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%β (original formula) and HOMA2%β (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 index at 30 min (r = 0.80), insulin/glucose ratio at 30 min (r = 0.71) and ratio of the area under the curve for insulin to glucose at 0-30 min (r = 0.74). Both the HOMA%β and HOMA2%β 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%β and HOMA%β represent acceptable compromises, although HOMA2%β 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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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 Synchrone 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 homoestatic 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 $t = (r_{xy} - r_{xz}) * \sqrt{(n-3) * (1 + r_{yz})/2 \left[1 - (r_{xy})^2 - (r_{xz})^2 - (r_{yz})^2 + 2 * r_{xy} * r_{xz} * r_{yz}\right]}$, 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>$20 * I_0/G_0 - 3.5$</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$_{30}$ [6,7]</td>
<td>$I_{30}/G_{30}$</td>
<td>43.8</td>
<td>22.0–169.6</td>
</tr>
<tr>
<td>Insulin/glucose ratio$_{120}$ [6,7]</td>
<td>$I_{120}/G_{120}$</td>
<td>36.9</td>
<td>14.8–69.7</td>
</tr>
<tr>
<td>Insulin ratio$_{30}$ [18]</td>
<td>$I_{30}/G_{0}$</td>
<td>9.3</td>
<td>2.8–17.3</td>
</tr>
<tr>
<td>Insulin ratio$_{120}$ [18]</td>
<td>$I_{120}/G_{0}$</td>
<td>4.5</td>
<td>1.7–9.8</td>
</tr>
<tr>
<td>Insulinogenic index$_{30}$ [6,7]</td>
<td>$(I_{30} - I_{0})/(G_{30} - G_{0})$</td>
<td>157.2</td>
<td>50.1–1561.5</td>
</tr>
<tr>
<td>Insulinogenic index$_{120}$ [6,7]</td>
<td>$(I_{120} - I_{0})/(G_{120} - G_{0})$</td>
<td>150.5</td>
<td>–1109.2–972.1</td>
</tr>
<tr>
<td>CIR$_{30}$ [29]</td>
<td>$100 * I_{30}/G_{30} * (G_{30} - 3.89)$</td>
<td>141.2</td>
<td>76.5–506.1</td>
</tr>
<tr>
<td>CIR$_{120}$ [29]</td>
<td>$100 * I_{120}/G_{120} * (G_{120} - 3.89)$</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>$[(0.5 * I_0) + I_{120} + (0.5 * I_{120})] ÷ [(0.5 * G_0) + G_{120} + (0.5 * G_{120})]$</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\(_{120}\ min\), the insulin/glucose ratio\(_{30}\ min\), and the insulin/glucose ratio\(_{120}\ min\) and AUC insulin/glucose \(_{30}\ min\) (data not shown).

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 insulinoergic 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 minutes (\(\Delta I_{15/\Delta G_{15}}\) and \(\Delta I_{30/\Delta G_{30}}\)), and found that the insulinoergic index\(_{30}\ min\) (\(\Delta I_{10/\Delta G_{30}}\)) 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 insulinoergic 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 (\(r = 0.49\)).

### Table 3

<table>
<thead>
<tr>
<th>Index</th>
<th>Reference method: AIRg</th>
<th>Spearman’s rank (r)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fasting-based indices</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HOMA%beta</td>
<td>0.62*</td>
<td>0.24, 0.83</td>
<td></td>
</tr>
<tr>
<td>HOMA2%beta</td>
<td>0.65*</td>
<td>0.28, 0.84</td>
<td></td>
</tr>
<tr>
<td><strong>OGTT-derived indices</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin/glucose ratio(_{30}\ min)</td>
<td>0.71*</td>
<td>0.35, 0.87</td>
<td></td>
</tr>
<tr>
<td>Insulin/glucose ratio(_{120}\ min)</td>
<td>0.40</td>
<td>–0.06, 0.71</td>
<td></td>
</tr>
<tr>
<td>Insulin ratio(_{30}\ min)</td>
<td>0.08</td>
<td>–0.39, 0.51</td>
<td></td>
</tr>
<tr>
<td>Insulin ratio(_{120}\ min)</td>
<td>–0.36</td>
<td>–0.69, 0.10</td>
<td></td>
</tr>
<tr>
<td>Insulinoergic index(_{30}\ min)</td>
<td>0.80*</td>
<td>0.53, 0.92</td>
<td></td>
</tr>
<tr>
<td>Insulinoergic index(_{120}\ min)</td>
<td>–0.02</td>
<td>–0.46, 0.42</td>
<td></td>
</tr>
<tr>
<td>CIR(_{30})</td>
<td>0.49*</td>
<td>0.04, 0.77</td>
<td></td>
</tr>
<tr>
<td>CIR(_{120}\ min)</td>
<td>0.42</td>
<td>–0.33, 0.54</td>
<td></td>
</tr>
<tr>
<td>AUC I/G(_{30}\ min)</td>
<td>0.74*</td>
<td>0.41, 0.89</td>
<td></td>
</tr>
<tr>
<td>AUC I/G(_{120}\ min)</td>
<td>0.42</td>
<td>–0.03, 0.72</td>
<td></td>
</tr>
</tbody>
</table>

CIR: corrected insulin response; AUC: area under the curve.

\(*P\) value <0.05;
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.
We therefore suggest HOMA2%beta be the preferred index for insulin secretion in children, as it allows the use of a wider spectrum of glucose values in children and adults that are physiological in this age group. In conclusion, our results suggest that the insulin/glucose ratio at 30 min or the AUC insulin/glucose at 30 min 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 FSIVGTT 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 at 30 min, the AUC insulin/glucose at 30 min and the insulinogenic index at 30 min 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