.5 vs. 5.3; p=0.034) in participants with IR compared with the no IR group. As well, we observed higher medians of fasting insulin (13.2 vs. 6.8; p < 0.001), serum insulin after OGTT (75.1 vs. 29.8; p < 0.001), HOMA-IR (3.1 vs. 1.4; p < 0.001) and triglycerides (135 vs. 75; p < 0.001) in participants with IR compared with the no IR group (Table 2).

3.4. Characteristics of the study population based on hyperinsulinemia after OGTT

Equally, we found a higher mean of fasting glucose (93.0 vs. 85.3; p < 0.001), postprandial glucose (126.3 vs. 85.7; p < 0.001) and glycated haemoglobin A1c (5.6 vs. 5.3; p=0.004) in participants with hyperinsulinemia after OGTT compared with the group without this condition. Moreover, we observed higher medians of fasting insulin (12.1 vs. 7.2; p < 0.001), serum insulin after OGTT (112.8 vs. 31.1; p < 0.001), HOMA-IR (3.0 vs. 1.5; p < 0.001) and triglycerides (130.5 vs. 77.5; p < 0.001) in participants with hyperinsulinemia after OGTT compared with the normal group (Table 3).

3.5. Generalized linear models from Poisson family to assess the association between elevated TGI and IR or hyperinsulinemia after OGTT

In the crude Poisson regression model to calculate the

Table 2
Characteristics of the study population based on IR (N=118).

Variables	No IR (n=89)	IR (n=29)	P value
Elevated triglycerides/glucose index	11 (36.7)	19 (63.3)	<0.001
Age (years)	36.5 ± 10.9	39.4 ± 12.5	0.230
Male	20 (95.2)	1 (4.8)	0.023
BMI (kg/m^2)	22.5 ± 1.6	23.4 ± 1.3	0.004
Fasting glucose (mg/dL)	84.2 ± 5.7	94.0 ± 10.0	<0.001
Postprandial glucose (mg/dL)	85.1 ± 20.9	115.4 ± 29.0	<0.001
Fasting insulin (μU/mL)	6.8 (4.8–8.4)	13.2 (11.6–16.7)	<0.001
Serum insulin after OGTT (μU/mL)	29.8 (20.2–45.3)	75.1 (60.3–109.7)	<0.001
Glycated haemoglobin A1c (%)	5.3 ± 0.3	5.5 ± 0.5	0.034
HOMA-IR	1.4 (1.0–1.8)	3.1 (2.5–3.8)	<0.001
Triglycerides (mg/dL)	75 (56–97)	135 (108–171)	<0.001
Triglycerides/glucose index	8.1 ± 0.4	8.8 ± 0.5	<0.001
FT3 (pg/mL)	3.1 ± 0.4	3.1 ± 0.4	0.997
FT4 (ng/dL)	1.3 ± 0.2	1.2 ± 0.2	0.013
TSH (μU/mL)	2.3 (1.4–3.2)	2.3 (1.6–2.8)	0.864

Data expressed as mean ± standard deviation, median (interquartile range) or number (percentage).

Table 3
Characteristics of the study population based on hyperinsulinemia after OGTT (N=118).

Variables	No hyperinsulinemia after OGTT (n=98)	Hyperinsulinemia after OGTT (n=20)	P value
Elevated triglycerides/glucose index	18 (60.0)	12 (40.0)	<0.001
Age (years)	36.6 ± 11.1	40.3 ± 12.5	0.185
Male	20 (95.2)	2 (4.8)	0.120
BMI (kg/m^2)	22.6 ± 1.6	23.1 ± 1.5	0.283
Fasting glucose (mg/dL)	85.3 ± 6.9	93.0 ± 10.8	<0.001
Postprandial glucose (mg/dL)	85.7 ± 21.3	126.3 ± 23.8	<0.001
Fasting insulin (μU/mL)	7.2 (4.8–9.2)	12.1 (10.1–18.5)	<0.001
Serum insulin after OGTT (μU/mL)	31.1 (21.1–48.3)	112.8 (103.1–134.1)	<0.001
Glycated haemoglobin A1c (%)	5.3 ± 0.3	5.6 ± 0.5	0.004
HOMA-IR	1.5 (1.1–2.0)	3.0 (2.1–4.3)	<0.001
Triglycerides (mg/dL)	77.5 (59–123)	130.5 (103–195)	<0.001
Triglycerides/glucose index	8.2 ± 0.5	8.8 ± 0.6	<0.001
FT3 (pg/mL)	3.1 ± 0.4	3.2 ± 0.4	0.574
FT4 (ng/dL)	1.3 ± 0.2	1.1 ± 0.2	0.001
TSH (μU/mL)	2.3 (1.4–3.1)	2.4 (1.8–3.5)	0.360

Data expressed as mean ± standard deviation, median (interquartile range) or number (percentage).

Table 4
Generalized linear models from Poisson family with robust standard errors to assess the association between elevated triglycerides/glucose index and IR or Hyperinsulinemia after OGTT.

Outcomes	Variables	Crude PR (95% CI)	P value	Adjusted PR (95% CI)[a]	P value
IR	Normal triglycerides/glucose index	Reference	–	Reference	–
	Elevated triglycerides/glucose index	5.57 (2.92–10.64)	<0.001	6.36 (3.41–11.86)	<0.001
Hyperinsulinemia after OGTT	Normal triglycerides/glucose index	Reference	–	Reference	–
	Elevated triglycerides/glucose index	4.00 (1.98–9.76)	<0.001	4.19 (1.81–9.70)	0.001

[a] Adjusted by: age (years), sex, FT3 (pg/mL) and TSH (μU/mL).

association between elevated TGI and IR, compared with the normal TGI group, the prevalence of IR was higher (PR=5.57; 95%CI: 2.92–10.64). Similarly, the association remained in the adjusted model for age (years), sex, FT3 (pg/mL) and TSH (μU/mL) (aPR=6.36; 95%CI: 3.41–11.86) (Table 4).

In the crude Poisson regression model to evaluate the association between elevated TGI and hyperinsulinemia after OGTT, compared with the normal TGI group, the prevalence of hyperinsulinemia after OGTT was higher (PR=4.00; 95%CI: 1.98–9.76). Finally, after adjusting for age (years), sex, FT3 (pg/mL) and TSH (μU/mL), the association remained significant (aPR=4.19; 95%CI: 1.81–9.70) (Table 4).

4. Discussion

4.1. Main findings

Few studies have assessed the usefulness of the TGI for IR in Hispanic populations [17,22,25,26] and this is the first one conducted in Peru. We found that the elevated TGI was associated with both IR and hyperinsulinemia after OGTT in a sample of healthy adults (euthyroid and with a normal BMI).

4.2. Comparison with other studies

Different studies have compared the TGI with the hyperinsulinemic-euglycemic clamp (gold standard) [20] and other surrogate markers [19,21–24]. In this sense, research conducted in adults have reported a better performance of TGI compared to the triglycerides/HDL-Cholesterol ratio (TG/HDL-C) [21,22,24], although a study in the US did not find differences in their performance [23]. TGI has also proven to be a better marker than the apolipoprotein B (apoB)/apolipoprotein A-I (apoA-I) ratio, visceral adiposity index (VAI) and other traditional lipid ratios [21,24]. In addition, Vasques (2010) found that the TGI presented a slightly better performance when compared with the HOMA-IR index [19].

The TGI has also been tested in other ethnic groups in the USA [23,24,34] and China [21]. Furthermore, some studies have shown its usefulness for recognizing IR not only in adults but also in children [35,36] and adolescents [37]. Hence, the TGI has proven to be a reliable marker for IR in different populations, and probably the one of choice when the hyperinsulinemic-euglycemic clamp or HOMA-IR are not available.

4.3. Results interpretation

IR is a multifactorial metabolic condition that arises when target tissues have a null or attenuated response to normal circulating insulin concentrations [1,2]. It is triggered by the changes in lipid metabolism, altered glucose disposal, increased inflammation and changes in the gastrointestinal microbiota [2,38]. We found that elevated TGI was useful for discriminating IR individuals. This can be understood by the fact that one of the key mechanisms in the modulation of IR is glucolipotoxicity [2,4,21,38].

Independently, triglycerides could largely explain the results of the TGI for IR, even better than glucose. This is because hypertriglyceridemia has been shown to be both the cause and the consequence of impaired glucose metabolism [39]. When there is an ectopic accumulation of lipids in the liver and skeletal muscle, action of insulin could be impeded by inhibiting insulin receptor binding, leading to a decreased synthesis of hepatic glycogen and reduced muscle glucose uptake [2,4,17,38]. In other words, insulin-stimulated glucose utilization is limited by increased fatty acid oxidation [38].

Glucose is the other TGI marker and it has a bidirectional relationship with insulin. Glucose influences insulin biosynthesis and secretion, while insulin plays a key role in glucose uptake and metabolism [1,40]. In basal conditions, glucose-stimulated pancreatic secretion is biphasic [41,42]. The first phase starts when the glucose levels increase, releasing insulin from the β-cell

secretory granules. The second phase is the period of sustained secretion until normoglycemia is restored [1,41]. However, some metabolic conditions (such as IR) may arise when there are trafficking-impaired ATP-sensitive potassium channels, in response to alterations in glucose levels [43,44].

4.4. Relevance and implications

IR is a metabolic condition that has been linked with different diseases, such as T2DM [2,3], hypertension [6], non-alcoholic fatty liver disease [45], cancer [7,8], polycystic ovary syndrome [9], chronic kidney disease [10] and brain disorders [11,12]. Thus, adequate screening of people at risk and early diagnosis are essential.

To date, the hyperinsulinemic-euglycemic clamp remains the gold standard for IR and HOMA-IR is the most widely used alternative. However, both measures have some limitations. First, the hyperinsulinemic-euglycemic clamp is considered very expensive, labour-intensive and time-consuming [14]. Second, insulin determination to calculate the HOMA-IR is not always possible due to the lack of accessibility by the population with low incomes [17]. Third, both measures have limitations regarding their repeatability and reproducibility [46–48]. On the other hand, triglycerides and glucose are low-cost and routine biochemical tests [17,22,25]. Thus, TGI could be considered as an inexpensive, easy-to-measure alternative when the first two are not available.

Metabolic syndrome is a multiplex risk factor for several cardiometabolic diseases [49] and a worldwide rapidly growing epidemic condition [50], especially in developing countries [51]. Peru is a middle-income country that has undergone a nutritional transition in recent years [28,52], with an increase of the prevalence of non-communicable diseases, such as overweight, obesity, metabolic syndrome and T2DM [27,28,52]. Thus, in order to delay or prevent the acute onset of these conditions, an early detection of IR is necessary, preferably with accurate, accessible and easy-to-measure methods. TGI has proven to be a reliable marker for this purpose [19–24,34–36] and it should be used in Peruvian health facilities, especially in primary care.

4.5. Limitations

Limitations of the study should be highlighted. First, it was not possible to assess causality between the evaluated variables due to the cross-sectional nature of the study. Second, we used HOMA-IR to measure IR and not the hyperinsulinemic-euglycemic clamp (gold standard); however, HOMA-IR is the most widely used model and previous studies have shown a very high correlation between the two measures. Third, we used information collected from medical records, which could have presented some errors at the time of being filled; nevertheless, we carried out a rigorous evaluation of the data quality in order to reduce the possibility of information bias. Fourth, the study was conducted in a single private medical centre, so our results cannot be generalized to the Hispanic population; however, given the consistency of our findings with those described in other evaluated populations, we believe that they could be extrapolated to Hispanic euthyroid populations with normal BMI.

5. Conclusions

Elevated TGI was associated with IR markers in a sample of euthyroid adults without T2DM and with a normal BMI. Prospective follow-up cohorts should corroborate these results and determine optimal cut-off points for different age groups. In addition, future studies in the Peruvian population should develop predictive models for IR using this and other biomarkers, such as ferritin [53], thyroid hormones [29], anthropometric measures, etc.

The simplicity of the TGI calculation from two routine and low-cost biochemical tests makes it the first-choice alternative when the hyperinsulinemic-euglycemic clamp or HOMA-IR are not available.

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Conflicts of interest

The authors have no potential competing interests.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.dsx.2018.09.010.

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