Estimating insulin secretion in youth using simple indices derived from the oral glucose tolerance test

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Abstract

Aim. – Simple estimates of insulin secretion feasible for large epidemiological studies have been proposed in adults, but have been little evaluated in young people. For this reason, this study examined the correlation between OGTT-derived and fasting-based indices of insulin secretion against the acute insulin response to glucose (AIRg) in children.

Methods. – Twenty subjects (nine boys and 11 girls; mean [SD] age: 9 [2] years) were studied. Their mean (SD) BMI Z score was 1.5 (0.8). All participants had normal fasting and 2-h post-load glucose. Each subject underwent an insulin-modified minimal model frequently sampled intravenous glucose tolerance test (FSIVGTT) as the reference method, and a 3-h OGTT. AIRg was computed from the FSIVGTT. A total of ten indices were calculated using OGTT data, while HOMA%beta (original formula) and HOMA2%beta (computer-based) were computed from fasting samples. Correlations were established using Spearman’s rank correlations.

Results. – Of the ten indices derived from the OGTT, those most closely correlated with the AIRg (using FSIVGTT) included the insulinogenic indext30 min (r = 0.80), insulin/glucose ratio t30 min (r = 0.71) and ratio of the area under the curve for insulin to glucose t0-30 min (r = 0.74). Both the HOMA%beta and HOMA2%beta correlated modestly with AIRg (r = 0.62 and r = 0.65, respectively).

Conclusion. – Our results suggest that OGTT-derived measures of insulin secretion provide adequate estimates of first-phase insulin secretion in youth. HOMA2%beta and HOMA%beta represent acceptable compromises, although HOMA2%beta may be preferable in younger individuals, as it allows for a wider spectrum of insulin and glucose values that are physiological in this age group.

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Keywords: Insulin secretion; OGTT; FSIVGTT; Children; HOMA%B

Résumé

Estimer la sécrétion d’insuline chez l’enfant en utilisant des indices dérivés de l’hyperglycémie provoquée par voie orale.

Objectif. – Des mesures simples qui estiment la sécrétion d’insuline et qui peuvent être utilisées dans les études épidémiologiques ont été validées chez l’adulte, mais ont été peu étudiées chez l’enfant. Nous avons examiné la corrélation entre des indices de sécrétion d’insuline dérivés de l’hyperglycémie provoquée par voie orale (HGPO) et des indices à jeun, comparativement à la phase précoce de l’insulinosécrétion en réponse au glucose (AIRg), chez l’enfant.

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† Dr. Marie Lambert passed away on February 20, 2012. She will be remembered for her leadership and devotion to the QUALITY cohort.
Méthodes. – Vingt enfants, moyenne d’âge (DS) : 9 (2) ans, ont été étudiés : neuf garçons et 11 filles. Ils présentaient un Z-score moyen pour l’IMC de 1,5 (DS = 0,8). La glycémie à jeun et la glycémie deux heures après HGPO étaient normales chez tous les sujets. Chaque enfant a réalisé une hyperglycémie provoquée par voie intraveineuse (HGPIV) (métode de référence), et une HGPO sur trois heures. L’AIRg a été calculé à partir de l’HGPIV et comparé à dix indices dérivés de l’HGPO et à deux indices dérivés des échantillons à jeun : HOMA%beta (formule originale) et HOMA2%beta (formule informatique). Les corrélations ont été évaluées par le test de corrélation de Spearman.

Résultats. – Des dix indices dérivés de l’HGPO, les trois qui présentaient les meilleures corrélation avec l’AIRg (dérivée de l’HGPIV) étaient : l’indice insulinogénique t30 min ($r = 0,80$), le ratio insuline/glucose t30 min ($r = 0,71$) et le ratio de l’aire sous la courbe d’insuline/glucose t0–30 min ($r = 0,74$). Pour les formules à jeun, le HOMA%beta et HOMA2%beta étaient en corrélation modeste avec l’AIRg ($r = 0,62$ et 0,65, respectivement).

Conclusion. – Nos résultats suggèrent que les indices dérivés de l’HGPO fournissent une estimation adéquate de la sécrétion d’insuline chez l’enfant. Le HOMA2%beta et le HOMA%beta représentent un compromis acceptable. HOMA2%beta est peut-être préférable, car il permet l’utilisation d’un plus large spectre d’insulinémie et de glycémie physiologiques chez l’enfant.

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Mots clés : Sécrétion d’insuline ; HGPO ; HGPIV ; Enfant ; HOMA%B

1. Introduction

Maintaining a normal blood glucose level is the result of a delicate balance between insulin secretion by the pancreatic beta cells and peripheral tissue responsiveness — referred to as ‘sensitivity’ — to insulin action [1]. When this system becomes dysregulated, abnormal glucose homeostasis sets in, leading to impaired fasting glucose (IFG), impaired glucose tolerance (IGT) and, eventually, type-2 diabetes mellitus (DM2). Pancreatic beta cells need to maintain serum glucose levels within a narrow physiological range while accounting for hepatic glucose production and ambient insulin sensitivity. In addition, the beta cells must adapt to the highly variable input of meals in terms of timing, quantity and composition, as well as their rate of ingestion. Several hormones (such as gut peptides and incretins) also influence insulin secretion [2]. Thus, it is not surprising that, given the complexity of the physiological processes at hand, measuring insulin secretion in vivo has proven to be a challenge.

Recent evidence suggests that impairment of beta-cell response to chronic fuel excess may be the initial mechanism leading to insulin resistance and eventual DM2 [3]. Given the importance of impaired insulin secretion in the pathogenesis or, perhaps more specifically, the initiation of DM2, simple methods for its measurement are required for both large population-based studies and clinical practice. Several methods for quantifying insulin secretion using intravenous administration of glucose have been proposed. The current gold-standard method for measuring insulin secretion is the hyperglycaemic clamp [4]. The most commonly used method, the modified minimal model frequently sampled intravenous glucose tolerance test (FSIVGTT), uses a computer-based mathematical model to measure insulin secretion after a bolus injection of intravenous glucose, followed 20 min later by a bolus intravenous dose of either insulin or tolbutamide [4,5]. The FSIVGTT is an invasive time- and labour-intensive approach and, therefore, has limited clinical applicability, and is also not suitable for epidemiological studies. For this reason, surrogate measures of insulin secretion derived from both fasting blood samples and the oral glucose tolerance test (OGTT) have been developed, and appear to be well correlated with estimations derived from clamp studies in adults [6,7].

Little work, however, has been done to evaluate the performance of these surrogate measures in youth.

Thus, the objective of the present study was to examine the agreement between the acute insulin response to glucose (AIRg) with both fasting-based and OGTT-derived indices of insulin secretion in children.

2. Methods

2.1. Study population

Subjects were recruited as a convenience sample if they were 6–18 years of age and of normal weight, but also if they were overweight or obese. Those known to be pregnant, or to have a chronic illness or diabetes were excluded from the study. Written informed consent was obtained from both the participants and their parents. This study received ethics approval from the CHU Sainte-Justine Ethics Review Board.

Each subject had a baseline physical examination that included measurements of height, weight and blood pressure. Body mass index (BMI) was computed as weight in kg divided by height in m². BMI percentiles and Z scores were calculated using the 2000 US Centers for Disease Control and Prevention (CDC) growth-chart reference values [8]. Pubertal stage was scored according to Tanner stages [9,10]. Each participant also underwent an insulin-modified minimal model FSIVGTT and 3-h OGTT within a period of six to eight weeks. The order in which each child underwent these evaluations was determined using block randomization. The FSIVGTT was carried out at the Hotel-Dieu Hospital Research Center, while the OGTT took place at the CHU Sainte-Justine. All tests were done after an overnight fast. EMLA cream (AstraZeneca Pharmaceuticals LP, Wilmington, DE, USA), a topical anaesthetic, was applied 60 minutes prior to all venous access.

2.2. Insulin-modified FSIVGTT

Two flexible indwelling intravenous catheters were inserted into both antecubital veins. The first catheter served to administer intravenous glucose and later insulin, while the second was used for blood sampling. Catheter patency was ensured using
a slow infusion of 0.9% saline. Two samples of fasting insulin and glucose were obtained at –20 minutes and –10 minutes of the test. At time 0 minute, 11.4 g/m² of glucose were injected as 50% dextrose over 60–90 seconds. Twenty minutes later, 1.6 U/m² of insulin (Humulin Regular, Eli Lilly, Indianapolis, IN, USA) were injected over 60–90 seconds [11,12]. Saline flushes were used to ensure adequate delivery of both glucose and insulin injections. Blood samples (3 mL) were collected in tubes containing EDTA at 2, 4, 8, 19, 22, 23, 25, 30, 40, 50, 70, 90, 120, 180 and 240 minutes after the administration of glucose. Samples were immediately centrifuged and frozen for later analysis.

2.3. OGTT

A flexible indwelling intravenous catheter was inserted into one antecubital vein for sampling. Catheter patency was maintained with a slow infusion of 0.9% saline. Two samples of fasting insulin and glucose were obtained at –20 minutes and –10 minutes of the test. At time 0 minute, the subject received 1.75 g/kg of glucose (maximum 75 g) ingested over five minutes. Blood samples (5 mL) were collected in tubes containing EDTA at 30, 60, 90, 120 and 180 minutes after the administration of glucose. Samples were immediately centrifuged and frozen for later analysis.

2.4. Biochemical analyses

Blood samples were analyzed as a batch at the CHU Sainte-Justine clinical biochemistry laboratory. Plasma insulin was measured with the ultrasensitive Access® Immunoassay System (Beckman Coulter Inc., Brea, CA, USA), which has no cross-reactivity with proinsulin or C-peptide [13]. Plasma glucose concentrations were determined with the Beckman Coulter Synchron CX7 Delta analyzer using the glucose-oxidase method.

2.5. Calculations

The AIRg, which measures first-phase insulin secretion, was computed from the FSIVGTT using the MINMOD computer program (Millennium version 6.02, Richard N. Bergman, 2004) [12,14]. This served as the reference measure of insulin secretion in the study.

Ten indices of insulin secretion were derived from the OGTT; their calculation is described in Table 1. Fasting indices, including both the original-formula homoeostatic model assessment for beta-cell function (HOMA%beta) and the computer-based version (HOMA2%beta), were calculated based on the averages of two fasting-glucose and two fasting-insulin values from samples drawn at the onset of the OGTT. The HOMA%beta (original model) score was calculated according to the formula in Table 1, while the HOMA2%beta was calculated using the HOMA2 calculator v2.2, available online at http://www.dtu.ox.ac.uk/homa. With the exception of the HOMA%beta, all other indices were calculated using SI units. The HOMA%beta used metric values for fasting insulin (μU/mL) while fasting glucose was expressed in mmol/L.

2.6. Statistical analyses

Correlations were established using Spearman’s rank correlations. All analyses were performed using SAS 9.2 (SAS Institute Inc., Cary, NC, USA). The difference in correlations was tested using the formula $t = (r_{xy} - r_{xz}) * \sqrt{(n-3) * (1 + r_{xy} * r_{xz})/2} \sqrt{(1 - (r_{xy})^2 - (r_{xz})^2 - (r_{yz})^2 + 2 * r_{xy} * r_{xz} * r_{yz})}$, described by Dawson and Trapp [15]. Significance was accepted at $P < 0.05$. Bland-Altman plots were used to examine the magnitude of the differences between indices across the range of values after standardization of each measure for consistency in units.

3. Results

Twenty healthy children were recruited into the present study, and their baseline characteristics are presented in Table 2. By design, no participant had abnormal glucose metabolism. All pubertal stages were represented in this sample. The median value of AIRg was 268.6 (range: 104.1–1489.0). The median and range of all fasting-based and OGTT-derived indices of insulin secretion are shown in Table 1.

### Table 1

<table>
<thead>
<tr>
<th>Index</th>
<th>Formula</th>
<th>Median</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fasting-based indices</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HOMA%beta [21]</td>
<td>$20 \times I_0/G_0-3.5$</td>
<td>82.1</td>
<td>25.0–180.3</td>
</tr>
<tr>
<td>HOMA2%beta [22]</td>
<td>Computer model</td>
<td>90.2</td>
<td>40.0–148.0</td>
</tr>
<tr>
<td><strong>OGTT-derived indices</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin/glucose ratio</td>
<td>$I_{30}/G_{30}$</td>
<td>43.8</td>
<td>22.0–169.6</td>
</tr>
<tr>
<td>Insulin/glucose ratio</td>
<td>$I_{120}/G_{120}$</td>
<td>36.9</td>
<td>14.8–69.7</td>
</tr>
<tr>
<td>Insulin ratio</td>
<td>$I_0/I_0$</td>
<td>9.3</td>
<td>2.8–17.3</td>
</tr>
<tr>
<td>Insulin ratio</td>
<td>$I_{20}/I_0$</td>
<td>4.5</td>
<td>1.7–9.8</td>
</tr>
<tr>
<td>Insulinogenic index</td>
<td>$(100 - I_{30} - I_0)/(G_{30} - G_0)$</td>
<td>157.2</td>
<td>50.1–1561.5</td>
</tr>
<tr>
<td>Insulinogenic index</td>
<td>$(120 - I_{30} - I_0)/(G_{120} - G_0)$</td>
<td>150.5</td>
<td>–1109.2–972.1</td>
</tr>
<tr>
<td>CIR 120 [29]</td>
<td>$100 \times I_{30}/G_{30} \times (G_{30} - 3.89)$</td>
<td>141.2</td>
<td>76.5–506.1</td>
</tr>
<tr>
<td>CIR 20 [29]</td>
<td>$100 \times I_{20}/G_{120} \times (G_{120} - 3.89)$</td>
<td>66.6</td>
<td>7.7–204.4</td>
</tr>
<tr>
<td>AUC I/G 30 [17]</td>
<td>$(I_0 + I_{30})/(G_0 + G_{30})$</td>
<td>29.9</td>
<td>14.7–96.7</td>
</tr>
<tr>
<td>AUC I/G 120 [17]</td>
<td>$[(0.5 \times I_0) + I_{120} + (0.5 \times I_{120})] / [(0.5 \times G_0) + G_{60} + (0.5 \times G_{120})]$</td>
<td>36.3</td>
<td>14.1–92.7</td>
</tr>
</tbody>
</table>

I: insulin; G: plasma glucose; CIR: corrected insulin response; AUC: area under the curve
Spearman’s rank correlation coefficient and 95% confidence interval (CI) for both fasting-based and OGTT-derived measures of insulin secretion against the AIRg are presented in Table 3. HOMA%beta (original model) and HOMA2%beta (computer-based model) scores were both similarly and modestly correlated with the AIRg. Of the OGTT-derived indices, three showed more robust correlations with the AIRg: the insulin/glucose ratio\(_{30}\) min, the insulinogenic index\(_{30}\) min and the area under the curve (AUC) for insulin/glucose\(_{30}\) min. Correlations between the HOMA2%beta, the insulin/glucose ratio\(_{30}\) min and the insulinogenic index\(_{30}\) min, as well as the AUC insulin/glucose\(_{30}\) min, with the AIRg are illustrated in Fig. 1. Also observed were negative correlations between both the insulin ratio\(_{120}\) min (\(r = -0.36\)) and the insulinogenic index\(_{120}\) min (\(r = -0.02\)) with AIRg, although neither correlation was statistically significant.

The difference between each pair of correlations was also tested to determine whether some indices were more strongly correlated with the AIRg than others (Table S1; see supplementary material associated with this article online). While the HOMA%beta, HOMA2%beta, insulinogenic index\(_{30}\) min, insulin/glucose ratio\(_{30}\) min and AUC insulin/glucose\(_{30}\) min all performed similarly against the AIRg, the insulinogenic index\(_{30}\) min consistently outperformed the insulin/glucose ratio\(_{120}\) min, insulin ratio\(_{30}\) min, insulin ratio\(_{120}\) min and corrected insulin response (CIR)\(_{120}\) min, as well as the AUC insulin/glucose\(_{30}\) min and AUC insulin/glucose\(_{120}\) min.

In general, the results of the Bland-Altman plotting of the insulinogenic index\(_{30}\) min and AIRg revealed that the magnitude of the differences between both indices were consistent and close to the line of identity across most values, with less agreement for the more extreme values (Fig. 2). Findings were similar for the AUC insulin/glucose\(_{30}\) min and the insulin/glucose ratio\(_{30}\) min (data not shown).

4. Discussion

In this sample of healthy young people, the OGTT-derived indices of insulin secretion that showed the best correlation to the AIRg were the insulin/glucose ratio\(_{30}\) min (\(r = 0.71\)), the insulinogenic index\(_{30}\) min (\(r = 0.80\)) and the AUC insulin/glucose\(_{30}\) min (\(r = 0.74\)). Predictably, indices derived from the OGTT using data from the first 30 min of the test correlated better with the AIRg than those using data from the full 120 min. This is in keeping with the fact that the AIRg estimates first-phase insulin secretion. Furthermore, when examining fasting-based indices of insulin secretion, the HOMA%beta (\(r = 0.62\)) and HOMA2%beta (\(r = 0.65\)) performed similarly, with modest correlations with the AIRg.

Only one paediatric study, by Bacha et al. [16], has evaluated how OGTT-derived measures of beta-cell function performed against the hyperglycaemic clamp in a group of 26 prepubertal children, aged 7–12 years. Specifically, they assessed the correlation between the ratio of the early incremental insulin/glucose responses at both 15 minutes and 30 min (\(\Delta I_{15}/\Delta G_{15}\) and \(\Delta I_{30}/\Delta G_{30}\)), and found that the insulinogenic index\(_{30}\) min (\(\Delta I_{30}/\Delta G_{30}\)) had a modest correlation with first-phase insulin secretion (\(r = 0.56\)) [16]. However, this was not in keeping with either the present study findings or with Herzberg-Schäfer et al. [17], who found a more robust correlation between the insulinogenic index\(_{30}\) min and the AIRg (\(r = 0.72\)) in adults. The differences in methodology (FSIVGTT vs the clamp; Pearson’s correlation versus Spearman’s correlation coefficient) as well as the different populations (Bacha et al. studied exclusively prepubertal children) may well account for the difference in correlations.

The present study examined a broader range of OGTT-derived indices of insulin secretion such as previously studied in adults, but never in younger subjects. Our present finding that the AUC insulin/glucose\(_{30}\) min was strongly correlated with the AIRg was in keeping with Herzberg-Schäfer et al. [17], who found that this index was the best-ranked index for assessing genetically determined beta-cell function in adults. Hanson et al. [18] examined how the insulin/glucose ratio\(_{30}\) min performed against the AIRg in Pima Indians (mean age: 31 years; standard deviation: 12 years), and found a slightly less robust, yet statistically significant, correlation in the subset of subjects with normal glucose tolerance (\(r = 0.49\)).
The correlations observed in the present study between fasting-based indices of insulin secretion and the AIRg are consistent with previously published data. Indeed, Conwell et al. [5] examined the correlation between fasting-based indices of insulin secretion and the AIRg (minimal model) derived from the FSIVGTT in 18 obese Caucasian youths aged 8–18 years. They found a modest correlation between the HOMA%beta and the AIRg ($r = 0.60$), similar to that of the present study. Uwaifo and colleagues [19] examined the correlation between fasting-based indices of beta-cell function and measures of first-phase and steady-phase insulin secretion derived from the hyperglycaemic clamp in 31 healthy children, 6–12 years of age, but did not evaluate OGTT-derived indices. When compared with clamp-derived first-phase insulin secretion, the authors found that the ratio of fasting insulin to fasting glucose (Spearman’s rank $r = 0.86$) and fasting insulin ($r = 0.85$) were more robust measures of insulin secretion than the HOMA%beta ($r = 0.69$). Similarly, on comparing clamp-derived steady-phase insulin secretion, the ratio of fasting insulin to fasting glucose ($r = 0.80$) and fasting insulin ($r = 0.79$) slightly outperformed the HOMA%beta ($r = 0.72$) [19]. Gungor et al. [20] compared pancreatic beta-cell function using the hyperglycaemic clamp with simple fasting-based estimates of insulin secretion in a group of 156 children and adolescents. The authors noted strong correlations between fasting insulin, ratio of fasting insulin to fasting glucose and HOMA%beta to both first-phase insulin secretion...
Our study demonstrates that HOMA2%beta performs as well as HOMA%beta (original model) in estimating insulin secretion, of insulin and glucose values in children and adults extends well below this cut-off point. Similarily, the CIR requires a minimum glucose<sub>30 min</sub> of 3.89 mmol/L. Herzberg-Schäfer et al. [17] excluded 17 subjects (out of 1364) because of negative values in one or more insulin secretion indices, but failed to discuss the implication of these exclusions. Likewise, the lower limit of glucose values in the Uwaifo et al. study [19] was 2.9 mmol/L. Consequently, the calculation of HOMA%beta was impossible for some otherwise healthy children in that study. The limitation of using the HOMA%beta in young people, in whom values of insulin and glucose may be in the lower range of the spectrum for otherwise healthy children, has yet to be addressed in the literature.

The HOMA2%beta formula was developed to estimate insulin secretion across a broader range of insulin and glucose values than the HOMA%beta [22]. Despite this, surprisingly, no study in young people could be found examining the correlation of HOMA2%beta with an intravenous glucose test. Our study demonstrates that HOMA2%beta performs as well as HOMA%beta (original model) in estimating insulin secretion, and we therefore suggest HOMA2%beta be the preferred surrogate estimate of insulin secretion in children, given its ability to estimate insulin secretion using the physiological spectrum of insulin and glucose values in this population.

While the present study found no out-of-bound values for fasting-based indices of insulin secretion, these limitations were encountered with the OGTT-derived indices. Negative values were observed for the insulinogetic index<sub>120 min</sub> in 5/20 (25%) of our participants. These negative values were attributable to lower glucose values at time<sub>120</sub> vs time<sub>0</sub> (in other words, a negative delta glucose). All subjects had higher insulin levels at time<sub>120</sub> than at time<sub>0</sub>. The possibility of obtaining negative values for the insulinogetic index has previously been reported in adults: Faulenbach et al. [24] examined the rates of negative insulinogetic indices<sub>30 min</sub> across three large cohorts (the San Antonio Heart Study, the Japanese-American Community Diabetes Study and the Genetics of NIDDM), and reported that 1.6% of adults with normal glucose tolerance had a negative insulinogetic index<sub>30 min</sub>. Those negative values, as in the present study, resulted from the paradoxical glucose decrement in subjects with normal glucose tolerance [24]. Interestingly, Faulenbach et al. also reported that negative values in diabetic adults were the result of insulin rather than glucose decrements, a finding that was confirmed in adult cystic-fibrosis patients [25]. The physiological foundation and clinical significance of these negative indices, however, remains uncertain [24]. For this reason, we suggest that selecting the insulin/glucose ratio<sub>30 min</sub> or the AUC insulin/glucose<sub>30 min</sub> as measures of insulin secretion may be preferable in young subjects, as such measures will avoid problematic and otherwise non-interpretable negative values.

The small sample size of the present study, although comparable to other studies involving a paediatric population, remains a limitation: correlation coefficients are more susceptible to outliers in smaller samples. For this reason, Spearman’s rank correlations were used to obviate the problem by examining correlations in rank. Also, it was not possible to test the effect of gender, ethnicity and stage of sexual maturity on correlations between indices due to the limited sample size. Furthermore, our small sample size may have limited our ability to detect all significant differences between pairs of correlations. Our present results are also restricted to youth with normal glucose metabolism and, thus, may not apply to those with abnormal glucose tolerance or DM2. Indeed, in adults, there is some controversy regarding the preferred method of measuring insulin secretion in patients with DM2 [26]. Finally, the current gold-standard approach for measuring insulin secretion is the hyperglycemic clamp [4], which was not used in the present study. Nonetheless, the first-phase insulin secretion measured by FSIIVGTT has been validated against the clamp [27,28], and is widely used in the literature as a reference method for estimating insulin secretion [2,4].

In conclusion, our results suggest that the insulin/glucose ratio<sub>30 min</sub>, the AUC insulin/glucose<sub>30 min</sub> and the insulinogetic index<sub>30 min</sub> derived from the OGTT are robust estimates of first-phase insulin secretion in young subjects, with the first two indices having the added advantage of not generating negative values, the significance of which remains uncertain. The HOMA2%beta and HOMA%beta scores represent an acceptable compromise. However, given the limited performance at the lower physiological ranges of insulin and glucose of the original HOMA method, the HOMA2%beta model may be preferable in youth, as it allows the use of a wider spectrum of insulin and glucose values that are physiological in this age group.
Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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Appendix A. Supplementary data

Supplementary material (Table S1) associated with this article can be found at http://www.sciencedirect.com, at doi:10.1016/j.diabet.2012.02.002.

References