Limited Accuracy of Surrogates of Insulin Resistance during Puberty in Obese and Lean Children at Risk for Altered Glucoregulation

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This study evaluated the accuracy of surrogate indexes of insulin sensitivity (SI) in children. Surrogates (homeostasis model assessment index of insulin resistance, quick insulin sensitivity index, and 40/insulin ratio index) were cross-sectionally investigated in 66 obese and lean children (17 Tanner stage I, 19 Tanner stage II–III, and 30 Tanner stage IV–V) as indexes of insulin resistance in comparison with the minimal model. The pubertal decrease in SI was found with the minimal model (−47%; P = 0.01), but not with surrogates, which were not correlated to SI. Baseline insulin (Ib) did not mirror the decrease in SI, did not significantly change when plotted against pubertal stage or age, and was not correlated to SI. Ib and surrogates were positively correlated with the body mass index. The disposition index, which quantifies the feedback between SI and insulin release, was widely scattered and decreased during puberty (P = 0.05). The specificity and sensitivity of surrogates as predictors of insulin resistance were poor (e.g. 81.1% and 30.7%, respectively, for the homeostasis model assessment index of insulin resistance). Thus, during puberty, surrogates are not accurate predictors of insulin resistance. Because reference methods are rather expensive and invasive, additional studies of alternative techniques for evaluating SI are needed to allow accurate measurement of insulin resistance in children. (J Clin Endocrinol Metab 90: 761–767, 2005)

Recent studies have renewed interest in measurement of insulin sensitivity (SI) during puberty. Indeed, during puberty, plasma insulin levels increase, and SI decreases along with multiple other physical and hormonal changes (1). This decrease in SI has been well demonstrated with both the minimal model (1–5) and the glucose clamp (6, 7).

The minimal model method, which is based on calculation of an individual's parameters of glucose disposal during an iv glucose tolerance test (IVGTT) (8), has been repeatedly used in children (4, 5, 9) and is generally considered an accurate alternative to the euglycemic glucose clamp for calculating SI. However, both the glucose clamp and the IVGTT are too time-consuming (requiring a 3-h period) (10) and expensive to be generalized for clinical practice. They are thus most often replaced by simple techniques, the most attractive being the calculation of surrogate indexes of SI from baseline values of plasma glucose (Gb) and plasma insulin (Ib).

The most widely used of these indexes is the homeostasis model assessment (HOMA) index of insulin resistance (HOMA-IR). It can be calculated using computer software (11, 12), but the simple formula, fasting insulin (µU/ml) × fasting glucose (mmol/liter)/22.5 (11), approximates it quite well. Therefore, this index is based on the concept that the product insulin × glucose is a measurement of insulin resistance, with both insulin and glucose increasing when SI decreases, a simplistic assumption that seems rather logical.

Other surrogates have been proposed such as the quantitative SI check index (QUICKI) (13) or the ratio 40/insulin (14), which provides a fair and very simple evaluation of minimal model-derived SI.

In fact, all of these surrogates give relatively good results in adult obese or lean sedentary subjects, as repeatedly demonstrated by numerous studies (15, 16). By contrast, in several populations, their validity has been challenged. In diabetics, when advanced β-cell failure makes insulin unable to increase in response to lowered SI despite some optimistic reports (14), it has been shown that it is no longer possible to accurately predict SI with the usual surrogates (17). A similar loss of reliability of surrogates has been reported in situations of elevated SI (athletes and patients suffering from reactive hypoglycemia) (18). It appears, therefore, that surrogates are useful and accurate tools in some definite situations (i.e. nondiabetic sedentary adults of either normal or high body weight), but that investigators should be careful to employ them only in situations where their validity has actually been demonstrated.

We investigated the validity of these surrogates during puberty in both normal and overweight children, a situation where previous studies using sophisticated methods have clearly shown important (30–50%) changes in SI. Although it has become usual in such subjects to use the surrogates of
Subjects and Methods

Study population

The study population consisted of 66 children. These children were selected from a database of 300 IVGTTs performed in children. IVGTTs were performed in children at the request of the families who wanted a precise check of the glucose reguloregulatory function of children for various reasons (familial cases of diabetes or impaired glucose tolerance, future treatment by diabetogenic drugs such as corticosteroids or GH, or isolated finding of a high blood glucose level). All of these IVGTTs were included in the database. Subjects from this database were screened for medical history and biological data. Children with abnormal IVGTT response (i.e., lowered insulin peak) were excluded from the study. Children with human leukocyte antigen DR3 or DR4 genotypes were also excluded as were those exhibiting significant levels of antibodies directed against pancreatic islet, glutamic acid decarboxylase, or insulin. There were also four cases of maturity-onset diabetes of the young, which were excluded from study.

Pubertal development was assessed by physical examination according to Tanner classification (19, 20) (prepubertal, Tanner stage I; pubertal, Tanner stage II–III; postpubertal, Tanner stage IV–V). The subjects were further subdivided into lean children (n = 30; 10 prepubertal (two boys and eight girls), eight pubertal (seven boys and one girl), and 12 postpubertal (five boys and seven girls)) and obese children (n = 36; seven prepubertal (four boys and three girls), 11 pubertal (four boys and seven girls), and 18 postpubertal (nine boys and nine girls)). There were 31 boys and 35 girls. There were nine prepubertal (four boys and three girls), seven postmenarchal girls (three boys and four girls), and 18 postpubertal (nine boys and nine girls) cases of maturity-onset diabetes of the young, which were excluded from study.

This study was performed in accordance with the local ethical regulation, and in each case informed consent was obtained from the family before IVGTT. The constitution of a database of IVGTTs has been approved by the local ethical committee.

IVGTT protocol

After a 12-h fast, at 0900 h a cannula was placed in the cephalic vein at the level of the cubital fossa for blood sampling. A glucose injection (0.5 g/kg, solution at 30%) was administered in the contralateral cephalic vein slowly over precisely 3 min. Blood samples were drawn twice before the glucose bolus and 1, 3, 4, 8, 10, 15, 19, 20, 22, 30, 41, 70, 90, and 180 min after glucose injection. Insulin (0.02 U/kg body weight, i.e., 1 or 2 U) was injected iv immediately after the 19 min sample. The 1 and 3 min samples were used for determination of the insulin early secretory phase (21). The other samples were necessary for minimal model calculations.

Assessment of β-cell function

First phase insulin secretion (21) was calculated by the sum of insulin concentrations at 1 and 3 min after the end of glucose injection (t(tmax)). The acute insulin response to glucose (AIRg) was also calculated, i.e., the mean insulinemia above baseline between 1 and 10 min (22). A product AIRg × SI was also calculated as a glucose disposition index according to Kahn and co-workers (22).

Measurements of SI

A minimal model analysis of the IVGTT was performed according to Bergman’s method (23, 24) with the software TISPAG from University of Montpellier (Montpellier, France) (25), which uses a nonlinear least square estimation. SI was calculated from the following equations: equation I, dG(t)/dt = −(p1 + (X(t)) G(t) + p1 G(t) + p1; equation II, G(t) = G0; equation III, dX(t)/dt = −p2 X(t) + p3 (I(t) – Ib); and equation IV, X(t) = 0, where G(t) and I(t) are plasma glucose and insulin concentrations, X(t) is the insulin concentration in a compartment remote from plasma (insulin action), and p1 to p3 are model parameters. Go is the glucose concentration that would be obtained immediately after injection if there were instantaneous mixing in the extracellular fluid compartment. Gb and Ib are the basal values of glucose and insulin. Parameter p1 represents the fractional disappearance rate of glucose independent of any insulin response. p3 and p2 determine the kinetics of insulin transport into and out of, respectively, the remote insulin compartment where insulin action is expressed. SI is an index of the influence of plasma insulin on glucose’s own effect on the glucose concentration. Thus, SI is equal to −p3/p2.

Surrogates

HOMA. HOMA%S is provided by J. Levy’s software (11, 12). We applied this simple calculation, which has been validated in comparison with the euglycemic clamp (26). The insulin resistance (IR) index is defined as: IR = insulin/(22.5 e−3.6 gluco), simplified to Ib × Gb divided by 22.5, where Ib is the basal insulin concentration (microunits per milliliter), and Gb is the basal glucose level (millimoles per liter). Lower HOMA-IR values indicate greater SI, whereas higher HOMA-IR values indicate lower SI (insulin resistance).

QUICKI. The QUICKI was proposed by Katz et al. (13). It is equal to: 1/[(log(Gb) (mg/dl) + log(Ib) (μU/ml))].

Index 40/insulin ratio (40/I). This index is based on the observation that fasting glucose actually has little relevance for predicting SI and behaves almost as a constant in the above formulas. We have proposed an even simpler surrogate, SI = a/I, which can predict minimal model results if an accurate value of a is applied (in our laboratory, a = 40) (14).

Statistics

Data are expressed as the mean ± se. The normality of parameters was assessed by the normality test of Kolmogorov and Smirnov. P < 0.05 was considered significant. To detect differences, parametric tests for unpaired data (one-way ANOVA, with post hoc Schelf tests) were used if appropriate. Linear and nonlinear correlations were assessed by least square fitting with StatView for Windows (SAS Institute, Inc., Cary, NC; copyright 1992–1998, version 5.0).

The sensitivity of surrogates to detect insulin resistance was calculated as the number of truly positive subjects divided by the sum of true positives and false negatives, with that sum representing the total number of insulin-resistant patients in the sample of subjects. The specificity was calculated as the number of truly negative subjects divided by the sum of false positives and true negatives. The positive predictive value was calculated as the number of truly positive subjects divided by the sum of true positives and false positives. The negative predictive value was calculated as the number of truly negative subjects divided by the sum of true negatives and false negatives. All four indexes were expressed as percentages (27).

Results

Subject characteristics

The anthropometric characteristics are shown in the Table 1. There was no difference in sex and age between lean and obese subjects of the same pubertal stage. However, there were significant differences in weight and body mass index (BMI) between the two groups.

Metabolic differences were also observed between the two groups (Table 2). The prepubertal lean group had significantly lower fasting glucose (Gb) than the prepubertal obese group. In addition, the pubertal lean group had significantly lower fasting insulin (Ib) than the pubertal obese group.
Changes in SI, fractional disappearance rate of glucose, and AIRg during puberty

In the whole sample of children (i.e. whatever the BMI), increasing pubertal stage was associated with a decrease in minimal model SI. There was a significant difference between prepubertal and postpubertal groups (P < 0.05; Fig. 1). This decrease was also significant if SI was plotted against age (P = 0.01; data not shown). However, if the evolution of SI across pubertal stages was investigated separately in the two sexes, it did not reach significance (Fig. 2).

There was no significant change in Ib as a function of either age or pubertal stage (data not shown), and Ib was not correlated with SI.

Minimal model parameters during puberty, such as SI and insulin first phase response (expressed as either AIRg or Ib), did not significantly change.

As shown in Fig. 3A, the product SI × Ib, which is assumed to be a constant, is widely scattered and only exhibits a nonsignificant tendency to decrease with pubertal stage. Therefore, in our sample of children, the feedback loop SI × Ib = constant is not found.

As shown in Fig. 3B, the disposition index (AIRg × SI) significantly decreased with the puberty (P < 0.05). The post hoc test showed a significant difference in the disposition index between prepubertal and postpubertal groups (P < 0.05).

The classical hyperbolic relationship between SI and AIRg, which underlies the concept of disposition index, was not found (Fig. 4).

Surrogates of SI in subgroups of children

The results of HOMA-IR, QUICKI, and 40/I were not different between the two groups and did not significantly change during puberty, nor did other usual surrogates. Thus, the decrease in SI during puberty was not significantly detected with QUICKI, 40/I, or HOMA-IR, nor was it detected with the HOMA%S (determined by J. Levy’s simulation software), although it was detected by the minimal model.

When looking for an effect of either age or Tanner stage on Ib, HOMA-IR, HOMA%S, 40/I, and QUICKI, we were unable to find any significant difference. Similarly, we did not find any influence of BMI on SI. However, there were significant correlations between BMI and HOMA%S, HOMA-IR, 40/I, and QUICKI results, but these correlations were rather loose (r = -0.24 and P = 0.04, r = 0.25 and P = 0.04, r = -0.27 and P = 0.02, r = -0.22 and P = 0.04, respectively).

Correlations between SI and surrogates

The expected correlations between SI and surrogates, such as HOMA-IR, HOMA%S, QUICKI, and 40/I (Fig. 5), were not found in our sample of children in either the whole group or subgroups of lean or obese subjects.

Predictive value of surrogates

We studied the distribution of SI and HOMA-IR. The Kolmogorov-Smirnov test showed that the distribution of SI and HOMA-IR was not normal. Therefore, SI and HOMA-IR were log-transformed to calculate the cut-off values corresponding to the limits of quintiles of distribution (SI <1.68 and HOMA-IR >2.76 for the whole group). If we define insulin resistance as a value of SI below the upper limit of the lower quintile, we can calculate to what extent a value of surrogate within the upper quintile (for indexes of resistance) or within the lower quintile (for indexes of sensitivity) can actually predict this insulin resistance.

There were four true positive, 10 false positive, nine false negative, and 43 true negative results for the HOMA-IR. These results are summarized in Table 3 and show that a value of HOMA-IR situated in the highest quintile is a poor predictor of insulin resistance in terms of both specificity and sensitivity. Similar results were found for all other surrogates (Table 3).

### Table 1. Anthropometric characteristics of the subjects (mean ± SEM)

<table>
<thead>
<tr>
<th>Pubertal stage (n = 30; lean subjects)</th>
<th>P (mean lean vs. obese)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (M/F)</td>
<td>I II–III IV–V All lean</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>9.6 ± 0.45 13.1 ± 0.22 16.25 ± 0.44 13.2 ± 0.57</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>30.78 ± 1.85 42.22 ± 1.85 52.27 ± 1.27 42.42 ± 1.93</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>1.38 ± 0.03 1.56 ± 0.03 1.65 ± 0.07 1.53 ± 0.02</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>15.83 ± 0.27b 17.33 ± 0.32b 19.2 ± 0.39b 17.58 ± 0.33</td>
</tr>
<tr>
<td>ns, Not significant.</td>
<td>4/3 4/7 8/10 16/20 NS</td>
</tr>
</tbody>
</table>

**NS, Not significant.** Systeme International units: for glucose, mmol/liter (conversion factor, 0.05551); for insulin, pmol/liter (conversion factor, 6.0).

### Table 2. Basal fasting glucose (Gb) and fasting insulin (Ib)

<table>
<thead>
<tr>
<th>Pubertal stage (n = 30; lean subjects)</th>
<th>P (all lean vs. obese)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gb (mg/dl)</td>
<td>I II–III IV–V All lean</td>
</tr>
<tr>
<td>78.4 ± 8.6a</td>
<td>81.6 ± 3.4 83.7 ± 1.8 81.4 ± 1.4</td>
</tr>
<tr>
<td>Ib (μU/ml)</td>
<td>9.4 ± 0.48 9.1 ± 0.89b 11.41 ± 1.51 10.1 ± 0.75</td>
</tr>
<tr>
<td>90.3 ± 3.06</td>
<td>84.7 ± 2.8 79.6 ± 2.3 83.2 ± 1.6 NS</td>
</tr>
<tr>
<td>9.00 ± 0.43</td>
<td>13.18 ± 1.36 10.38 ± 0.78 10.97 ± 0.62 NS</td>
</tr>
</tbody>
</table>

**NS, Not significant.** Systeme International units: for glucose, mmol/liter (conversion factor, 0.05551); for insulin, pmol/liter (conversion factor, 6.0).
Discussion

The aim of this study was to investigate whether the usual surrogates may safely predict SI in lean and obese children, as repeatedly demonstrated in lean and obese adults. Our main finding is that the expected correlations between SI and surrogates in children between 6 and 18 yr are poor, suggesting a limited accuracy of these surrogates as predictors of SI in this context.

This finding is potentially important, because surrogates, due to their low cost and simplicity, have become very popular among endocrinologists for measuring SI, even in situations where their reliability has not been investigated. It is clear that in a large part of the population surrogates are quite accurate measurements of SI (10, 11, 26). By contrast, there are several important situations where this accuracy has been seriously challenged, including diabetes (14), ageing (17, 18), training (28), and postprandial reactive hypoglycemia (29). We thus think that it is important to clearly define in which populations surrogates are reliable and in which they are irrelevant.

Some methodological aspects of this study need to be discussed. In this paper SI was measured with the minimal model. Beside the gold standard, which is the glucose clamp, this method is surely an alternative gold standard due to the number of high level studies that have demonstrated its accuracy. This technique has been the subject of specific methodological studies in children and is thus a well recognized method in this age range.

In adults, a host of studies have repeatedly demonstrated (10, 11, 26) fair reliability (at least in some defined populations) of the HOMA for predicting IVGTT or clamp-derived SI measurements.
Concerning children, two recent papers suggest that the HOMA-IR is well correlated with both IVGTT (30) and clamp (31) measurements of SI. Our study does not rule out the possibility of some degree of validity of surrogates in selected samples of teenage children, but it indicates that at this age, as previously reported in adults, there are populations in whom these surrogates become irrelevant. Our sample of children, which includes relatives of type 1 and type 2 diabetics, may be characterized by mild compensated disturbances in either insulin secretion or SI, and such defects may explain the loss of validity of surrogates, as discussed below. However, children prone to glucoregulatory disturbances are clearly the population in whom such measurements may have clinical usefulness; thus, it would not be logical to remove them from the study.

Surrogate measurements of SI are based on fasting insulin values. Therefore, their validity obviously relies on the ability of insulin to increase in response to insulin resistance. It would seem logical to assume that glucose values may be included in the calculation of the surrogate, but the quite similar reliabilities of the glucose/insulin ratio (32) and the glucose × insulin product (as in the HOMA-IR) clearly show that glucose has actually little or no predictive value for this calculation, so that the major predictor of SI is, in fact, insulinemia alone. The relationships between insulin secretion and SI have been extensively investigated by the team of Bergman (9, 33, 34). Insulin release has been shown to mirror insulin resistance according to a hyperbolic homeostatic relationship, i.e. a curve governed by the formula: insulin release × SI = constant. The validity of the surrogates of SI is restricted to the situations where insulin is able to mirror SI, such as sedentary nondiabetic lean and obese adults. By contrast, this homeostatic loop is disturbed in most situations, and in this case surrogates appear to become inaccurate.

The period of puberty seems to be a time when SI and insulinemia exhibit a rather weak relationship, because we evidence with the minimal model in our sample of children for the classical decrease in SI during puberty, whereas insulin does not significantly mirror this evolution and appears in this sample of subjects to mirror adiposity rather than SI. It seems logical to speculate that this dissociation between Iβ
TABLE 3. Indexes to calculate the diagnostic values of surrogates for predicting SI

<table>
<thead>
<tr>
<th>Diagnostic values</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Positive predictive value (%)</th>
<th>Negative predictive value (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HOMA-IR</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>30.7</td>
<td>81.1</td>
<td>28.5</td>
<td>82.7</td>
</tr>
<tr>
<td>Obese</td>
<td>57.1</td>
<td>93.1</td>
<td>66.6</td>
<td>90</td>
</tr>
<tr>
<td>Lean</td>
<td>14.3</td>
<td>78.2</td>
<td>16.6</td>
<td>75</td>
</tr>
<tr>
<td>HOMA%S</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>69.23</td>
<td>18.87</td>
<td>17.31</td>
<td>71.43</td>
</tr>
<tr>
<td>Obese</td>
<td>57.14</td>
<td>10.34</td>
<td>13.33</td>
<td>50.00</td>
</tr>
<tr>
<td>Lean</td>
<td>85.71</td>
<td>26.09</td>
<td>26.09</td>
<td>85.71</td>
</tr>
<tr>
<td>QUICKI</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>61.5</td>
<td>17.0</td>
<td>15.4</td>
<td>64.3</td>
</tr>
<tr>
<td>Obese</td>
<td>42.9</td>
<td>3.4</td>
<td>9.7</td>
<td>20.0</td>
</tr>
<tr>
<td>Lean</td>
<td>71.4</td>
<td>26.1</td>
<td>22.7</td>
<td>75.0</td>
</tr>
<tr>
<td>40/I</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>69.23</td>
<td>18.87</td>
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<td>85.71</td>
</tr>
</tbody>
</table>

and SI is the main explanation for the failure of surrogates to be accurate predictors of SI.

A more sensitive approach of this feedback (compared with the product SI × Ib) is the disposition index AIRg × SI (22), which is assumed to be a constant. This disposition index has been recently studied during puberty (4). It was shown to be markedly decreased (~30%) when children progressed from stage I to stage III–IV, so that a marked decrease in SI was not fully compensated by an increase in AIRg. We observed the same decrease, although it was less significant in our study because the study was cross-sectional. In fact, rather than a weakly significant change in AIRg × SI, our study shows a large scattering of values of this disposition index, which appears far from constant. It is clear that the feedback loop between insulin action and insulin release is markedly altered during puberty for largely unknown physiological reasons.

If physiological relationships explaining this upset of the feedback loop between SI and Ib were detected, they would be helpful for proposing the development of new surrogates suitable for this period of life. In our study the relationships between SI × Ib and both age and BMI in this period of life appear rather erratic and do not provide any clear direction for research. In Goran’s paper (4), a host of possible hormonal mechanisms are investigated. A possible explanation could be the pubertal increase in androstenedione, but this issue remains unclear.

Guzzaloni et al. (35), in a large database of 405 obese subjects, found an increase in HOMA-IR and a decrease in QUICKI. However, this study did not compare surrogates to a reference method for measuring SI (such as the clamp or the minimal model) and was unable to evidence concordance or discordance between these two approaches. Recent studies have shown that in adults, hyperinsulinemia and insulin resistance, although frequently associated, may also exist separately and thus represent two different varieties of the metabolic syndrome (36). In children, it is likely that the same situation exists, because a recent longitudinal study has demonstrated that at this age, hyperinsulinemia appears to precede the decline in SI (37). It is thus logical to find that indexes based on baseline insulin levels may imply many false positive diagnoses of insulin resistance.

Unless future investigations provide a more precise understanding of the determinants of the feedback loop between insulin release and SI during the teen years, this study leads us to recommend extreme caution using surrogates of SI in this period of life. Studies aimed at measuring SI in children between 6–18 yr of age should clearly employ dynamic methods. Because the glucose clamp, the minimal model, and the insulin suppression test are rather invasive, measurements of SI during oral glucose tolerance tests (38) or meal tests (39) are probably easier to employ than the former methods and may represent a promising alternative. A recent study has validated in children two indexes of SI derived from the oral glucose tolerance test (38). Recent works (40, 41) have used this approach to estimate both insulin secretion and SI in peripheral tissues in relation to Tanner pubertal stage. This approach has been shown to fairly detect the physiological decrease in SI (40) and to find an insulin-resistant state in adolescent girls and young women characterized by a history of precocious pubarche (41). On the whole, these recent papers suggest that this alternative approach of SI during puberty is a promising method.

Conclusion

Predicting SI with surrogates (such as HOMA-IR) is possible. It is clear that in a large part of the population, surrogates are quite accurate measurements of SI. By contrast, there are several important situations where this accuracy has been seriously challenged. In this study, we observe that surrogates should not be used as an index of SI in obese and lean children during puberty. Due to the invasiveness and the cost of reference methods, such as glucose clamp or IVGTT, it is important to assess more thoroughly the validity of simpler and less invasive techniques suitable for this period of life.

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