Validation of a simple index (SI\textsubscript{isOGTT}) of insulin sensitivity in a population of sedentary men

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Abstract

Aim. – The ongoing obesity epidemic is associated with numerous health problems related to altered metabolic function. Among these is type 2 diabetes, characterized by lowered insulin sensitivity (IS). Consequently, the development of simple indices to assess IS has research and clinical importance. The SI\textsubscript{isOGTT}, a new index of IS, was recently described by Bastard et al. (Diabetes & Metabolism 2007;33:261–8), and validated in sedentary, non-diabetic, overweight and obese postmenopausal women. The aim of the present study was to validate the index in men.

Methods. – The data used in this project came from sedentary men (n = 36), aged 34–53 years, all of whom underwent a hyperinsulinaemic–euglycaemic clamp and 2-hour oral glucose tolerance test (OGTT). Correlations with M/I (glucose infusion rate [GIR] divided by insulin concentration), GIR and GIR divided by fat-free mass (FFM) were obtained by four well-known indices (HOMA, QUICKI, Cederholm and Matsuda) as well as with the new SI\textsubscript{isOGTT} index. Pearson correlations and Bland–Altman analyses were obtained for every index versus clamp value.

Results. – The best correlate of IS in the present study was the SI\textsubscript{isOGTT} (r = 0.84, P < 0.0001). The agreement of this method with the hyperinsulinaemic–euglycaemic clamp, as assessed by Bland–Altman plots, was similar to those of the other indices and to those previously described in postmenopausal women.

Conclusion. – The new index proposed by Bastard et al. is as good a predictor of IS in sedentary men as the other commonly used indices, and appears to be as reliable in this population as it was in the original study of postmenopausal women.

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Keywords: Insulin sensitivity; Hyperinsulinaemic–euglycaemic clamp; Oral glucose tolerance test; Sedentary men; Insulin sensitivity surrogate indices

Résumé

Validation d’un indice simple (SI\textsubscript{isOGTT}) évaluant la sensibilité à l’insuline dans une population d’hommes sédentaires.

Objectif. – L’épidémie d’obésité qui sévit actuellement est associée à de multiples anomalies métaboliques. Parmi celles-ci, on compte le diabète de type 2 qui est caractérisé par une diminution de la sensibilité à l’insuline (SI). De ce fait, la mise au point d’indices simples destinés à évaluer la SI est importante d’un point de vue clinique. Un nouvel indice de SI a récemment été décrit par Bastard et al. (Diabetes & Metabolism 2007;33: 261–8) et validé dans une cohorte constituée de femmes sédentaires non-diabétiques en surpoids et de femmes obèses ménopausées. L’objectif de la présente étude était de valider cet indice chez l’homme.

Méthodologie. – Les données utilisées dans ce projet proviennent d’hommes sédentaires (n = 36), de 34 à 53 ans, qui ont tous été soumis à un clamp euglycémique-hyperinsulinémique et à une hyperglycémie prolongée orale de deux heures. Des corrélations ont été obtenues entre le ratio M/I et le débit de perfusion de glucose (par unité de masse totale et par masse maigre) avec quatre indices bien connus (HOMA, QUICKI, Cederholm et Matsuda) ainsi qu’avec le nouvel indice (SI\textsubscript{isOGTT}). Des analyses de concordance (Bland–Altman) avec la méthode de référence (M/I) ont été réalisées pour chaque indice étudié.

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1. Introduction

The ongoing obesity epidemic has led to a massive increase in type 2 diabetes, resulting in the need for simple tools that are capable of accurately detecting impaired insulin sensitivity (IS). Lowered IS, known to be a major contributor to the pathogenesis of type 2 diabetes [1,2], is also associated with several other altered metabolic states, such as polycystic ovary syndrome and multiple cardiovascular disorders [3]. The gold-standard technique for assessing IS in humans is hyperinsulinaemic-euglycaemic clamp (HIEG clamp) [4–6]. However, this is a complicated technique that requires qualified personnel and significant financial resources. Furthermore, it is time-consuming and, thus, not easily adaptable to the clinical setting. This explains, in part, the ongoing search for simpler and more efficient ways to estimate IS using readily available clinical data.

The quantitative insulin-sensitivity check index (QUICKI) and homoeostasis model assessment (HOMA) are the two simplest indices based on fasting variables, and both have been validated in the wider population [7,8]. Nevertheless, indices derived from oral glucose tolerance test (OGTT) data are considered to be more accurate estimates of IS, as assessed by HIEG clamp, compared with fasting indices [9–11]. Their power to discriminate [12], and their accuracy [7] and reproducibility [13], have all been validated. The OGTT also allows for characterization of glucose tolerance as well as providing an evaluation of insulin secretion.

However, a recently published study has reported a new index that shows better correlation with IS assessed by HIEG clamp [14] than most commonly used indices. This index – called the “simple index assessing IS” (SIisOGTT) – uses the following formula: $SI_{isOGTT} = 1/[\log \sum_t \text{glucose}_{0-30-90-120} [\text{mmol/L}]} + \log \sum_t \text{insulin}_{0-30-90-120} [\mu\text{IU/mL}])$. The authors validated this index in a population of sedentary, non-diabetic, overweight and obese postmenopausal women, and found it to be better and easier to apply than other commonly used indices.

However, the validity of this approach still needs to be demonstrated in other populations. For this reason, the aim of the present study was to validate the new index in a population of sedentary men, aged 34–53 years, with a wide range of body mass index (BMI) scores and IS. HIEG clamp and OGTT data were obtained for all subjects to allow the necessary measurements to be made.

2. Methods

2.1. Subjects

A cohort of 36 sedentary men, aged 34–53 years, took part in the present study. This population included ten men who were the normal-weight controls (BMI ≤ 25), ten who were obese (BMI > 30) with normal glucose tolerance (measured by OGTT) and 16 who were obese with impaired glucose tolerance. Sedentary lifestyle was defined as the absence of participation in any physical activity over the previous 3 months or more, as used in Boucard et al. [15]; their physical-activity habits were assessed as described elsewhere [16]. All potential study subjects underwent medical examination, a medical-history questionnaire and a 75-g OGTT prior to inclusion. Criteria for exclusion from the study have been reported elsewhere [16]. The research protocol was approved by the Laval University ethics committee, and all participants gave their written informed consent.

2.2. Body composition

Body weight was measured to the nearest 0.1 kg using calibrated balance, including a tension gauge (Intertechology Inc., Don Mills, ON, Canada) and a digital panel indicator (Beckman Industrial Series 600, Beckman Coulter Canada Inc., Mississauga, ON, Canada). Standing height was measured to the nearest millimetre using a wall stadiometer. Lean body mass and fat mass were evaluated by the hydrostatic weighing technique as described elsewhere [15]. Waist circumference (WC) was measured at the level halfway between the iliac crest and the last rib margin in duplicate, using a flexible steel metric tape to the nearest 0.1 centimetre. Resting blood pressure was measured using a mercury manometer, and was reported as the average of four measurements taken on the right arm of subjects sitting for 30 minutes or more.

2.3. Oral glucose tolerance test and insulin sensitivity/resistance indices

After an overnight fast, an OGTT with a 75-g glucose load was performed. Blood samples were collected through a venous catheter from an antecubital vein at −15, 0, 30, 60, 90 and 120 minutes following glucose ingestion for determination of plasma glucose and insulin concentrations [17].
Plasma glucose was measured enzymatically, whereas plasma insulin was measured by radioimmunoassay with polyethylene glycol separation, as previously described [18,19]. All measures were performed in duplicate. Glucose tolerance was qualified according to the standard clinical cut-off points [16].

2.4. Hyperinsulinaemic–euglycaemic clamp

The HIEG clamp was performed following a 12-hour overnight fast, as reported elsewhere [20–22]. To avoid the well-documented acute effects of exercise on IS [23,24], all participants were instructed to refrain from taking any exercise on the 3 days prior to the HIEG clamp. The food intake of the subjects was also standardized on the day preceding the clamp: macronutrient composition was controlled and the caloric value of the meals was calculated from resting energy expenditure (as measured in Tremblay et al. [25] and as described in White et al. [26]).

An antecubital vein was cannulated with a catheter for infusion of the insulin and 20% glucose. A vein from the contralateral arm was also cannulated to allow sampling for determination of plasma insulin and glucose levels. Fasting blood was drawn for baseline measurements. A continuous infusion of insulin (Humulin; 40 mU/m² per minute) was then started, producing arterial insulin in the upper physiological range of approximately 500 pmol. Blood samples were drawn every 5 minutes for measurement of plasma glucose, and insulin levels measured every 10 minutes. The glucose infusion rate (GIR) was adjusted to achieve a steady-state plasma glucose of 5.5 mmol/L, thus preventing insulin-independent, increased glucose uptake due to hyperglycaemia [27].

GIR (M) and M/I (GIR divided by insulin concentration) values were calculated after 2 hours. Plasma insulin and glucose concentrations were measured as described for the OGTT. Clinical blood evaluations (for HbA1c and lipid profiles) were measured in Tremblay et al. [25] and as described in White et al. [26].

Table 1

Clinical characteristics of the 36 study subjects.

<table>
<thead>
<tr>
<th>Group</th>
<th>Glucose intolerant (n = 16)</th>
<th>Obese (n = 10)</th>
<th>Sedentary controls (n = 10)</th>
<th>Combined (n = 36)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>41.5 ± 5.2a</td>
<td>44.2 ± 6.5a</td>
<td>44.5 ± 3.8b</td>
<td>43.1 ± 5.3</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>35.3 ± 4.0b</td>
<td>32.5 ± 3.4a</td>
<td>24.0 ± 1.9b</td>
<td>31.4 ± 5.8</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>117.8 ± 9.4a</td>
<td>112.0 ± 10.1a</td>
<td>89.1 ± 6.9b</td>
<td>108.2 ± 15.1</td>
</tr>
<tr>
<td>Fat mass (kg)</td>
<td>34.5 ± 10.2a</td>
<td>33.3 ± 8.8a</td>
<td>14.9 ± 3.0b</td>
<td>28.7 ± 12.0</td>
</tr>
<tr>
<td>Percentage of fat (%)</td>
<td>31.4 ± 6.2a</td>
<td>32.2 ± 4.7a</td>
<td>19.9 ± 3.4b</td>
<td>28.4 ± 7.3</td>
</tr>
<tr>
<td>Fat-free mass (kg)</td>
<td>73.1 ± 7.5b</td>
<td>68.9 ± 4.6a</td>
<td>59.7 ± 4.7b</td>
<td>68.6 ± 8.5</td>
</tr>
<tr>
<td>Fasting glucose (mmol/L)</td>
<td>5.9 ± 0.4b</td>
<td>5.8 ± 0.4a</td>
<td>5.6 ± 0.5b</td>
<td>5.8 ± 0.4</td>
</tr>
<tr>
<td>Fasting insulin (μIU/mL)</td>
<td>26.8 ± 16.0a</td>
<td>17.4 ± 9.1ab</td>
<td>12.9 ± 5.5b</td>
<td>20.3 ± 13.3</td>
</tr>
<tr>
<td>HOMA</td>
<td>7.1 ± 4.5b</td>
<td>4.5 ± 2.6ab</td>
<td>3.3 ± 1.5b</td>
<td>5.3 ± 3.7</td>
</tr>
<tr>
<td>QUICKI</td>
<td>0.30 ± 0.02a</td>
<td>0.32 ± 0.03b</td>
<td>0.33 ± 0.02b</td>
<td>0.31 ± 0.03</td>
</tr>
<tr>
<td>Cederholm</td>
<td>11.7 ± 2.9a</td>
<td>17.5 ± 3.0b</td>
<td>23.9 ± 7.4a</td>
<td>16.7 ± 6.7</td>
</tr>
<tr>
<td>Matsuda</td>
<td>26.3 ± 12.7a</td>
<td>43.0 ± 25.1ab</td>
<td>60.9 ± 33.1b</td>
<td>40.6 ± 26.9</td>
</tr>
<tr>
<td>SÏÎ OGTT</td>
<td>0.199 ± 0.008b</td>
<td>0.209 ± 0.011b</td>
<td>0.217 ± 0.013b</td>
<td>0.207 ± 0.013</td>
</tr>
<tr>
<td>M/I</td>
<td>0.0046 ± 0.0028a</td>
<td>0.0068 ± 0.0038b</td>
<td>0.0120 ± 0.0046b</td>
<td>0.0072 ± 0.0047</td>
</tr>
</tbody>
</table>

Values are mean ± standard deviation; ANOVA’s were performed between groups, Values that share the same letter are not statistically different, while values with different letters are statistically different, according to the Tuckey HSD post-hoc test ($P<0.05$).
Table 2
Correlation between insulin sensitivity/resistance indices and hyperinsulinaemic–euglycaemic clamp results in the 36 sedentary men studied.

<table>
<thead>
<tr>
<th>Indices</th>
<th>M or GIR (mg/min per kilogram)</th>
<th>GIR (mg/min per kilogram fat-free mass)</th>
<th>M/I</th>
</tr>
</thead>
<tbody>
<tr>
<td>HOMA-IR</td>
<td>( r = -0.52^* )</td>
<td>( r = -0.51^* )</td>
<td>( r = -0.64^* )</td>
</tr>
<tr>
<td></td>
<td>( z = 1.562 )</td>
<td>( z = 1.562 )</td>
<td>( z = 1.474 )</td>
</tr>
<tr>
<td></td>
<td>( P = 0.118 ) vs SI&lt;sub&gt;is&lt;/sub&gt;</td>
<td>( P = 0.118 ) vs SI&lt;sub&gt;is&lt;/sub&gt;</td>
<td>( P = 0.141 ) vs SI&lt;sub&gt;is&lt;/sub&gt;</td>
</tr>
<tr>
<td>QUICKI</td>
<td>( r = 0.52^* )</td>
<td>( r = 0.50^* )</td>
<td>( r = 0.65^* )</td>
</tr>
<tr>
<td></td>
<td>( z = 1.584 )</td>
<td>( z = 1.655 )</td>
<td>( z = 1.420 )</td>
</tr>
<tr>
<td></td>
<td>( P = 0.113 ) vs SI&lt;sub&gt;is&lt;/sub&gt;</td>
<td>( P = 0.098 ) vs SI&lt;sub&gt;is&lt;/sub&gt;</td>
<td>( P = 0.156 ) vs SI&lt;sub&gt;is&lt;/sub&gt;</td>
</tr>
<tr>
<td>Cederholm</td>
<td>( r = 0.78^* )</td>
<td>( r = 0.76^* )</td>
<td>( r = 0.79^* )</td>
</tr>
<tr>
<td></td>
<td>( z = 0.319 )</td>
<td>( z = 0.237 )</td>
<td>( z = 0.421 )</td>
</tr>
<tr>
<td></td>
<td>( P = 0.750 ) vs SI&lt;sub&gt;is&lt;/sub&gt;</td>
<td>( P = 0.813 ) vs SI&lt;sub&gt;is&lt;/sub&gt;</td>
<td>( P = 0.674 ) vs SI&lt;sub&gt;is&lt;/sub&gt;</td>
</tr>
<tr>
<td>Matsuda</td>
<td>( r = 0.66^* )</td>
<td>( r = 0.63^* )</td>
<td>( r = 0.78^* )</td>
</tr>
<tr>
<td></td>
<td>( z = 0.630 )</td>
<td>( z = 0.785 )</td>
<td>( z = 0.507 )</td>
</tr>
<tr>
<td></td>
<td>( P = 0.529 ) vs SI&lt;sub&gt;is&lt;/sub&gt;</td>
<td>( P = 0.432 ) vs SI&lt;sub&gt;is&lt;/sub&gt;</td>
<td>( P = 0.612 ) vs SI&lt;sub&gt;is&lt;/sub&gt;</td>
</tr>
<tr>
<td>SI&lt;sub&gt;is&lt;/sub&gt;OGTT</td>
<td>( r = 0.74^* )</td>
<td>( r = 0.73^* )</td>
<td>( r = 0.84^* )</td>
</tr>
</tbody>
</table>

M, GIR: glucose infusion rate; M/I: glucose infusion rate divided by insulin concentration; \( ^* \) \( p < 0.001 \) (correlation with clamp results); the value in **bold** indicates a trend toward statistical significance.

In the clamp than the new index being validated. In fact, the highest correlation with the M/I ratio based on the absolute \( r \) value was the new index (SI<sub>is</sub>OGTT). However, although the SI<sub>is</sub> had a somewhat higher \( r \) value with M/I, this correlation was not statistically significantly different from that obtained with the other indices. Similar results were obtained when comparing all index-derived values with GIR, except for the SI<sub>is</sub>, which showed a trend towards being better than QUICKI for predicting GIR expressed as mg/min per kilogram FFM. Also, the Cederholm index yielded higher \( r \) values than the SI<sub>is</sub> with GIR expressed by kilogram of either body mass or FFM although, again, this was not statistically significantly different. In general, the \( r \) values were higher with indices calculated using multiple OGTT values.

Fig. 1. Bland–Altman analyses of two indices (Matsuda and SI<sub>is</sub>OGTT) compared with the gold-standard measurement (hyperinsulinaemic–euglycaemic clamp).
The Bland–Altman analyses (Fig. 1) show the agreement between two methods (SIisOGTT and Matsuda) and the gold standard (data not shown for the other indices). However, the results were similar for all five indices: most (Matsuda, Cederholm and HOMA-IR) had two points outside the ± 1.96 SD (5.5% of subjects) range, whereas the SIisOGTT had one (2.7%) and the QUICKI had three (8.3%) such points. However, from these data, it is not possible to conclude that any one method had better agreement than the others.

4. Discussion

The present study examined the relationships between the reference measures of IS and M/I, as well as the values of GIR relative to body mass and FFM, and five surrogate indices derived from OGTT or fasting plasma measures. The aim was to validate a newly described index (SIisOGTT) in a population of sedentary men, who had a wide range of body composition and IS, using data collected from a study designed to examine the relationship between muscle phenotypes and IS. This new index had previously been validated in a population of overweight and obese postmenopausal women [14], and the authors had suggested the need for further validation in different populations.

In general, in the present study, all indices correlated well with the results of the HIEG clamp. Fasting indices had somewhat weaker correlations than the OGTT-derived indices in terms of absolute \( r \) values, yet statistically significant differences between indices could not be found, possibly due to sample-size limitations. The only statistical trend observed in the study points to a significant cluster of points outside the 0.5% range, whereas the SIisOGTT had one (2.7%) such point. However, from these data, it is not possible to conclude that any one method had better agreement than the others.

In the original report by Bastard et al. [14], the authors claimed that their index is easier to use than other OGTT-derived indices to further justify its application; this is certainly true in that fewer sampling times are required (0, 30, 90, 120 minutes) to generate good or even better estimates of IS. However, all of these indices require similar calculations, as well as several glucose and insulin measures derived from the OGTT and, consequently, are all dependent on reliable OGTT data. Although such data are often easily obtainable and reliable in a research setting, not all clinical centres necessarily offer the same rigorous evaluation of their patients, nor do all necessarily measure glucose and insulin at as many time-points during the test. These real-life factors emphasize the continuing need for an index based on standard-procedure data that are easily obtained in a clinical setting.

5. Conclusion

The new SIisOGTT index proposed by Bastard et al. performed as well as—but not significantly better than—other widely accepted OGTT-derived indices in our study population of sedentary men. The insulin dose appeared to have no impact on the reliability of this index, making it applicable to a wider range of situations. As with existing approaches, the new index uses insulin and blood glucose levels as measured over the course of an OGTT, but has the advantage of using fewer time-points. Nevertheless, such data are not routinely collected in clinical settings and, so, preclude the widespread use of the new index outside of the research community.

6. Conflicts of interest

None.

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