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Validity and reliability of simple surrogate indexes to evaluate beta-cell function and insulin sensitivity

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ABSTRACT

***Background**: Simple surrogate indexes (SSI) to assess beta-cell function, insulin sensitivity (IS) and insulin resistance (IR) are an easy and economic tool used in clinical practice to identify glucose metabolism disturbances.* ***Aim**: To evaluate the validity and reliability of SSI that estimate beta-cell function, IS and IR using as a reference the parameters obtained from the frequently sampled intravenous glucose tolerance test (FSIVGTT).* ***Material and Methods**: We included 62 subjects aged 20-45 years, with a normal body mass index and without diabetes or prediabetes. SSI were compared with the acute insulin response to glucose (AIRg), insulin sensitivity index (Si) and disposition index (DI) obtained from the FSIVGTT using the minimal model approach. Half of the participants (n = 31) were randomly selected for a second visit two weeks later to evaluate the reliability of all the variables.* ***Results**: HOMA1-%B and HOMA2-%B had a significant correlation with AIRg (Spearman Rho (r_s) = 0.33 and 0.37 respectively, $p < 0.01$). The SSI evaluating IS/IR that showed stronger correlation ($r_s > 0.50$) with Si were fasting insulin, HOMA1-IR, HOMA2-IR, HOMA1-%S, HOMA2-%S, QUICKI, and the McAuley index. The parameters that showed good reliability with an intraclass correlation coefficient (ICC) > 0.75 were AIRg, HOMA1-%S, HOMA2-%S, and QUICKI.* ***Conclusions:** Our results suggest that most of the SSI are useful and reliable.*

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***Key words:** Glucose Tolerance Test; Insulin Resistance; Insulin Secretion; Validation Study.*

Validez y confiabilidad de índices subrogados para evaluación de la función de células beta y sensibilidad a la insulina

***Antecedentes:** Los índices simples subrogados (ISS) que evalúan la función de célula beta, sensibilidad a la insulina (SI) y resistencia a la insulina (RI) son herramientas sencillas y económicas que se usan en la práctica clínica para identificar alteraciones del metabolismo de la glucosa.* ***Objetivo**: Evaluar la validez y confiabilidad de ISS para estimar la función de célula beta, SI y RI usando como referencia los parámetros de la prueba de tolerancia a la glucosa intravenosa con muestreo frecuente (FSIVGTT).* ***Material y Métodos**: Se incluyeron 62 sujetos*

de 20-45 años, con índice de masa corporal normal y sin diabetes mellitus o prediabetes. Los ISS se compararon con la respuesta aguda de la insulina a la glucosa (AIRg), índice de sensibilidad a la insulina (Si) e índice de disposición (DI) obtenidos de la FSIVGTT en base al modelo mínimo. La mitad de los participantes (n = 31) se seleccionaron aleatoriamente para acudir dos semanas después y evaluar la confiabilidad de todas las variables. ***Resultados****: HOMA1-%B y HOMA2-%B presentaron una correlación significativa con AIRg (Rho de Spearman (r_s) = 0,33 and 0,37, respectivamente, p < 0,01). Los ISS para evaluar SI/RI que mostraron mayor correlación (rs > 0,50) con Si fueron insulina en ayuno, HOMA1-IR, HOMA2-IR, HOMA1-%S, HOMA2-%S, QUICKI y el índice de McAuley. Los parámetros que tuvieron buena confiabilidad (coeficiente de correlación intraclase > 0,75) fueron AIRg, HOMA1-%S, HOMA2-%S y QUICKI.* ***Conclusiones****: La mayoría de los ISS son instrumentos útiles y confiables.*

Palabras clave: *Estudio de validación; Prueba de tolerancia a la glucosa; Resistencia a la insulina; Secreción de insulina.*

Insulin sensitivity (IS) is defined as the ability of insulin to exert its physiological effects of glucose uptake in muscle and adipose tissue and to suppress hepatic gluconeogenesis[1]. The approaches to evaluate IS include direct methods (hyperinsulinemic euglycemic glucose clamp and insulin suppression test) and indirect methods (frequently sampled intravenous glucose tolerance test and oral glucose tolerance test)[2]. The hyperinsulinemic euglycemic glucose clamp (HEGC) is the gold standard to quantify IS. Disadvantages of the HEGC include that is expensive, requires specialized equipment and trained personnel, therefore, it is mainly used for research purposes. IS obtained from the frequently sampled intravenous glucose tolerance test (FSIVGTT) has been validated against the HEGC[3-5], however, skill is required to perform this test. In addition, specific equipment is indispensable. Stumvoll et al. suggested that IS could be predicted from simple parameters[6]. Many indexes to assess IS or insulin resistance (IR) have been developed using formulas derived from fasting glucose and insulin concentrations or from the oral glucose tolerance test[2,7]. These simple surrogate indexes (SSI) are inexpensive, easy to perform and represent tools that any health professional can use to recognize an increased risk to develop alterations in glucose metabolism and to make timely interventions. Thus, the aim of this study was to identify which of the SSI to evaluate beta-cell function, IS and IR correlates better with the acute insulin response to glucose (AIRg), insulin sensitivity index (Si) and disposition index (DI) obtained from the FSIVGTT using the minimal model approach. In addition, we evaluated the reliability of the SSI and the parameters derived from the FSIVGTT to identify consistency over time.

Materials and Methods

Description of participants and ethics

The study was approved by the Comité de Ética y de Investigación del Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán and followed the principles established in the Declaration of Helsinki. Selection criteria included women and men, aged 20-45 years, with BMI between 18.5-24.9 kg/m^2, without diabetes or prediabetes and not taking medications that could alter beta-cell function/IS. Participants received a full explanation of the purpose and procedures, and informed consent was obtained.

Study design

Cross-sectional study to correlate the SSI with the parameters obtained from the FSIVGTT. In a screening visit, after participants informed consent was obtained, a 2-hour oral glucose tolerance test (OGTT) with a load of 75-g was performed. Participants that showed a fasting glucose concentration < 100 mg/dL and a glucose concentration < 140 mg/dL 2-h after the OGTT were included in the study. One week later, the modified 3-h FSIVGTT was carried out using an insulin infusion

(0.03 U/kg) and collecting blood samples at -15, -10, -5, 0, 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 19, 22, 24, 25, 27, 30, 40, 50, 60, 70, 90, 100, 120, 140, 160, and 180 minutes[8]. Glucose concentrations and lipid panel were measured with the automatic equipment UniCel DxC 600 Synchron Clinical System, Beckman Coulter. Insulin concentrations were measured using an immunoassay system with the automatic equipment Access 2, Beckman Coulter. Anthropometric measurements (weight, height, waist, and hip circumference), body composition (evaluated by bioelectrical impedance analysis using the Jawon Medical tetrapolar equipment model ioi 353) and blood pressure (using an Omron automatic digital blood pressure monitor model HEM-781INT) were obtained. Diet was evaluated with a 24-h dietary recall and physical activity with the questionnaire developed at Laval University, validated for Mexican population[9]. After this evaluation, half of the participants (n = 31) were randomly selected to attend an additional visit two weeks later and a second modified FSIVGTT was performed to calculate the SSI and evaluate their reliability. Participants were advised to maintain their eating habits and physical activity; this was corroborated with a 3-day food record and with the physical activity questionnaire. Food consumption data was analyzed with the Food Processor Analysis Software version 11.4.412 by ESHA Research 2016.

Beta-cell function and insulin sensitivity/ resistance

The parameters obtained from the modified FSIVGTT with the minimal model approach (AIRg, Si and DI) were calculated using the statistical program MinMod Millenium 6.02. The FSIVGTT was chosen instead the HEGC because we wanted to assess the performance of SSI that evaluate beta-cell function against AIRg and DI. Table 1 shows how the SSI were calculated and the cut-off values to diagnose IR[7,10-30]. Only SSI derived from fasting glucose, insulin, HDL cholesterol, triglycerides concentrations, BMI and waist circumference were calculated since only glucose was measured during the OGTT.

Statistical analysis

Variables distribution was evaluated with Kolmogorov-Smirnov normality test. The clinical and metabolic characteristics of the participants are described in means ± standard deviations or medians (interquartile range) as appropriate. Correlations between anthropometric measurements, biochemical values or SSI and the parameters obtained from the FSIVGTT were calculated with Spearman's rank correlation coefficient due to the nonparametric distribution, 95% confidence intervals (CI) were also calculated. In addition, coefficients of determination were estimated (r_s^2). Reliability was assessed using intraclass correlation coefficients (ICC) at 95% CI. Changes in body weight, eating habits and physical activity of participants who attended a second evaluation 2 weeks later were compared using paired *t* test or Wilcoxon matched-pairs test, according to the variables' distribution. Data were analyzed using IBM SPSS Statistics version 25.0 software, a p value $< 0,05$ was considered significant.

Results

Characteristics of the study population (n = 62) are described in Table 2. The sample consisted mainly of women (74.2%), with a mean age of 24.7 ± 4.3 years, with normal BMI (21.6 ± 1.7 kg/m^2). The remaining clinical and metabolic parameters were within reference values. The validity of HOMA1-%B (HOMA percentage of beta-cell function) and HOMA2-%B was evaluated against the AIRg and DI and is presented in Table 3. Both SSI of beta-cell function showed a significant correlation ($p < 0.01$) with the AIRg ($r_s = 0.330$ and 0.374, respectively), but only a tendency to correlate with the DI ($p < 0.10$). Fasting insulin and FGIR (fasting glucose-to-insulin ratio) also correlated significantly with the AIRg and DI, showing a stronger association with the AIRg. Table 4 shows the correlations between Si obtained with the FSIVGTT and the SSI to evaluate IS or IR, anthropometric measurements, and biochemical values. Waist circumference and HDL cholesterol in women and triglycerides in both sexes revealed a significant correlation ($p < 0.05$) with Si ($r_s = -0.362$, 0.312, -0.317, respectively). Waist-to-height ratio (WHtR), body fat percentage and HDL cholesterol in both sexes showed a tendency ($p < 0.20$) to correlate with Si ($r_s = -0.227$, -0.181, 0.177, respectively). All the SSI of IS or IR were significantly correlated with Si, except the METS-IR (metabolic score for insulin resistance) and

Table 1. Simple surrogate indexes to evaluate insulin sensitivity and beta-cell function

Index	Description / Calculation	Cut-off value
Fasting insulin[7,11]	• Fasting insulin concentration in mU/L	IR: ≥ 12
FGIR[12]	• Fasting glucose (mg/dL) / Fasting insulin (mU/L)	IR: < 4.5
HOMA1-IR[13-15]	• [Fasting glucose (mg/dL) * Fasting insulin (mU/L)] / 405 • [Fasting glucose (mmol/L) * Fasting insulin (mU/L)] / 22.5	IR: ≥ 2.3-2.7
HOMA1-%B[13,16]	• [20 * Fasting insulin (mU/L)] / [Fasting glucose (mmol/L) -3.5] • [20 * Fasting insulin (mU/L)] / [(Fasting glucose (mg/dL) / 18) -3.5]	Normal: 100% Lower values are associated to loss of pancreatic response
HOMA1-%S[17]	• (1 / HOMA1-IR) * 100	Normal: 100% Lower values are associated to IR
HOMA2-IR[14,15]	• Using the HOMA2 Calculator version 2.2.3 of the University of Oxford based on the model modified by Levy et al[18] and downloaded from the website https://www.dtu.ox.ac.uk/homacalculator/	IR: ≥1.2-1.8
HOMA2-%B[16]		Normal: 100% Lower values are associated to IR or loss of pancreatic response
HOMA2-%S[16]		
QUICKI[7,10,19,20]	• 1 / [Log(Fasting insulin (mU/L))] + [Log (Fasting glucose (mg/dL))]	IR: <0.33-0.357
METS-IR[21]	• [Log((2 * Fasting glucose (mg/dL)) + Fasting triglycerides (mg/dL)) * BMI (kg/m^2)] / [Log(HDL cholesterol (mg/dL))]	IR: >51.13
TG/HDL ratio[22,23]	• Fasting triglycerides (mg/dL) / HDL cholesterol (mg/dL)	IR: ≥3.5
TyG index[24,25]	• Ln[Fasting triglycerides (mg/dL) * Fasting glucose (mg/dL) / 2]	IR: ≥8.8
TyG-BMI index[10,26]	• TyG index * BMI (kg/m^2)	IR: ≥208
TyG-WC index[26]	• TyG index * Waist circumference (cm)	NS
TyG-WHtR index[27]	• TyG index * Waist-to-height ratio [Waist circumference (cm) / Height (cm)]	NS
McAuley index[7,11]	• Exp {2.63 – [0.28 * Ln(Fasting insulin (mU/L))] – [0.31 * Ln(Fasting triglycerides (mg/dL))]}	IR: ≤5.8
LAP model[28,29]	• Men: [Waist circumference (cm) – 65] * Fasting triglycerides (mmol/L) • Women: [Waist circumference (cm) – 58] * Fasting triglycerides (mmol/L)	IR: ≥17.91
VAI index[30]	• Men: {Waist circumference (cm) / [39.68 + (1.88 * BMI (kg/m^2))]} * [Fasting triglycerides (mmol/L) / 1.03] * [1.31 / HDL cholesterol (mmol/L)] • Women: {Waist circumference (cm) / [36.58 + (1.89 * BMI (kg/m^2))]} * [Fasting triglycerides (mmol/L) / 0.81] * [1.52 / HDL cholesterol (mmol/L)]	Normal: 1 Higher values are associated to IR

FGIR: fasting glucose-to-insulin ratio, HOMA-IR: homeostatic model assessment of insulin resistance, %B: percentage of beta-cell function, %S: percentage of insulin sensitivity, QUICKI: quantitative insulin sensitivity check index, METS-IR: metabolic score for insulin resistance, TG/HDL: triglycerides/high-density lipoprotein, TyG: the product of triglycerides and glucose levels, WC: waist circumference, NS: not specified, WHtR: waist-to-height ratio, LAP: lipid accumulation product, VAI: visceral adiposity index.

Table 2. Clinical and metabolic characteristics of the study population

	n = 62
Female sex (%)	46 (74.2%)
Age (years)	24.7 ± 4.3
Weight (kg)	58.3 ± 8.2
BMI (kg/m^2)	21.6 ± 1.7
Waist circumference (cm)	72.4 ± 5.7
Hip circumference (cm)	93.0 ± 4.0
Body fat (%)	26.2 ± 4.6
SBP (mmHg)	101.8 ± 10.7
DBP (mmHg)	67.9 ± 6.6
Triglycerides (mg/dL)	79.5 (59.5-99.2)
Total cholesterol (mg/dL)	166.5 ± 28.9
LDL cholesterol (mg/dL)	98.3 ± 21.5
HDL cholesterol (mg/dL)	50.0 ± 12.3
Fasting glucose (mg/dL)	81.0 ± 6.8
Two-hour post load glucose (mg/dL)	80.8 ± 16.6
Fasting insulin (mU/L)	5.3 (3.7-6.8)
Si [x10^{-4} min^{-1}·(mU/L)$^{-1}$]	5.7 (4.5-7.6)
AIRg [mU·L^{-1}·min]	594.2 (381.0-1017.5)
DI (Si x AIRg)	3757.5 (2336.0-5574.7)
HOMA1-IR	1.00 (0.76-1.44)
HOMA1-%B	100.3 (76.7-151.9)
HOMA1-%S	112.5 ± 45.5
HOMA2-IR	0.66 (0.47-0.89)
HOMA2-%B	89.9 (76.9-110.5)
HOMA2-%S	151.8 (111.8-209.2)
QUICKI	0.38 ± 0.03
FGIR	15.2 (12.8-23.1)
METS-IR	30.9 ± 3.8
TG/HDL ratio	1.56 (1.21-2.16)
TyG index	8.08 ± 0.44
TyG-BMI index	175.43 ± 18.43
TyG-WC index	586.97 ± 65.13
TyG-WHtR index	3.60 ± 0.34
McAuley index	9.2 ± 1.8
LAP model	10.6 (7.0-16.3)
VAI index	1.07 (0.84-1.54)

Values are means ± standard deviation or medians (interquartile range) according to the variables' distribution. SBP: systolic blood pressure, DBP: diastolic blood pressure.

the TyG-BMI index (triglyceride glucose-BMI). The SSI that showed stronger correlations with Si ($r_s > 0.50$) were fasting insulin, HOMA1-IR (homeostatic model assessment of insulin resistance), HOMA2-IR, HOMA1-%S (HOMA percentage of insulin sensitivity), HOMA2-%S, QUICKI (quantitative insulin sensitivity check index) and McAuley index (r_s = -0.524, -0.546, -0.540, 0.546, 0.543, 0.546, 0.556, respectively). However, none of the coefficients of determination (r_s^2) were greater than 0.5. The higher r_s^2 (> 0.250) observed were for McAuley index, HOMA1-IR; HOMA1-%S, QUICKI, HOMA2-%S, HOMA2-IR and fasting insulin (Table 4). Finally, reliability analyses of the parameters obtained from the FSIVGTT and the SSI of IS, IR or beta-cell function are shown in Table 5. All the ICC were statistically significant ($p \leq 0.01$), except for the DI and HOMA1-%B. The parameters or indexes of glucose metabolism that showed a good reliability (ICC > 0.75) were the AIRg (ICC: 0.881, 95% CI: 0.752, 0.942), HOMA1-%S (ICC: 0.806, 95% CI: 0.597, 0.906), HOMA2-%S (ICC: 0.778, 95% CI: 0.540, 0.893) and QUICKI (ICC: 0.792, 95% CI: 0.568, 0.900). No statistically significant changes ($p \geq 0.05$) were found in body weight, energy, macronutrients, sugar and fiber consumption, and physical activity in the participants who were randomly selected to attend a second visit for the reliability evaluation.

Discussion

Many SSI have been developed to evaluate beta-cell function, IS and IR. The validity of the SSI to evaluate IS or IR has been assessed in different studies using as a reference the results of the HEGC or the FSIVGTT. We found that all the SSI were significantly correlated with Si; except the METS-IR and TyG-BMI. However, these two indexes include the BMI as a variable in their formula. In this study we included subjects with BMI in a normal range to avoid the confounder effect of adiposity in IS, however this might explain the lack of correlations with anthropometric and body composition parameters. Ascaso et al.[7] evaluated the ability of some SSI to identify IR in subjects with normal glucose metabolism. This study reported higher correlations between Si and SSI in comparison to this study for HOMA1-IR (r = -0.660 vs. r_s = -0.546), QUICKI (r = 0.660 vs. r_s =

Table 3. Correlations between DI and AIRg from the FSIVGTT and SSI to evaluate beta-cell function or insulin sensitivity/resistance (n=62)

	AIRg			DI		
	r_s (95% CI)	p	r_s^2	r_s (95% CI)	p	r_s^2
HOMA1-%B	0.330 (0.080, 0.528)	< 0.01	0.108	0.211 (-0.041, 0.432)	0.09	0.044
HOMA2-%B	0.374 (0.133, 0.575)	< 0.01	0.139	0.238 (-0.008, 0.456)	0.06	0.056
Fasting insulin	0.496 (0.268, 0.673)	< 0.01	0.246	0.260 (0.004, 0.484)	0.04	0.067
FGIR	-0.497 (-0.680, -0.275)	< 0.01	0.247	-0.270 (-0.486, -0.014)	0.03	0.072

Spearman correlation coefficients (r_s) were calculated according to the data distribution with their 95% confidence intervals (CI) and the squared values of the correlation coefficients (r_s^2).

Table 4. Correlations between Si from the FSIVGTT and SSI to evaluate insulin sensitivity/resistance, anthropometric parameters, and biochemical values (n=62)

	r_s (95% CI)	p	r_s^2
BMI	-0.002 (-0.287, 0.255)	0.98	< 0.001
Waist circumference	-0.138 (-0.374, 0.115)	0.28	0.019
Women	-0.362 (-0.617, -0.049)	0.01	0.131
Men	0.094 (-0.504, 0.639)	0.72	0.008
Waist-hip ratio	-0.082 (-0.324, 0.157)	0.52	0.006
Waist-to-height ratio	-0.227 (-0.454, 0.025)	0.07	0.051
Percentage of body fat	-0.181 (-0.408, 0.084)	0.15	0.032
Triglycerides	-0.317 (-0.544, -0.033)	0.01	0.100
HDL cholesterol	0.177 (-0.061, 0.410)	0.16	0.031
Women	0.312 (0.004, 0.127)	0.03	0.097
Men	0.061 (-0.457, 0.648)	0.82	0.003
Fasting insulin	-0.524 (-0.683, -0.297)	< 0.01	0.274
HOMA1-IR	-0.546 (-0.703, -0.334)	< 0.01	0.298
HOMA2-IR	-0.540 (-0.693, -0.323)	< 0.01	0.291
HOMA1-%S	0.546 (0.322, 0.704)	< 0.01	0.298
HOMA2-%S	0.543 (0.321, 0.706)	< 0.01	0.294
QUICKI	0.546 (0.322, 0.704)	< 0.01	0.298
FGIR	0.494 (0.249, 0.674)	< 0.01	0.244
METS-IR	-0.147 (-0.386, 0.106)	0.25	0.021
TG/HDL ratio	-0.353 (-0.578, -0.114)	< 0.01	0.124
TyG index	-0.362 (-0.577, -0.116)	< 0.01	0.131
TyG-BMI index	-0.175 (-0.423, 0.101)	0.17	0.030
TyG-WC index	-0.299 (-0.508, -0.040)	0.01	0.089
TyG-WHtR index	-0.367 (-0.580, -0.131)	< 0.01	0.134
McAuley index	0.556 (0.347, 0.716)	< 0.01	0.309
LAP model	-0.370 (-0.594, -0.106)	< 0.01	0.136
VAI index	-0.418 (-0.621, -0.162)	< 0.01	0.174

Spearman correlation coefficients (r_s) were calculated according to the data distribution with their 95% confidence intervals (CI) and the squared values of the correlation coefficients (r_s^2).

Table 5. Reliability analyses for the parameters obtained from the FSIVGTT and the SSI to evaluate insulin sensitivity/resistance and beta-cell function (n = 31)

	ICC (95% CI)	P
Si	0.585 (0.140, 0.800)	< 0.01
AIRg	0.881 (0.752, 0.942)	< 0.01
DI	0.398 (-0.249, 0.710)	0.08
Fasting insulin	0.624 (0.219, 0.818)	< 0.01
HOMA1-IR	0.651 (0.277, 0.832)	< 0.01
HOMA1-%B	0.394 (-0.258, 0.708)	0.08
HOMA1-%S	0.806 (0.597, 0.906)	< 0.01
HOMA2-IR	0.631 (0.234, 0.822)	< 0.01
HOMA2-%B	0.549 (0.064, 0.782)	0.01
HOMA2-%S	0.778 (0.540, 0.893)	< 0.01
QUICKI	0.792 (0.568, 0.900)	< 0.01
FGIR	0.687 (0.351, 0.849)	< 0.01

Reliability was assessed using intraclass correlation coefficients (ICC) at 95% confidence intervals (CI).

0.546), McAuley index (r = 0.718 vs. r_s = 0.556), fasting insulin (r = -0.690 vs r_s = -0.524), and triglycerides (r = -0.631 vs. r_s = -0.317). Also, reported a significant correlation of Si with waist circumference (r = -0.640) and HDL cholesterol (r = 0.520). In our study these variables correlated significantly with Si only in women (r_s = -0.362 for waist circumference and r_s = 0.312 for HDL cholesterol) probably due to the reduced sample size of men. In contrast, Almeda-Valdés et al.[10] evaluated the correlation between SSI and the M-value adjusted by fat-free mass from the HEGC, finding lower but significant correlation coefficients in comparison with this study, for HOMA1-IR (r = -0.357 vs. r_s = -0.546), QUICKI (r = 0.348 vs. r_s = 0.546), and HOMA2-%S (r = 0.428 vs. r_s = 0.543). The validity of HOMA-IR, HOMA1-%S, HOMA2-%S, QUICKI, FGIR and McAuley index has been studied in other populations including children, adolescents, pregnant women, post-myocardial infarction, and post-renal transplant individuals; reporting similar results concerning the validity of these to estimate IS or IR[31-35]. HOMA1-%B validity has been assessed in children with and without obesity and adolescents but not in healthy adults[32,33]. Two studies compared HOMA1-%B with the first-phase insulin secretion (AIRg) and the second-phase insulin secretion, using the FSIVGTT, reporting significant correlations. In our study, both SSI of beta-cell function (HOMA1-%B and HOMA2-%B) showed a significant correlation coefficient with the AIRg (r_s = 0.330 and 0.374, respectively) and a tendency to correlate with DI (r_s = 0.211 and 0.238, respectively); this could indicate that SSI of beta-cell function are more associated to the first phase of insulin secretion. In addition, although DI evaluates the pancreatic response it is adjusted by the IS/IR state. To our knowledge, no studies have estimated the reliability of the SSI and the parameters obtained from the FSIVGTT. We found that all where significantly consistent over time, except the DI and HOMA1-%B. The more reliable indexes were the AIRg, HOMA1-%S, HOMA2-%S, and QUICKI. Limitations of this study should be acknowledged including the relatively small sample size to detect significant correlations with anthropometric measurements and biochemical parameters. However, in a post hoc analysis we calculated the probability of a type II error (power) among the highest correlation coefficients and obtained a > 90% and > 80% power for the evaluation of insulin sensitivity/resistance and beta-cell function, respectively. In addition, including only healthy subjects could decrease the strength of the correlations due to the low variability of the results. The reliability of all the SSI included in the validity analysis was not assessed because only fasting glucose and insulin concentrations were available. Finally, indexes derived from the OGTT were not evaluated since we wanted to include SSI that are easier to calculate using fasting samples only.

It is relevant to recognize which SSI are more accurate to estimate IS, IR or beta-cell function in contrast to direct and indirect measures of methods such as HEGC or FISVGTT, which are not always available due to the high cost and infrastructure required. SSI are an inexpensive, quick, and easy to interpret tools. Our results demonstrate that SSI are valid and reliable instruments to evaluate IS, IR and beta-cell function. Most of the SSI demonstrated significant correlations with the parameters obtained from the FSIVGTT and a good reliability in a group of young individuals with a normal BMI. The SSI to evaluate IS that showed higher coefficients for both validity and

reliability are the HOMA1-%S, HOMA2-%S and QUICKI. For the assessment of beta-cell function, HOMA2-%B showed the best results.

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References

1. Kang S, Tsai LT-Y, Rosen ED. Nuclear Mechanisms of Insulin Resistance. Trends Cell Biol. 2016; 26 (5): 341-51.
2. Muniyappa R, Lee S, Chen H, Quon MJ. Current approaches for assessing insulin sensitivity and resistance in vivo: advantages, limitations, and appropriate usage. Am J Physiol Endocrinol Metab. 2008; 294 (1): E15-26.
3. Saad MF, Anderson RL, Laws A, Watanabe RM, Kades WW, Chen YDI, et al. A comparison between the minimal model and the glucose clamp in the assessment of insulin sensitivity across the spectrum of glucose tolerance. Diabetes. 1994; 43 (9): 1114-21.
4. Finegood DT, Pacini G, Bergman RN. The insulin sensitivity index. Correlation in dogs between values determined from the intravenous glucose tolerance test and the euglycemic glucose clamp. Diabetes. 1984; 33 (4): 362-8.
5. Bergman RN, Prager R, Volund A, Olefsky JM. Equivalence of the insulin sensitivity index in man derived by the minimal model method and the euglycemic glucose clamp. J Clin Invest. 1987; 79 (3): 790-800.
6. Stumvoll M, Mitrakou A, Pimenta W, Jenssen T, Yki-Jarvinen H, Van Haeften T, et al. Use of the oral glucose tolerance test to assess insulin release and insulin sensitivity. Diabetes Care. 2000; 23 (3): 295-301.
7. Ascaso JF, Pardo S, Real JT, Lorente RI, Priego A, Carmena R. Diagnosing insulin resistance by simple quantitative methods in subjects with normal glucose metabolism. Diabetes Care. 2003; 26 (12): 3320-5.
8. Bergman RN, Ider YZ, Bowden CR, Cobelli C. Quantitative estimation of insulin sensitivity. Am J Physiol. 1979; 236 (6): E667-77.
9. López-Alvarenga J, Reyes-Díaz S, Castillo-Martínez L, Dávalos-Ibáñez A, González-Barranco J. Reproducibilidad y sensibilidad de un cuestionario de actividad física en población mexicana. Salud Publica Mex. 2001; 43: 306-12.
10. Almeda-Valdés P, Bello-Chavolla OY, Caballeros-Barragán CR, Gómez-Velasco DV, Viveros-Ruiz T, Vargas-Vázquez A, et al. Índices para la evaluación de la resistencia a la insulina en individuos mexicanos sin diabetes. Gac Med Mex. 2018; 154 (92): S50-5.
11. McAuley KA, Williams SM, Mann JI, Walker RJ, Lewis-Barned NJ, Temple LA, et al. Diagnosing Insulin Resistance in the General Population. Diabetes Care. 2001; 24 (3): 460-4.
12. Legro RS, Finegood D, Dunaif A. A Fasting Glucose to Insulin Ratio Is a Useful Measure of Insulin Sensitivity in Women with Polycystic Ovary Syndrome 1. J Clin Endocrinol Metab. 1998; 83 (8): 2694-8.
13. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia. 1985; 28 (7): 412-9.
14. Radikova Z, Koska J, Huckova M, Ksinantova L, Imrich R, Vigas M, et al. Insulin Sensitivity Indices: a Proposal of Cut-Off Points for Simple Identification of Insulin-Resistant Subjects. Exp Clin Endocrinol Diabetes. 2006; 114 (05): 249-56.
15. Geloneze B, Vasques ACJ, Stabe CFC, Pareja JC, Rosado LEFP de L, Queiroz EC de, et al. HOMA1-IR and HOMA2-IR indexes in identifying insulin resistance and metabolic syndrome: Brazilian Metabolic Syndrome Study (BRAMS). Arq Bras Endocrinol Metabol. 2009; 53 (2): 281-7.
16. Wallace TM, Levy JC, Matthews DR. Use and Abuse of HOMA Modeling. Diabetes Care. 2004; 27(6): 1487-95.
17. Ghasemi A, Tohidi M, Derakhshan A, Hasheminia M, Azizi F, Hadaegh F. Cut-off points of homeostasis model assessment of insulin resistance, beta-cell function, and fasting serum insulin to identify future type 2 diabetes: Tehran Lipid and Glucose Study. Acta Diabetol. 2015; 52 (5): 905-15.
18. Levy JC, Matthews DR, Hermans MP. Correct homeostasis model assessment (HOMA) evaluation uses the computer program. Diabetes Care. 1998; 21 (12): 2191-2.
19. Katz A, Nambi SS, Mather K, Baron AD, Follmann DA, Sullivan G, et al. Quantitative Insulin Sensitivity Check Index: A Simple, Accurate Method for Assessing Insulin Sensitivity In Humans. J Clin Endocrinol Metab. 2000; 85 (7): 2402-10.
20. Hrebícek J, Janout V, Malincíkova J, Horáková D, Cízek L. Detection of Insulin Resistance by Simple Quantitative Insulin Sensitivity Check Index QUICKI for Epidemiological Assessment and Prevention. J Clin Endocrinol Metab. 2002; 87 (1): 144-144.

21. Bello-Chavolla OY, Almeda-Valdes P, Gomez-Velasco D, Viveros-Ruiz T, Cruz-Bautista I, Romo-Romo A, et al. METS-IR, a novel score to evaluate insulin sensitivity, is predictive of visceral adiposity and incident type 2 diabetes. Eur J Endocrinol. 2018; 178 (5): 533-44.
22. Kannel WB, Vasan RS, Keyes MJ, Sullivan LM, Robins SJ. Usefulness of the triglyceride-high-density lipoprotein versus the cholesterol-high-density lipoprotein ratio for predicting insulin resistance and cardiometabolic risk (from the Framingham Offspring Cohort). Am J Cardiol. 2008; 101 (4): 497-501.
23. McLaughlin T, Reaven G, Abbasi F, Lamendola C, Saad M, Waters D, et al. Is there a simple way to identify insulin-resistant individuals at increased risk of cardiovascular disease? Am J Cardiol. 2005; 96 (3): 399-404.
24. Simental-Mendía LE, Rodríguez-Morán M, Guerrero-Romero F. The Product of Fasting Glucose and Triglycerides As Surrogate for Identifying Insulin Resistance in Apparently Healthy Subjects. Metab Syndr Relat Disord. 2008; 6 (4): 299-304.
25. Lee DY, Lee ES, Kim JH, Park SE, Park C-Y, Oh K-W, et al. Predictive Value of Triglyceride Glucose Index for the Risk of Incident Diabetes: A 4-Year Retrospective Longitudinal Study. PLoS One. 2016; 11 (9): e0163465.
26. Er L-K, Wu S, Chou H-H, Hsu L-A, Teng M-S, Sun Y-C, et al. Triglyceride Glucose-Body Mass Index Is a Simple and Clinically Useful Surrogate Marker for Insulin Resistance in Nondiabetic Individuals. PLoS One. 2016; (3): e0149731.
27. Lim J, Kim J, Koo SH, Kwon GC. Comparison of triglyceride glucose index, and related parameters to predict insulin resistance in Korean adults: An analysis of the 2007-2010 Korean National Health and Nutrition Examination Survey. PLoS One. 2019; 14 (3): e0212963.
28. Kahn HS. The "lipid accumulation product" performs better than the body mass index for recognizing cardiovascular risk: a population-based comparison. BMC Cardiovasc Disord. 2005; 5 (1): 26.
29. Godinjak A, Godinjak Z, Burekovic A, Surkovic I, Dizdarevic-Bostandzic A, Velija-Asimi Z. Insulin resistance and lipid accumulation product in corelation to body mass index in women with polycystic ovary syndrome. Med Arch. 2012; 66 (6): 409-11.
30. Amato MC, Giordano C, Galia M, Criscimanna A, Vitabile S, Midiri M, et al. Visceral Adiposity Index: A reliable indicator of visceral fat function associated with cardiometabolic risk. Diabetes Care. 2010; 33 (4): 920-2.
31. Oterdoom LH, de Vries APJ, van Son WJ, van der Heide JJH, Ploeg RJ, Gansevoort RT, et al. Validation of Insulin Resistance Indexes in a Stable Renal Transplant Population. Diabetes Care. 2005; 28 (10): 2424-9.
32. Conwell LS, Trost SG, Brown WJ, Batch JA. Indexes of Insulin Resistance and Secretion in Obese Children and Adolescents: A validation study. Diabetes Care. 2004; 27 (2): 314-9.
33. Gungor N, Saad R, Janosky J, Arslanian S. Validation of surrogate estimates of insulin sensitivity and insulin secretion in children and adolescents. J Pediatr. 2004; 144 (1): 47-55.
34. Cohen O, Epstein GS, Weisz B, Homko CJ, Sivan E. Longitudinal assessment of insulin sensitivity in pregnancy. Validation of the homeostasis model assessment. Clin Endocrinol (Oxf). 2006; 64 (6): 640-4.
35. Moura FA, Carvalho LSF, Cintra RMR, Martins NV, Figueiredo VN, Quinaglia e Silva JC, et al. Validation of surrogate indexes of insulin sensitivity in acute phase of myocardial infarction based on euglycemic-hyperinsulinemic clamp. Am J Physiol Metab. 2014; 306 (4): E399-403.