Abstract

Aim. – The objective of the study was to examine the correlation between three methods of measuring insulin sensitivity (IS) – namely, the frequently sampled intravenous glucose tolerance test (FSIVGTT), indices derived from the oral glucose tolerance test (OGTT) and fasting indices (HOMA-IR, QUICKI, fasting insulin [INS0]) – and the gold-standard method, the hyperinsulinaemic–euglycaemic clamp (HEC) test, in children.

Methods. – A total of 20 children [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 glucose metabolism. Each child underwent a 3-h HEC (40 mU/m²/min of insulin), an insulin-modified minimal-model FSIVGTT and a 3-h OGTT. The clamp-derived IS was calculated, using DeFronzo’s metabolized glucose index and Bergman’s IS index. Correlations were established using Spearman’s rank correlations.

Results. – The two clamp-derived measures were highly correlated (r = 0.85), and the IS measured from the FSIVGTT was well correlated with both clamp measures [r = 0.69, 0.74]. Of the nine indices derived from the OGTT, the three with the highest correlation with clamp results were the ISI Matsuda [r = 0.63, 0.68], SIisOGTT [r = 0.53, 0.65] and log sum insulin [r = −0.64, −0.75]. Fasting indices of IS had similar correlations to clamp results: HOMA-IR [r = −0.55, −0.56]; QUICKI [r = 0.55, 0.57]; and INS0 [r = −0.59, −0.63].

Conclusion. – While fasting-based indices of IS are a suitable option for large cohorts, OGTT-derived indices may represent a useful compromise for obtaining both clinical (glucose tolerance) and physiological (insulin sensitivity) information, making them particularly useful for large-scale physiological and epidemiological studies.

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Keywords: Insulin sensitivity; Euglycaemic clamp; FSIVGTT; Oral glucose tolerance test; Child

Résumé

Comparaison entre différents indices permettant d’estimer la sensibilité à l’insuline chez l’enfant et la méthode de référence du clamp hyperinsulinémique euglycémique.

Abbreviations: CVD, Cardiovascular Disease; HEC, Hyperinsulinaemic–Euglycaemic Clamp; FIGR, Fasting Insulin-To-Glucose Ratio; FSIVGTT, Frequently Sampled Intravenous Glucose Tolerance Test; OGTT, Oral Glucose Tolerance Test; IS, Insulin Sensitivity; HOMA, Homoeostasis Model Assessment; QUICKI, Quantitative Insulin-Sensitivity Check Index; BMI, Body Mass Index; M, Metabolized Glucose.

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But. – Étudier chez l’enfant les corrélations entre trois approches différentes de la mesure de la sensibilité à l’insuline (SI) et la méthode de référence du clamp hyperinsulinémique euglycémique (CHE). Les méthodes évaluées ont été : l’hyperglycémie provoquée par voie intraveineuse (HGPIV), les indices dérivés de l’hyperglycémie provoquée par voie orale (HGPO) et les indices à jeun (HOMA-IR, QUICKI et insulinémie à jeun [INS0]).

Méthodes. – Vingt enfants (neuf garçons et 11 filles), âgés en moyenne de 9 ± 2 ans, tous normotolérants au glucose et présentant une cote Z moyenne pour l’IMC de 1,5 ± 0,8 ont été inclus dans l’étude. Un CHE (40 mU/m²/min d’insuline), une HGPIV et une HGPO, d’une durée de trois heures chacune, ont été réalisés. La SI a été mesurée au cours du CHE selon les indices de DeFronzo et de Bergman. Les corrélations ont été estimées par le test de corrélation de Spearman.

Résultats. – Les deux mesures de SI dérivées du CHE étaient en corrélation étroite (r = 0,85). La SI estimée par HGPIV présentait des corrélations de 0,69 et 0,74 avec les deux mesures du clamp. Des neuf indices dérivés de l’HGPO, les trois qui montraient les meilleures corrélations avec les mesures du clamp étaient : ISI Matsuda (r = 0,63, 0,68), SIisOGTT (r = 0,53, 0,65) et Log sum insulin (r = −0,64, −0,75). Des corrélations similaires avec le CHE ont été trouvées pour les indices à jeun : HOMA-IR (r = −0,055, −0,56), QUICKI (r = 0,55, 0,57), et INS0 (r = −0,59, −0,63).

Conclusions. – Bien que les indices à jeun estimant la SI soient un choix approprié pour les grandes cohortes, les indices dérivés de l’HGPO représentent une option intéressante puisqu’ils apportent des informations cliniques (degré de tolérance au glucose) ainsi que physiologiques (SI).

Mots clés : Sensibilité à l’insuline ; Clamp hyperinsulinémique euglycémique ; HGPIV ; HGPO ; Enfant

1. Introduction

Insulin resistance is the central component of several conditions that are now seen more frequently in young people, including obesity, polycystic ovarian syndrome and diabetes [1,2]. Furthermore, the results of several large population-based studies suggest that the clustering of CVD risk factors is highest in children and adolescents with the highest degree of insulin resistance [3–5], making this group most at risk for developing CVD, type 2 diabetes, and premature mortality. These findings provide a rationale for the measurement of IS in youth to identify this high-risk group, to ascertain its associated features and to evaluate interventions aimed at decreasing insulin resistance.

The measurement of IS remains a challenge. The current gold-standard test, the HEC, involves a constant-rate insulin infusion with concomitant, variable glucose infusion to maintain euglycaemia. The HEC is an invasive time- and labour-intensive approach that is not suitable for epidemiological and diagnostic studies [6]. The modified minimal-model FSIVGTT uses a computer-based mathematical model to measure IS after bolus injection of intravenous glucose, followed 20-min later by a bolus intravenous dose of either insulin or tolbutamide [7]. This method, while validated in young people [8], has the same limitations as the HEC in terms of feasibility for epidemiological and clinical purposes. Surrogate measures of IS derived from the OGTT have also been developed, and appear to be well correlated with estimations derived from clamp studies in adults [9–17]. Little work, however, has so far been done to evaluate the performance of these surrogate measures in youth. Surrogate estimates of IS from fasting values of glucose and insulin have been developed, and are well validated in adult populations [18,19]. These fasting indices are more readily acceptable to the patient, more cost-effective and easier to use, however validation studies of such surrogate measures in children remain scarce [7,20].

The objective of the present study was to examine the degree to which three different approaches to measuring IS correlate with the gold-standard HEC in healthy children—namely, the FSIVGTT, indices derived from the OGTT and selected fasting indices (HOMA, QUICKI and fasting insulin). To our knowledge, this is the first study to examine the criterion validity of each of these three methods against the gold-standard HEC in a healthy paediatric population.

2. Design and methods

2.1. Study population

Children between 6 and 18 years of age, with heights and weights between the 5th and 95th percentiles for age and gender (thus, including normal weight and overweight/obese youth), were eligible for the present study. Children who were known to be pregnant, to have a chronic illness or to have diabetes were excluded. Participants were recruited as a convenience sample. Written informed consent was obtained from all participants and their parents. The study also received ethical approval from the Sainte-Justine Hospital Ethics Review Board.

Each child had a baseline physical examination that included measurements of height, weight and blood pressure. BMI was computed as weight in kg divided by height in m². BMI percentiles and Z scores were calculated according to the US CDC growth-chart reference values of 2000 [21]. Stage of sexual maturity was scored according to Tanner stages [22,23]. Each child underwent a 3-h HEC, an insulin-modified minimal-model FSIVGTT and a 3-h OGTT within a period of six to eight weeks. The order in which each child underwent these evaluations was determined by block randomization. HEC and FSIVGTT were carried out at the Hotel-Dieu Hospital Research Centre, while all other procedures and measurements were done at the Sainte-Justine Hospital. All tests were carried out after an overnight fast. EMLA cream (AstraZeneca, Mississauga, ON, Canada), a topical anaesthetic, was applied 60 min prior to all venous access.
2.2. Hyperinsulinaemic–euglycaemic clamp test

Two flexible indwelling intravenous catheters were inserted: the first, in the antecubital vein, was used for intravenous administration of glucose (20% dextrose), and comprised labeled glucose and insulin; the second, inserted in a retrograde fashion in the dorsum of the contralateral hand, was used for blood sampling. The hand was kept in a heated box at 60°C for sampling ‘arterialized’ blood. Catheters were kept patent with a slow infusion of 0.9% saline. Three samples of fasting insulin and glucose were obtained at times −30, −20 and −10 min. At time 0 min, loading doses of insulin (Humulin Regular, Eli Lilly, Toronto, ON, Canada), at 7 mU/kg of body weight, and D [6,6-2H2]-glucose (200 mg) were administered, followed by a constant insulin (40 mU/m2/min) and D2-glucose infusion (2 mg/min). D2-glucose was infused to determine the rate of glucose appearance (Ra), which allows correction of the glucose infusion rate in case of incomplete hepatic glucose-production inhibition during the hyperinsulinaemia plateau. A glucose infusion as a 20% dextrose solution was initially set at 2 mg/kg/min, then adjusted (by increments of 0.5–2 mg/kg/min every 5–10 min) to maintain euglycaemia based on glucose values, measured by a glucose analyzer (Beckman Instruments, Fullerton, CA, USA). Euglycaemia was defined as the average of three baseline measures of glucose at times −30, −20 and −10 min, plus or minus 10%. If the average baseline glucose value was less than 4 mmol/L, glucose was ‘clamped’ at 4 mmol/L during the procedure; if the average baseline glucose value was greater than 5 mmol/L, glucose was clamped at 5 mmol/L. Additional blood samples were drawn at times −30, −10, 150, 160, 170 and 180 min, then rapidly centrifuged and frozen at −80°C for later analysis.

2.3. Insulin-modified FSIVGTT

Two flexible indwelling intravenous catheters were inserted into both antecubital veins. The first catheter was used for intravenous administration of glucose and, later, insulin, while the second was used for blood sampling. Catheters were kept patent with a slow infusion of 0.9% saline. Two samples of fasting insulin and glucose were obtained at times −20 and −10 min. At time 0 min, glucose at 11.4 g/m2 was injected as 50% dextrose over 60–90 s. Twenty minutes later, insulin (Humulin Regular, Eli Lilly) at 1.6 units/m2 was injected over 60–90 s [24,25]. Saline flushes were used to ensure adequate delivery of both glucose and insulin injections. Blood samples (3 mL) were collected in EDTA-containing tubes at times 2, 4, 8, 19, 22, 23, 25, 30, 40, 50, 70, 90, 120, 180 and 240 min after the administration of glucose. Samples were rapidly centrifuged and frozen for later analysis.

2.4. Oral glucose tolerance test (OGTT)

A flexible indwelling intravenous catheter was inserted into the antecubital vein for blood sampling. The catheter was kept patent with a slow infusion of 0.9% saline. Two samples of fasting insulin and glucose were obtained at times −20 and −10 min. At time 0 min, the participant received 1.75 g/kg of glucose (maximum 75 g), which was delivered over 5 min. Blood samples (5 mL) were collected in EDTA-containing tubes at times 30, 60, 90, 120 and 180 min after the administration of glucose. Samples were rapidly centrifuged and frozen for later analysis.

2.5. Biochemical analyses

Every 10 min during the clamp test, plasma glucose was determined on site at the Hotel-Dieu Research Centre using a glucose analyzer (Beckman Instruments). All other blood samples were analyzed in batches at the Sainte-Justine Hospital clinical biochemistry laboratory. Plasma insulin was measured with the ultrasensitive Access™ immunoassay system (Beckman Coulter, Brea, CA, USA), which has no cross-reactivity with either proinsulin or C-peptide [26]. Plasma glucose concentrations were determined, using the Beckman Coulter CX-7 analyzer and the glucose-oxidase method.

2.6. Insulin-sensitivity measurements derived from the clamp

Two formulas were used to estimate IS from the clamp results. The first was that described by DeFronzo in 1979 [6]. M was calculated for 20-min study intervals according to his formula (Table S1; supplementary material associated with this article online). Total M was calculated as the mean of each of the last five 20-min periods of the study [6]. The second index of IS from the clamp is also widely used [16,27], and is slightly easier to calculate (Table S1; supplementary material associated with this article online) [24].

The rates of total glucose appearance (Ra) were determined from D2-glucose enrichment. Values were calculated according to the non-steady-state equations of Steele [28], using 200 mL/Kg as the glucose distribution volume and 0.65 for the pool fraction. Hepatic glucose production was calculated by subtracting the glucose infusion rate from Ra.

2.7. Indices of insulin sensitivity

The FSIVGTT-based index of IS was computed, using MINMOD computer software (version Millennium 6.02, Richard N. Bergman, 2004), to determine an IS index for each subject. The nine formulas used to derive estimates of IS from the OGTT data are outlined in Table S1; supplementary material associated with this article online. The OGTT-derived indices selected were those validated in adults against the clamp, and are arguably the most widely used in the literature. Fasting indices are also described in Table S1; supplementary material associated with this article online, and were calculated based on the averages of two fasting glucose and two fasting insulin values from samples drawn at the onset of the OGTT.

2.8. Statistical analyses

Correlations were established using Spearman’s rank correlations. All analyses were performed using R version...
Table 1
Patients' characteristics.

<table>
<thead>
<tr>
<th>Characteristics (n = 20)</th>
<th>Median (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), mean (SD)</td>
<td>9 (7–13)</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>11 (55%)</td>
</tr>
<tr>
<td>Body mass index (kg/m²), mean Z score (SD)</td>
<td>1.5 (−0.2–2.7)</td>
</tr>
<tr>
<td>Body mass index category, n (%)</td>
<td></td>
</tr>
<tr>
<td>Normal weight</td>
<td>4 (20%)</td>
</tr>
<tr>
<td>Overweight</td>
<td>7 (35%)</td>
</tr>
<tr>
<td>Obese</td>
<td>9 (45%)</td>
</tr>
<tr>
<td>Tanner stage, n (%)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>3 (16%)</td>
</tr>
<tr>
<td>2</td>
<td>8 (41%)</td>
</tr>
<tr>
<td>3</td>
<td>2 (11%)</td>
</tr>
<tr>
<td>4</td>
<td>3 (16%)</td>
</tr>
<tr>
<td>5</td>
<td>4 (21%)</td>
</tr>
<tr>
<td>SS clamp glucose (mmol/L), mean (SD)</td>
<td>4.73 (0.44)</td>
</tr>
<tr>
<td>SS clamp insulin (pmol/L), mean (SD)</td>
<td>328.6 (61.88)</td>
</tr>
<tr>
<td>HGP (μmol/kg/min), mean (SD)</td>
<td>3.22 (1.38)</td>
</tr>
<tr>
<td>% HGP suppression, mean (SD)</td>
<td>92.33 (3.75)</td>
</tr>
<tr>
<td>M values (mg/kg/min), mean (SD)</td>
<td>9.47 (3.67)</td>
</tr>
<tr>
<td>IS clamp values (dL/kg/min/uU/mL), mean (SD)</td>
<td>2.66 × 10⁻³ (1.24 × 10⁻³)</td>
</tr>
<tr>
<td>SI MINMOD ([μU/L⁻¹.min⁻¹]), mean (SD)</td>
<td>5.54 (2.27)</td>
</tr>
</tbody>
</table>

n: number of participants; SD: standard deviation; SS: steady-state; HGP: hepatic glucose production during clamp test; IS: index of insulin sensitivity derived from Bergman; SI MINMOD: insulin sensitivity derived from the modified minimal-model frequently sampled intravenous glucose tolerance test (FSIVGTT).

Table 2
Correlations between clamp estimates of insulin-sensitivity indices (ISI) and indices derived from the FSIVGTT, OGTT and fasting surrogate measures of insulin sensitivity.

<table>
<thead>
<tr>
<th></th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Correlation coefficient</td>
<td>95 % CI</td>
</tr>
<tr>
<td><strong>Based on FSIVGTT</strong></td>
<td>0.74</td>
<td>0.45, 0.90</td>
</tr>
<tr>
<td><strong>Based on OGTT</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ISI Gutt[6]</td>
<td>0.07</td>
<td>−0.39, 0.50</td>
</tr>
<tr>
<td>ISI Matsuda 120[6]</td>
<td>0.63</td>
<td>0.25, 0.85</td>
</tr>
<tr>
<td>ISI Matsuda 180[6]</td>
<td>0.61</td>
<td>0.22, 0.83</td>
</tr>
<tr>
<td>ISI Cederholm[6]</td>
<td>0.26</td>
<td>−0.22, 0.65</td>
</tr>
<tr>
<td>ISI Stumvoll[6]</td>
<td>0.52</td>
<td>0.10, 0.79</td>
</tr>
<tr>
<td>OGIS 120[6]</td>
<td>0.31</td>
<td>−0.15, 0.66</td>
</tr>
<tr>
<td>OGIS 180[6]</td>
<td>0.59</td>
<td>0.20, 0.82</td>
</tr>
<tr>
<td>ISI Belfiore[6]</td>
<td>0.21</td>
<td>−0.26, 0.60</td>
</tr>
<tr>
<td>ISI Avignon[6]</td>
<td>0.49</td>
<td>0.06, 0.77</td>
</tr>
<tr>
<td>SIₐ,OGIS[6]</td>
<td>0.53</td>
<td>0.10, 0.80</td>
</tr>
<tr>
<td>Log sum insulin 120[6]</td>
<td>−0.64</td>
<td>−0.85, −0.27</td>
</tr>
<tr>
<td>Log sum insulin 180[6]</td>
<td>−0.68</td>
<td>−0.87, −0.33</td>
</tr>
<tr>
<td><strong>Based on fasting sample</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>−0.55</td>
<td>−0.80, −0.14</td>
</tr>
<tr>
<td>QUICKI</td>
<td>0.55</td>
<td>0.14, 0.80</td>
</tr>
<tr>
<td>Fasting insulin</td>
<td>−0.59</td>
<td>−0.82, −0.20</td>
</tr>
</tbody>
</table>

FSIVGTT: modified minimal-model frequently sampled intravenous glucose tolerance test; OGTT: oral glucose tolerance test; OGIS: oral glucose insulin sensitivity; HOMA-IR: homoeostasis model assessment for insulin resistance; QUICKI: quantitative insulin-sensitivity check index.

a Based on 2-h OGTT.
b Based on 3-h OGTT.
Table 2. The three indices that showed the highest correlation to clamp-derived measures (Table 2). Also, the correlations between fasting indices of IS and clamp measures were similar to those between the FSIVGTT-derived index and clamp measures, as well as among the three best OGTT-derived indices and clamp measures. Furthermore, after adjusting total M values for hepatic glucose-production inhibition (using labeled glucose values), all correlations remained identical.

To ascertain whether some indices were more strongly correlated to the clamp (M total) than others, the difference between dependent correlations was also tested (Table S2; see supplementary material associated with this article online). Overall, the selected indices performed similarly against the clamp, although the small sample size in the present study may limit its ability to detect a significant difference.

4. Conclusion

In a group of children aged 6–13 years, measurement of IS using the FSIVGTT, OGTT and fasting measures were moderately to highly correlated to the gold-standard HEC test. In particular, three indices derived from the OGTT showed the strongest correlations to clamp results—namely, the ISI Matsuda, SI0,OGTT and Log sum insulin. Similar findings have been observed in adults, with these indices all correlating strongly (r = 0.57–0.65) to clamp results [16]. While studies in youth have correlated OGTT-derived indices against fasting indices of IS [30–32], only one has correlated OGTT-derived indices to the gold-standard HEC in this population. Yeckel et al. [35], in 38 obese individuals aged 8–18 years, found that the ISI Matsuda [10] as well as Soonthornpum’s index [34], which includes urinary glucose in its calculation, both correlated strongly to clamp-derived results (r = 0.78 and r = 0.74, respectively). The higher correlations noted by Yeckel et al. may be explained in part by the fact that only children with insulin-resistant states were studied (see below).

Fasting indices of IS, including the HOMA-IR, QUICKI and fasting insulin, were also well correlated to the HEC in the present study. However, previous studies have noted incongruent results when comparing clamp-derived IS with surrogate measures in healthy paediatric subjects. Uwaifo et al. [35] correlated clamp-derived (both hyperglycemic and euglycemic clamp studies) indices of IS with surrogate measures derived from fasting insulin and glucose values in a group of 31 healthy six- to 12-year-olds, and found correlations similar in magnitude to those of our present study (Spearman’s r = 0.51–0.69). Schwartz et al. [36] examined, in 300 subjects ages 13 and 15 years, correlations between clamp-derived IS and HOMA, QUICKI, fasting insulin and FIGR, and found slightly lower correlations compared with ours (Pearson’s r = 0.43–0.54). In contrast, in 156 African-American and white youths, Gungor et al. [20] found much stronger correlations for the HOMA IS (Spearman’s r = 0.86–0.91) and QUICKI (Spearman’s r = 0.86–0.91). When Conwell et al. [7] correlated FSIVGTT-derived IS to surrogate measures, including HOMA and QUICKI, in 18 obese prepubertal and pubertal adolescents, they found stronger correlations between HOMA-IR and IS (r = −0.81 to −0.90) as well as between QUICKI and IS (r = 0.81–0.90) than in our present study (r = 0.49 and r = 0.50, respectively). The discrepancies among these studies may be explained in part by the different populations studied: it appears that correlations with fasting indices may be stronger in obese or insulin-resistant individuals. Indeed, Silfen et al. [32] found that the fasting glucose to insulin ratio (FGIR) and QUICKI did not correlate as strongly to OGTT-derived measures of IS in non-obese girls with premature adrenarche as in their obese counterparts. Similar stronger correlations of fasting indices to clamp results in individuals with insulin-resistant states have also been documented in adults [27]. However, in healthy adults, fasting surrogate indices have proved to be no better than fasting insulin alone in predicting insulin resistance [37]. Other factors that may explain such discrepancies include age, ethnicity, pubertal status and size of the studied cohort [36].

In trying to determine which index of IS is optimal for clinical research in children, an understanding of the advantages and disadvantages of each method is essential. While the HEC remains the gold standard, it measures IS in a controlled, fixed state at a given insulin concentration, and reflects mainly the peripheral aspects of IS. One possible strategy to correct for this, particularly in obese subjects, would be to normalize clamp results on
fat-free mass [38]. Nevertheless, clamp methodology limits its use in epidemiological studies. The FSIVGTT has the advantage of measuring the endogenous insulin response to an intravenous glucose stimulus, thereby assessing both hepatic and peripheral IS. While simpler than the clamp test, it is still invasive and impractical. OGTT-derived indices have the advantage of measuring IS in a dynamic context, taking into consideration both the full spectrum of insulin concentrations as well as the impact of enteral hormone action, while assessing whole-body IS (including muscle and hepatic components). Although the dynamic context of the OGTT may better mimic normal physiology, it may also be seen as a disadvantage, as it is an open-loop, less-controlled system, with intrinsic variability attributable to absorption and digestion. Nevertheless, OGTT-derived indices can provide additional information such as glucose tolerance and estimation of β-cell secretion, which are of clinical and physiological interest. Finally, fasting indices have the advantage of simplicity although, as already discussed, they do not perform as well in insulin-sensitive populations. In addition, they reflect IS in a fasting steady-state that is predominantly determined by hepatic IS, and they provide no information on glucose tolerance. It is in this light that OGTT-derived indices may provide the best compromise between simplicity, performance against clamp-derived measures of IS and additional clinically valid information, such as glucose tolerance. The IS indices based on a 2-h OGTT performed similarly to those using data from the 3-h OGTT in our study, suggesting that a 2-h study provides sufficient information to allow estimations of IS in young people. For large cohorts, fasting-based indices are a practical and valuable alternative.

The major strength of the present study is its design, as all 20 participants underwent each of the three standardized protocols to measure IS, including the HEC test, the FSIVGTT and the OGTT. The small sample size remains this study’s main limitation, making it unable to test the effects of gender, ethnicity and stage of sexual maturity on correlations between indices.

In conclusion, the results of our present study suggest that both fasting and OGTT-derived indices provide a valid assessment of IS in youth. The OGTT may represent the best compromise for obtaining both clinical (glucose tolerance) and physiological (IS and insulin secretion) information, making this of particular interest for large epidemiological studies and clinicians alike. In addition, the 2-h OGTT appears to provide sufficient information to estimate IS in youth. However, further research is required to determine whether or not these findings are applicable to children with type 2 diabetes.

Conflict of interest statement

No potential conflicts of interest relevant to this article were reported.

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Appendix A. Supplementary data

Supplementary material (Tables S1 and S2) associated with this article can be found at http://www.sciencedirect.com, at doi:10.1016/j.diabet.2010.06.008.

References


