A lipid-parameter-based index for estimating insulin sensitivity and identifying insulin resistance in a healthy population

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Received 9 November 2007; received in revised form 20 February 2008; accepted 24 February 2008
Available online 14 October 2008

Abstract

Aim. – Insulin resistance needs to be identified as early as possible in its development to allow targeted prevention programmes. Therefore, we compared various fasting surrogate indices for insulin sensitivity using the euglycaemic insulin clamp in an attempt to develop the most appropriate method for assessing insulin resistance in a healthy population.

Methods. – Glucose, insulin, proinsulin, glucagon, glucose tolerance, fasting lipids, liver enzymes, blood pressure, anthropometric parameters and insulin sensitivity (Mffm/I) using the euglycaemic insulin clamp were obtained for 70 normoglycaemic non-obese individuals. Spearman’s rank correlations were used to examine the association between Mffm/I and various fasting surrogate indices of insulin sensitivity. A regression model was used to determine the weighting for each variable and to derive a formula for estimating insulin resistance. The clinical value of the surrogate indices and the new formula for identifying insulin-resistant individuals was evaluated by the use of receiver operating characteristic (ROC) curves.

Results. – The variables that best predicted insulin sensitivity were the HDL-to-total cholesterol ratio, the fasting NEFA and fasting insulin. The use of the lipid-parameter-based formula Mffm/I = 12 × [2.5 × (HDL-c/total cholesterol) – NEFA] – fasting insulin appeared to have high clinical value in predicting insulin resistance. The correlation coefficient between Mffm/I and the new fasting index was higher than those with the most commonly used fasting surrogate indices for insulin sensitivity.

Conclusion. – A lipid-parameter-based index using fasting samples provides a simple means of screening for insulin resistance in the healthy population.

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Résumé

Un index établi sur des paramètres lipidiques permet l’estimation de la sensibilité à l’insuline et le diagnostic de l’insulinorésistance dans une population saine.

But. – L’insulinorésistance doit être identifiée précocement de manière à cibler les populations pouvant bénéficier de stratégies préventives. En conséquence, nous avons comparé, dans une population saine, divers index d’insulinosensibilité/résistance avec le clamp euglycémique hyperinsulinémique et nous avons essayé de développer la méthode la plus appropriée pour dépister l’insulinorésistance dans une telle population.

Méthodes. – Les glycémie, l’insulinémie, la tolérance au glucose, le bilan lipidique, le bilan hépatique, la pression artérielle, les paramètres anthropométriques et la sensibilité à l’insuline (Mffm/I) quantifiée par le clamp euglycémique hyperinsulinémique, ont été obtenus pour 70 sujets normoglycémiques et non obèses. Le test de rang de Spearman a été utilisé pour déterminer les corrélations entre Mffm/I et les index d’insulinosensibilité. Un modèle de régression a été utilisé pour déterminer le poids de chaque variable et dériver une formule estimant au mieux l’insulinorésistance. La valeur clinique des index et de cette nouvelle formule pour identifier les sujets insulinorésistants a été évaluée par une analyse receiver operating characteristic (ROC).

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doi:10.1016/j.diabet.2008.02.009
1. Introduction

Insulin resistance is a major risk factor for type 2 diabetes and is frequently associated with cardiovascular disease (CVD) [1]. Early screening for insulin resistance could be of value as a way of monitoring populations with a high metabolic risk before the emergence of the classical markers of the ‘metabolic syndrome’. At present, the gold standard for measuring and quantifying insulin resistance is the hyperinsulinaemic euglycaemic clamp [2]. However, in clinical practice, this method is difficult and impractical. Therefore, a number of surrogate indices for insulin sensitivity have been developed, derived from fasting glucose and insulin levels, or based on the oral glucose tolerance test. Clearly, the reliability of these surrogate indices depends on the degree to which they correlate with direct measurements of insulin activity. In a healthy non diabetic population, surrogates of insulin action are not sufficiently efficient and do not appear to offer advantages over fasting plasma insulin concentration [3–5]. However, fasting plasma insulin measurement is not sensitive enough to be used as a tool for insulin-resistance screening in the apparently healthy population.

In the present study, we attempted to develop a simple and sensitive estimate of insulin resistance in a non obese normoglycose-tolerant population by using several metabolic markers in addition to measures of insulin.

2. Methods

A population of 70 subjects from the EGIR-RISC study cohort [6], corresponding to all of the subjects tested at the Human Nutrition Research Centre of Rhône-Alpes, was selected for this study. To be included in the study, subjects had to have a normal medical history, be clinically healthy, have a fasting plasma glucose less than 7.0 mmol/L (126 mg/dL), have a two-hour plasma glucose less than 11.1 mmol/L (200 mg/dL), and undergo a physical examination and routine clinical laboratory tests together with a hyperinsulinaemic euglycaemic glucose clamp. All participants were Caucasian and non diabetic, according to criteria of both the American Diabetes Association [7] and the World Health Organization [8]. The experimental protocol was approved by the ethics committee of the hospices civils de Lyon and performed according to the requirements of French law (Huriel law).

In vivo insulin sensitivity was assessed using the hyperinsulinaemic euglycaemic glucose clamp technique as previously described [9]. Briefly, four days before the clamp, the subjects were instructed to avoid exercise; then, after an overnight fast, an intravenous cannula was inserted into the cubital vein for infusing insulin and glucose (20%). Insulin (Actrapid) was infused at 40 mU m$^{-2}$ min$^{-1}$ to achieve hyperinsulinaemia. Blood samples were taken every 10 minutes for immediate glucose measurement, using a Roche Diagnostic Glucotrend 2 glucose analyzer. A variable rate of glucose infusion was given for 120 minutes and adjusted according to a negative feedback algorithm. Blood glucose levels were maintained at 4.5 mmol/L. The glucose disposal rate M (mg/kg/min) was calculated from measurements taken during the final 30 minutes of the clamp. Insulin sensitivity was expressed as the ratio of the M value [10] corrected for fat-free mass (ffm) to the Naperian logarithm of the average plasma insulin concentration from four samples taken over the final 30 minutes. The ability of insulin to stimulate glucose disposal varied continuously in our sample, precluding identification of any individual as either insulin-sensitive or insulin-resistant. As an operational definition of insulin resistance, we used an Mffm/I value in the lower quartile of distribution of our population. Mffm/I $\leq$ 11.24 mmol min$^{-1}$ kg$^{-1}$ I$^{-1}$.Ln (mU.L$^{-1}$) defined individuals with insulin resistance.

Fasting samples allowed calculating HOMA IR (11): $I_0/(22.5 \times e^{-\frac{\text{Log}(gly_0)}{6}})$. QUICKI (12): $1/\left[\text{Log}(I_0) + \text{Log}(gly_0)\right]$, revised QUICKI (13): $1/\left[\text{Log}(I_0) + \text{Log}(gly_0) + \text{Log}(FFA_0)\right]$, FIRI (14): $(gly_0 \times I_0)/25$, glucose-to-insulin ratio (15): Gly0/I0 and the McAuley index (4): $e^{(2.63 - 0.28(gly_0) - 0.31 \text{ln}(TG_0))}$, where gly0, I0, FFA0 and TG0 represented fasting plasma glucose, insulin, free fatty acids and triglycerides, respectively.

2.2. Other measurements

Plasma glucose was measured by the glucose oxidase method. Plasma insulin, proinsulin and C-peptide were measured in duplicate by a two-site fluorimunometric assay (AutoDELFIA Insulin kit, PerkinElmer, Turku, Finland) using monoclonal antibodies, with the following assay characteristics (for insulin, proinsulin and C-peptide, respectively): sensitivity 1–2, 0.3 and 5 pmol/L; within-assay variation 5, 6 and 5%; and between-assay variation 5%, 8% and 3.5%. The glucagon
assay (developed at the J. Holst laboratory in Copenhagen, Denmark) is highly specific for the free C terminus of the molecule and is, therefore, specific for pancreatic glucagon, with the following assay characteristics: sensitivity less than 1 pmol/L, within-assay CV less than 5% at 20 pmol/L and between-assay CV less than 12%.

Aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), total cholesterol, HDL cholesterol and triglycerides were routinely determined using an automatic analyzer (Modular, Roche-Diagnostic), and LDL cholesterol was calculated using Friedewald’s equation. Plasma non esterified fatty acids (NEFA) were measured as previously described [9].

Blood pressure, and waist and hip girths were measured according to standardized procedures, and waist-to-hip ratio (WHR) and body mass index (BMI) (kg/m²) were calculated. Percent ffm was evaluated by the TANITA TBF 300 bioimpedance balance (Tanita International Division, UK). Physical activity was measured by a CSA Actigraph (MTI: Manufacturing Technology, Fort Walton Beach, FL, USA) that was attached to a belt worn on the waist of each participant for 1 week. Qualitative information on physical activity was collected using the 7-day International Physical Activity Questionnaire (IPAQ).

2.3. Statistical analysis and calculations

Data are expressed as means (±S.D.). We used a multiple forward-regression analysis to determine the most reliable variables to assess insulin sensitivity among the following, including age, weight, height, BMI, waist and hip circumferences, WHR, % body fat, % ffm, fasting and postglucose-load insulin and glucose levels, fasting triglycerides (TG), total cholesterol, HDL cholesterol (HDL-c), LDL-c, non-HDL-c, HDL-c/TG, HDL-c/LDL-c, HDL-c/total cholesterol, ALT, AST, GGT, erythrocyte sedimentation rate (ESR), leucocytes, microalbuminuria, proinsulin, proinsulin/insulin, glucagon, C-peptide, physical activity, tobacco consumption, familial history of diabetes and familial history of cardiovascular disease. By this approach, we established a new index derived from the regression equation.

All correlations between Mffm/I and surrogate indices of insulin sensitivity were performed using the non parametric Spearman’s rank test. After performing a power calculation, our population of 70 subjects was large enough to assume that any correlation coefficient greater than 0.33 was significant (power: 0.80; P < 0.05). The clinical value of the fasting indices of insulin sensitivity to identify insulin-resistant individuals was evaluated by constructing receiver operating characteristic (ROC) curves. We limited our ROC curve constructions to the most used or relevant indices: fasting insulin; HOMA; QUICKI; revised QUICKI; and the McAuley index. The optimal cut-off value of each index was located by finding the point highest on the vertical axis, and furthest to the left on the horizontal axis. We determined the areas under the ROC curves (AUC ROC), and the sensitivity and specificity of the optimal cut-off points on the ROC curves. The AUC ROC curves are measures of predictive value, and were compared using the method of Hanley and McNeil [14]. Differences between the insulin-sensitive and insulin-resistant groups were assessed by the non parametric Mann–Whitney U test. The statistical analysis was conducted using MedCalc for Windows (version 8.2.1, MedCalc Software, Belgium), and P < 0.05 was considered statistically significant.

3. Results

The baseline characteristics of the subjects are presented in Table 1. By study design, all subjects were glucose–tolerant, and displayed a normal lipid profile and liver-enzyme status. Despite the homogeneity of the baseline characteristics of our study population, we observed a wide range of insulin-sensitivity.

Table 1
Clinical and metabolic characteristics of the subjects, and stratification of the population according to the insulin-sensitivity status as determined by Mffm/I value

<table>
<thead>
<tr>
<th></th>
<th>Total (N=70)</th>
<th>Insulin-sensitive (N=52)</th>
<th>Insulin-resistant (N=18)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>43 ± 7</td>
<td>43 ± 8</td>
<td>43 ± 5</td>
<td>NS</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>67.4 ± 12.4</td>
<td>66 ± 11.9</td>
<td>71.5 ± 13.2</td>
<td>NS</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>23.6 ± 3.4</td>
<td>23.1 ± 3.0</td>
<td>25.1 ± 4.0</td>
<td>NS</td>
</tr>
<tr>
<td>Waist (cm)</td>
<td>81 ± 11</td>
<td>79 ± 10</td>
<td>86 ± 12</td>
<td>0.03</td>
</tr>
<tr>
<td>WHR</td>
<td>0.85 ± 0.08</td>
<td>0.83 ± 0.07</td>
<td>0.89 ± 0.08</td>
<td>0.008</td>
</tr>
<tr>
<td>BP (mmHg)</td>
<td>114/74 ± 14/11</td>
<td>113/73 ± 18/11</td>
<td>115/76 ± 15/10</td>
<td>NS</td>
</tr>
<tr>
<td>TG (mmol/L)</td>
<td>0.96 ± 0.43</td>
<td>0.886 ± 0.377</td>
<td>1.165 ± 0.528</td>
<td>0.04</td>
</tr>
<tr>
<td>Total cholesterol (mmol/L)</td>
<td>4.77 ± 0.08</td>
<td>4.69 ± 0.71</td>
<td>4.99 ± 0.63</td>
<td>NS</td>
</tr>
<tr>
<td>HDL-c (mmol/L)</td>
<td>1.55 ± 0.4</td>
<td>1.62 ± 0.40</td>
<td>1.36 ± 0.34</td>
<td>0.01</td>
</tr>
<tr>
<td>LDL-c (mmol/L)</td>
<td>2.77 ± 0.63</td>
<td>2.67 ± 0.63</td>
<td>3.09 ± 0.52</td>
<td>0.004</td>
</tr>
<tr>
<td>AST (U/L)</td>
<td>26 ± 12</td>
<td>23 ± 7</td>
<td>32 ± 19</td>
<td>0.01</td>
</tr>
<tr>
<td>ALT (U/L)</td>
<td>23 ± 12</td>
<td>20 ± 12</td>
<td>31 ± 15</td>
<td>0.004</td>
</tr>
<tr>
<td>GGT (U/L)</td>
<td>22 ± 15</td>
<td>20 ± 11</td>
<td>31 ± 23</td>
<td>0.01</td>
</tr>
<tr>
<td>NEFA (mmol/L)</td>
<td>0.446 ± 0.198</td>
<td>0.401 ± 0.160</td>
<td>0.576 ± 0.244</td>
<td>0.004</td>
</tr>
<tr>
<td>Fasting glucose (mmol/L)</td>
<td>5.06 ± 0.4</td>
<td>5.06 ± 0.4</td>
<td>5.17 ± 0.3</td>
<td>NS</td>
</tr>
<tr>
<td>2-h OGTT glucose (mmol/L)</td>
<td>6.06 ± 1.32</td>
<td>5.88 ± 1.30</td>
<td>6.68 ± 1.22</td>
<td>0.004</td>
</tr>
<tr>
<td>Fasting insulin (mU/L)</td>
<td>4 ± 3</td>
<td>4 ± 2</td>
<td>6 ± 3</td>
<td>0.01</td>
</tr>
<tr>
<td>Mffm/I</td>
<td>15.12 ± 4.55</td>
<td>16.67 ± 3.76</td>
<td>10.29 ± 3.62</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

Mann–Whitney U test for comparisons between insulin sensitive and insulin resistant groups.
values as assessed by the hyperinsulinaemic euglycaemic clamp (Fig. 1). As expected, when separating subjects according to their insulin-sensitive status as defined above, we found that all metabolic markers except BMI, fasting glucose and cholesterol levels were significantly altered in the insulin-resistant group (Table 1).

We then performed multiple forward-regression analyses with Mffm/I as the dependent variable and all of the previously mentioned parameters as independent variables. We found that only three of those parameters—namely, fasting plasma insulin, NEFA and HDL-c/total cholesterol ratio—were independently and significantly correlated with the dependent variable (Table 2), and explained 53% of the variation of Mffm/I. The equation of the regression model was:

\[
\frac{\text{Mffm}}{I} = 14.55 + \left( 21.53 \times \frac{\text{HDL-c}}{\text{total cholesterol}} \right) - (0.65 \times \text{fasting insulin}) - (8.63 \times \text{NEFA}).
\]

HDL-c, total cholesterol and NEFA were expressed in mmol/L, and fasting insulin was expressed in mU/L. By simplifying this equation, we derived a new simple surrogate index of insulin sensitivity, expressed as:

\[
\text{New index} = 12 \times \left[ 2.5 \times \left( \frac{\text{HDL-c}}{\text{total cholesterol}} \right) - \text{NEFA} \right] - \text{fasting insulin}.
\]

Table 3

<table>
<thead>
<tr>
<th>Fasting indices</th>
<th>r</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting insulin</td>
<td>−0.52</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>HOMA</td>
<td>−0.52</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>QUICKI</td>
<td>0.52</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Revised QUICKI</td>
<td>0.66</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>McAuley index</td>
<td>0.57</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>FIRI</td>
<td>−0.51</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Glucose-to-Insulin</td>
<td>0.52</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>New index</td>
<td>0.79</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

We calculated the correlation coefficients between Mffm/I and fasting surrogate indices for insulin sensitivity (Table 3). Among the published indices evaluated in this study, the highest correlation coefficient was observed for the revised QUICKI (\(r = 0.66, P < 0.0001\)). Interestingly, we found a high correlation between Mffm/I and our new index (\(r = 0.79, P < 0.0001\)). To evaluate the agreement between the clamp and the new fasting index, a Bland–Altman plot was also built by plotting the difference between insulin sensitivity as measured by the clamp (Mffm/I) and insulin sensitivity as estimated by the new index vs the clamp–new index average result (Fig. 2). The plot shows good agreement between the two methods.

To assess the ability of the surrogate indices for insulin sensitivity to identify an insulin-resistant status, we constructed ROC curves (Fig. 3). By comparing curves of fasting-based indices of insulin sensitivity, we observed that, for our new index,
4. Discussion

Quantifying insulin sensitivity and identifying insulin-resistant subjects in an apparently healthy non-diabetic population is crucial for the development of prevention programmes to delay progression towards diabetes and cardiovascular complications. Several surrogate indices to estimate insulin action have been developed to quantify insulin sensitivity easily. These indices are based on fasting plasma insulin and glucose levels [11–13], or on OGTT results [15,16]. It has been previously shown that sophisticated combinations of glucose and insulin levels are no more useful than fasting insulin levels alone in estimating the degree of insulin sensitivity in a healthy population [3]. The correlation between clamp results and fasting insulin level in our study \((r = –0.52, P < 0.0001)\) was similar to those of HOMA-IR and QUICKI, but was not high enough to be used as an accurate estimate of insulin action. These results are explained by the absence of a significant correlation between the fasting glucose level and Mffm/I in this normoglycaemic, normoglycose-tolerant population, which had a narrow range of fasting glucose levels and a wide range of insulin-sensitivity levels. We observed that adding a parameter associated with an insulin-resistant status, such as the fasting TG level in the McAuley formula [4] or the fasting NEFA in the revised QUICKI formula [13,17], improved the ability of such surrogate indices to quantify insulin sensitivity in our healthy population. Pursuing the notion that it might be possible to improve the surrogate’s performance by considering several metabolic parameters, we developed a new index based on fasting insulin and lipid parameters. This index results from simplifying a multiple-regression equation involving a cluster of classical metabolic parameters. It is interesting to note that the three parameters that were independently related to insulin resistance, and explained the variations in this resistance, include two main components of the lipid profile (HDL-c/total cholesterol and NEFA) and the level of fasting insulin. The fasting NEFA level is independently correlated with Mffm/I \((r = –0.36, P < 0.0001)\) and is known to reflect the sensitivity of the antilipolytic action of insulin.

Increased lipolysis associated with a chronically elevated fasting NEFA level is a common feature of insulin resistance [18]. The fasting NEFA level is inversely correlated to insulin sensitivity as assessed by the hyperinsulinaemic euglycaemic clamp [13]. This excess lipolysis is thought to be implicated in the development of impaired glucose tolerance and type 2 diabetes [18]. In first-degree relatives of type 2 diabetes patients, the fasting plasma NEFA is increased, although fasting glucose and insulin are within normal ranges [1]. Lipolysis is normally suppressed by insulin, and it may be postulated that an increased fasting NEFA level may reflect insulin resistance in a predispose stage, before glucose homeostasis becomes defective. This could explain the stronger correlation observed between Mffm/I and the surrogate indices using fasting NEFA in the formula (for example, the revised QUICKI and our new index) [17]. It must be noted that the formula of our new index is predominantly dependent on the HDL-to-total cholesterol ratio. It is already known that subjects with an elevated total-to-HDL-c ratio are insulin-resistant [19]. Hypo-HDLaemia is a common feature

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of a high-risk metabolic syndrome and cardiovascular disease (CVD) profile [20–22], and is a component of the metabolic syndrome definition used by both the NCEP–ATP III [23] and IDF [24]. The HDL-to-total cholesterol ratio is the inverse of the atherogenic index, which has been widely validated as a strong predictor of CVD risk, being better than non-HDL-c predictors [25]. It should be noted that the TG-to-HDL-c ratio, which is predictive of LDL particle size and phenotype B [26], was recently shown to be a strong predictor of glucose disposal rates and HOMA values in a cohort of overweight and obese postmenopausal women [17]. However, the atherogenic index was a more reliable variable for assessing insulin sensitivity in our healthy cohort.

In this present report, we showed that the atherogenic index might be useful for the quantification of insulin resistance. It could be postulated that our new index, which includes the inverse of the atherogenic index, insulin level and level of excess lipolysis, may prove to be as useful for predicting cardiovascular risk as it is for estimating insulin resistance in an apparently healthy population.

Indeed, as a tool for estimating insulin resistance in an apparently healthy population, our lipid-parameter-based formula is more reliable than the most frequently used surrogate indices of insulin sensitivity published to date.

We also analyzed the ability of fasting indices to identify insulin-resistant subjects, using the ROC curves approach. The AUC ROC curves of our new index (0.867) were significantly (P < 0.0001) greater than those of other indices. This means that, independently of a cut-off value, our index offers a greater possibility of identifying insulin-resistant subjects than other surrogates of insulin-sensitivity studied so far. It should be emphasized that the classical definitions of the metabolic syndrome [23,24] that use central obesity and impaired glycaemia as two main components may have lower sensitivity in identifying insulin resistance in a non obese normoglycaemic population. Using the optimal cut-off value of our new index (≤−1.26) identified 88% of the insulin-resistant subjects of our healthy population, with a specificity of 77%. Considering such a performance, our lipid-based index may well prove to be a useful and simple tool for identifying insulin-resistant subjects in extensive epidemiological studies.

Nevertheless, our present study has several limitations. Indeed, we cannot be certain that our population is large enough to have enough power to assess the significance of the evaluated indices. The relevance of our lipid-based index needs to be confirmed in a larger healthy population and validated in less healthy populations. Furthermore, we should acknowledge that the lack of standardization in insulin measurement, and the cost implications of both NEFA and insulin assays, may limit the use of this lipid-based index in extensive studies.

5. Conclusion

Identifying and quantifying insulin resistance in apparently healthy populations offers the possibility of preventing the metabolic syndrome and its cardiovascular complications. We have developed a simple and accurate tool, based on lipid parameters, to assess insulin resistance from fasting blood samples. This index needs to be validated in a large cohort of healthy subjects and in other non diabetic populations. New prospective studies should be undertaken to determine if the formula presented here, which includes the atherogenic index, is of value in assessing absolute cardiovascular risk.

Acknowledgements

The RISC Study is partly supported by EU grant QLG1-CT-2001-01252. Additional support was provided by AstraZeneca (Sweden).

References


