Indexes of Insulin Resistance and Secretion in Obese Children and Adolescents

A validation study

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OBJECTIVE — To assess the concurrent validity of fasting indexes of insulin sensitivity and secretion in obese prepubertal (Tanner stage 1) children and pubertal (Tanner stages 2–5) adolescents using estimates from the modified minimal model frequently sampled intravenous glucose tolerance test (FSIVGTT) as a criterion measure.

RESEARCH DESIGN AND METHODS — Eighteen obese children and adolescents (11 girls and 7 boys, mean age 12.2 ± 2.4 years, mean BMI 35.4 ± 6.2 kg/m^2, mean BMI-SDS 3.5 ± 0.5, 7 prepubertal and 11 pubertal) participated in the study. All participants underwent an insulin-modified FSIVGTT on two occasions, and 15 repeated this test a third time (mean 12.9 and 12.0 weeks apart). S_i measured by the FSIVGTT was compared with homeostasis model assessment (HOMA) of insulin resistance (HOMA-IR), quantitative insulin-sensitivity check index (QUICKI), fasting glucose–to–insulin ratio (FGIR), and fasting insulin (estimates of insulin sensitivity derived from fasting samples). The acute insulin response (AIR) measured by the FSIVGTT was compared with HOMA of percent β-cell function (HOMA-β%), FGIR, and fasting insulin (estimates of insulin secretion derived from fasting samples).

RESULTS — There was a significant negative correlation between HOMA-IR and S_i ($r = -0.89$, $r = -0.90$, and $r = -0.81$, $P < 0.01$) and a significant positive correlation between QUICKI and S_i ($r = 0.89$, $r = 0.90$, and $r = 0.81$, $P < 0.01$) at each time point. There was a significant positive correlation between FGIR and S_i ($r = 0.91$, $r = 0.91$, and $r = 0.82$, $P < 0.01$) and a significant negative correlation between fasting insulin and S_i ($r = -90$, $r = -0.90$, and $r = -0.88$, $P < 0.01$). HOMA-β% was not as strongly correlated with AIR ($r = 0.60$, $r = 0.54$, and $r = 0.61$, $P < 0.05$).

CONCLUSIONS — HOMA-IR, QUICKI, FGIR, and fasting insulin correlate strongly with S_i assessed by the FSIVGTT in obese children and adolescents. Correlations between HOMA-β%, FGIR and fasting insulin, and AIR were not as strong. Indexes derived from fasting samples are a valid tool for assessing insulin sensitivity in prepubertal and pubertal obese children.

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The global increase in obesity in children and adolescents heightens the risk of insulin resistance and type 2 diabetes (1). Insulin resistance is proposed to have a pivotal role in the development of the metabolic syndrome ("Syndrome X") (2). Furthermore, clustering of cardiovascular risk factors is seen in children and adolescents with the highest degree of insulin resistance, suggesting that adult cardiovascular disease is more likely to develop in these young people (3,4). Hence, valid and reliable methods to measure insulin sensitivity in this at-risk population are essential to assess the presence and extent of insulin resistance, associated factors, progression over time, and the effect of pharmacological and lifestyle interventions.

The modified minimal model frequently sampled intravenous glucose tolerance test (FSIVGTT) is a method that assesses insulin sensitivity by a computed mathematical analysis of glucose and insulin dynamics after a bolus of intravenous glucose, followed 20 min later by a bolus of intravenous insulin or Tolbutamide. It is an accurate and valid technique for the measurement of insulin sensitivity in adults, adolescents, and children (5–8). This method has been used in studies assessing insulin sensitivity in young people (9). However, like the hyperinsulinemic-euglycemic clamp technique, it is time-consuming, invasive, expensive, labor intensive, requires experienced personnel, and is technically difficult to perform in obese young people.

In contrast, the homeostasis model assessment (HOMA) for insulin resistance (HOMA-IR) and the quantitative insulin-sensitivity check index (QUICKI) derive estimates of insulin sensitivity from the mathematical modeling of fasting plasma glucose and insulin concentrations. The fasting glucose–to–insulin ratio (FGIR) has also been proposed as a useful estimate of insulin sensitivity (10). However, validation studies of these derived indexes in pediatric populations are scarce. Uwaifo et al. (11) assessed the correlation between fasting and clamp-derived indexes of insulin secretion, sensitivity, and clearance in a cohort of normal and overweight children aged 6–12 years. Both QUICKI ($r = 0.67$–0.69) and HOMA-IR ($r = -0.51$ to -0.56) correlated signifi-

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Abbreviations: AIR, acute insulin response; FGIR, fasting glucose–to–insulin ratio; FSIVGTT, frequently sampled intravenous glucose tolerance test; HOMA, homeostasis model assessment; HOMA-β%, HOMA of percent β-cell function; HOMA-IR, HOMA of insulin resistance; QUICKI, quantitative insulin-sensitivity check index.

cantly with the clamp-derived measures, supporting the utility of both indexes in pediatric patients. Huang et al. (12) quantified the relationship between HOMA-IR and insulin sensitivity (from Tolbutamide-modified FSIVGTT) in 156 white and African-American children (mean age 9.7 ± 1.8 years). HOMA-IR was strongly correlated with FSIVGTT-measured insulin sensitivity, explaining 63.4% of the variance. The validity of QUICKI was not examined. While the results of these studies support the potential utility of derived indexes of insulin sensitivity in the general pediatric population, our understanding regarding the validity of derived indexes of insulin sensitivity in overweight and obese young people is less than complete. Indeed, no previous study has simultaneously evaluated the validity of the HOMA-IR and QUICKI in a cohort of exclusively obese children and adolescents. Therefore, the aim of this study was to assess the validity of derived indexes of insulin sensitivity and secretion using the modified (insulin) minimal model as a criterion measure in a cohort of obese prepubertal children and pubertal adolescents.

RESEARCH DESIGN AND METHODS

— Eighteen obese children and adolescents (aged 8–18 years, 7 prepubertal and 11 pubertal) were recruited to participate in the study. Obesity was defined as a BMI equal to or greater than the age- and sex-specific cut-points proposed by the International Obesity Task Force (13). The study was approved by the Royal Children's Hospital and Health Services District, Brisbane, and the University of Queensland ethics committees. Parents provided informed consent and children and adolescents provided informed assent before testing commenced.

Assessment of anthropometry and pubertal status

Weight was measured in light indoor clothing using a calibrated electronic scale (Tanita BWB-600; Wedderburn Scales, Brisbane, Australia). Height was measured using a calibrated wall-mounted Stadiometer (Holtain Instruments, Crymmych, U.K.). BMI was calculated by dividing the weight of the subject by the height squared (kg/m^2). BMI-SDS was calculated by the "LMS" method using 1990 British growth reference centiles (14). In the absence of available national data, this population was thought to be the most comparable, and this comparison has been made in a previous Australian study (15). Waist circumference was measured to the nearest 0.1 cm (16). Pubertal development stage was assessed by a single pediatric endocrinologist using the criteria of Marshall and Tanner (17,18).

Insulin-modified FSIVGTT

An insulin-modified FSIVGTT was performed on three occasions (time 1, 2, and 3) in the Day Procedure Unit of the Royal Children's Hospital. Test 2 was conducted 12.9 ± 2.6 (means ± SD) weeks after test 1, and test 3 was conducted 12.0 ± 2.4 weeks after test 2. Consumption of only water was permitted after 2200 the evening before testing. Following topical anesthetic (EMLA cream; AstraZeneca) application to the antecubital space of both arms, flexible indwelling intravenous catheters were inserted into one or both antecubital veins. Where available, one catheter was used for administration of glucose and insulin, and the other was used for drawing blood samples. Catheters were maintained patent with a slow 0.9% saline infusion. If only one intravenous catheter could be inserted (18 of 51 occasions), a bolus of 0.9% saline (minimum 5 ml) was administered to ensure sufficient flushing between administration of glucose or insulin and blood sample collection. Three samples for fasting glucose and insulin were obtained at times −20, −10, and 0 min. Glucose (0.3 g/kg) as 25% dextrose was administered intravenously over a 1-min period at time 0 min. Intravenous insulin 0.03 U/kg (Humulin Regular; Eli Lilly) was administered at time 20 min. Sufficient saline flush was used to ensure total delivery of the glucose and insulin doses. Blood samples (3 ml) were collected at times 0, 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 19, 22, 23, 24, 25, 27, 30, 35, 40, 50, 60, 70, 80, 90, 100, 120, 140, 160, and 180 min (relative to glucose administration), i.e., standard time points for 3 h after glucose injection. Blood was collected in chilled tubes containing lithium heparin. Plasma glucose was measured immediately using a Hitachi DDP automated analyzer (Tokyo, Japan) with an interassay coefficient of variation of 1.7%. Plasma samples for insulin were stored at −70°C and measured later using the IMx Microparticle Enzyme Immunoassay technology (Abbott, Tokyo, Japan). There is nil detectable cross-reactivity of this assay with C-peptide and 0.005% cross-reactivity with proinsulin. The mean inter- and intra-assay coefficients of variation were 4.5 and 4.0%, respectively. Glucose and insulin values were entered into the MINMOD computer program (version 3.0, Richard N. Bergman, 1994) for determination of S_i and acute insulin response (AIR) (an estimate of insulin secretory capacity) (19).

Derived indexes from fasting blood samples

The means of the fasting glucose and insulin samples collected at −20, −10, and 0 min were used in the calculations. The HOMA-IR, QUICKI, and FGIR were derived as estimates of insulin sensitivity. HOMA-IR was calculated using the formula fasting insulin (μU/ml) × fasting glucose (mmol/l)/22.5 assuming that normal young subjects have an insulin resistance of 1 (20). QUICKI was calculated as 1/(log fasting insulin [μU/ml] + log glucose [mg/dl]) (21). HOMA of percent β-cell function (HOMA-β%) was calculated as 20 × fasting insulin (μU/ml)/(fasting glucose [mmol]/l − 3.5) assuming that normal young adults have 100% β-cell function (20). FGIR was calculated as fasting glucose (mg/dl)/fasting insulin (μU/ml).

Statistical analysis

Analysis was performed using SPSS version 11.0 software for Windows (LEAD Technologies, 2001). Data are reported as means ± SD (range). Due to the skewed nature of the indexes, validity was evaluated using Spearman correlation coefficients. $P < 0.05$ was considered significant for all the data analyses.

RESULTS

— Eighteen caucasian children and adolescents (7 prepubertal and 11 pubertal) were studied. Baseline demographic characteristics and anthropometric measurements are shown in Table 1. The mean ± SD age was 12.2 ± 2.4, range 8.3–16.9 years, BMI 35.4 ± 6.2 kg/m^2, and BMI-SDS 3.5 ± 0.5. There was no history of gestational diabetes in the mothers of the participants and only one participant had a first-degree relative with type 2 diabetes.

Fasting indexes and the minimal model–derived measurements of S_i and

Table 1—*Physical characteristics of the subjects*

N	18
Sex (F/M)	11/7
Pubertal status—female (Tanner 1/Tanner 2–3/ Tanner 4–5)	1/5/5
Pubertal status—male (Tanner 1/Tanner 2–3/Tanner 4–5)	6/0/1
Age (years)	12.2 ± 2.4 (8.3–16.9)
Height (cm)	154.5 ± 9.0 (141.0–171.1)
Weight (kg)	85.1 ± 20.2 (60.3–139.4)
BMI (kg/m^2)	35.4 ± 6.2 (29.5–51.5)
BMI-SDS	3.5 ± +0.5 (2.9–4.4)
Waist circumference (cm)	108.9 ± 12.3 (92.0–144.0)

Data are *n* or means ± SD (range).

secretion (AIR) for times 1, 2, and 3 are presented in Table 2. None of the participants had diabetes or impaired fasting glycemia based on fasting glucose measurements. Fasting insulin was >90 pmol/l (15 μU/ml) in 13 subjects.

The correlations between fasting and minimal model–derived indexes of insulin sensitivity and insulin secretion are shown in Table 3. There was a significant negative correlation between HOMA-IR and S_i ($r = -0.89$, $r = -0.90$, and $r = -0.81$, all P values <0.01) and a significant positive correlation between QUICKI and S_i ($r = 0.89$, $r = 0.90$, and $r = 0.81$, all P values <0.01) at each time point. The correlation coefficients for HOMA-IR and S_i as well as QUICKI and S_i were similar in magnitude for all three tests. There was a significant positive correlation between FGIR and S_i ($r = 0.91$, $r = 0.91$, and $r = 0.82$, all P values <0.01) and a significant negative correlation between fasting insulin and S_i ($r = -90$, $r = -0.90$, and $r = -0.88$, all P values <0.01). HOMA-β% was not as strongly correlated with AIR ($r = 0.60$, $r = 0.54$, and $r = 0.61$, $P < 0.05$). FGIR and fasting insulin were correlated with AIR negatively and positively, respectively, with similar correlation coefficients to HOMA-β%.

CONCLUSIONS — The aim of this study was to assess the validity of fasting indexes of insulin sensitivity and secretion in obese children and adolescents with estimates from the modified (insulin) minimal model FSIVGTT. In this cohort, indexes of insulin sensitivity derived from fasting samples (HOMA-IR, QUICKI, FGIR, and fasting insulin) correlated strongly with S_i derived from the FSIVGTT. The high degree of correlation was stable when assessed on two separate occasions for the entire cohort and on three separate occasions in 15 of the subjects. HOMA-β% as a derived estimate of insulin secretion from fasting samples was less strongly correlated with AIR measured by the FSIVGTT. FGIR and fasting insulin were correlated with AIR negatively and positively, respectively, with similar correlation coefficients.

Obesity and type 2 diabetes are globally increasing health problems for young people, with significant individual and public health ramifications with respect to associated morbidity and mortality (22–24). The importance of measuring insulin resistance in this at-risk population has recently been highlighted (25). Measurement of insulin resistance is imperative to enhance understanding of its pathogenesis, progression, and complications, to facilitate assessment of prevention and intervention strategies, and to further investigate differences observed between population subgroups defined by ethnicity (26), sex (27,28), and pubertal stage (29). Establishing the validity of HOMA-IR and QUICKI to assess insulin sensitivity in obese children and adolescents is particularly important because the use of such indexes is simpler, cheaper, less labor intensive, less time-consuming, and more acceptable to young people than clamp studies or the FSIVGTT, especially if repeated measurements are needed. These simplified measures of insulin sensitivity may facilitate much needed clinical and epidemiological studies.

Previous studies have evaluated simple indexes for assessing insulin sensitivity in a wide range of conditions associated with insulin resistance, including pregnancy (30), renal dysfunction (31), aging (32), and the polycystic ovarian syndrome (33). In the original description of HOMA, this estimate of insulin resistance correlated well with estimates obtained by use of the euglycemic clamp in adults ($r = 0.88$, $P < 0.0001$) (20). In adult cohorts (both sexes) with differing glycemic status and normal or elevated blood pressure, HOMA-IR has been shown to significantly correlate with clamp-derived total glucose disposal (r values ranging between −0.70 and −0.83, $P < 0.001$) (34). In adults, insulin sensitivity estimated by QUICKI has been shown to significantly correlate with that measured by the glucose clamp ($r = 0.78$,

Table 2—*Fasting- and FSIVGTT-derived measures of insulin sensitivity and β-cell secretory capacity*

	Time 1	Time 2	Time 3
n	18	18	15
Fasting glucose (mmol/l)	4.9 ± 0.3 (4.4–5.4)	4.9 ± 0.3 (4.4–5.2)	4.9 ± 0.3 (4.4–5.2)
Fasting insulin (pmol/l)	152.8 ± 74.8 (58.0–312.6)	134.7 ± 82.8 (56.6–352.8)	119.8 ± 66.5 (41.6–294.4)
FGIR (conventional units)	5.28 ± 2.76 (1.97–1.33)	4.64 ± 2.91 (1.89–11.76)	4.10 ± 2.21 (1.38–9.81)
HOMA-IR	5.48 ± 2.55 (2.11–10.65)	4.84 ± 2.93 (1.99–13.07)	4.34 ± 2.49 (1.55–10.90)
QUICKI	0.30 ± 0.02 (0.28–0.34)	0.31 ± 0.02 (0.27–0.34)	0.32 ± 0.02 (0.27–0.36)
S_i (10^{-4} min^{-1}/(μU/ml))	1.4 ± 0.8 (0.3–3.1)	1.8 ± 1.1 (0.4–4.5)	2.0 ± 1.0 (0.5–4.2)
AIR (μU/ml)	1587.5 ± 636.5 (849.8–2992.5)	1464.5 ± 629.9 (658.0–2727.7)	1385.8 ± 583.3 (665.3–2495.0)
HOMA-β%	399 ± 259 (135–947)	344 ± 238 (126–832)	298 ± 155 (90–654)

Data are means ± SD (range).

Table 3—*Correlation matrix of fasting indexes to FSIVGTT-derived indexes of insulin sensitivity and insulin secretion*

	S_i	AIR
Combined measurements (n = 51)		
HOMA-IR	−0.89*	—
QUICKI	0.89*	—
FGIR	0.91*	−0.66*
Fasting insulin	−0.90*	0.69*
HOMA-β%	—	0.60*
Time 1 (n = 18)		
HOMA-IR	−0.89*	—
QUICKI	0.89*	—
FGIR	0.91*	−0.60*
Fasting insulin	−0.90*	0.63*
HOMA-β%	—	0.53†
Time 2 (n = 18)		
HOMA-IR	−0.90*	—
QUICKI	0.90*	—
FGIR	0.91*	−0.65*
Fasting insulin	−0.90*	0.67*
HOMA-β%	—	0.58†
Time 3 (n = 15)		
HOMA-IR	−0.81*	—
QUICKI	0.81*	—
FGIR	0.82*	−0.57†
Fasting insulin	−0.89*	0.59†
HOMA-β%	—	0.61†

*Significant at $P < 0.01$, †significant at $P < 0.05$.

$P < 0.001$) (21) ($r = 0.84$, $P < 0.001$) (35), the insulin-modified FSIVGTT ($r = 0.59$, $P < 0.001$) (21), and the insulin suppression test (nonobese: $r = -0.49$, $P < 0.001$; obese -0.61, $P < 0.001$) (35,36).

Few previous studies, however, have examined the validity of HOMA-IR and QUICKI in pediatric populations. In a study of prepubertal and pubertal obese children and adolescents, HOMA-IR and QUICKI were significantly correlated with indexes derived from the glycemic and insulinemic responses to an oral glucose tolerance test (37). In a cohort of prepubertal girls with premature adrenarche and/or obesity, FGIR and QUICKI were significantly correlated with OGTT measures of insulin sensitivity (38). Uwaifo et al. (11) reported significant correlations between HOMA-IR, QUICKI, and euglycemic-hyperinsulinemic clamp–derived indexes of insulin sensitivity ($r = -0.51$ and $r = 0.67$, respectively). Huang et al. (12) reported HOMA-IR to account for 63.4% of the variance in insulin sensitivity measured by the Tolbutamide-modified FSIVGTT. Compared with these previous studies, our study assessed an exclusively obese pediatric cohort with greater degress of insulin resistance. Moreover, comparisons were made at three distinct points in time over a mean period of 25 weeks. At each time point, we found HOMA-IR ($r = -0.81$ to -0.90, $P<0.01$) and QUICKI ($r = 0.81$–0.90) to be significantly correlated with the insulin-modified FSIVGTT. Notably, these correlations are stronger than those reported by Uwaifo et al. (11), who used the euglycemic-hyperinsulinemic clamp as a criterion measure of insulin sensitivity.

This study had several limitations that warrant consideration. First, the subjects did not have an oral glucose tolerance test before participating in the study. In other populations, the utility of HOMA-IR compared with clamp-derived indexes of insulin resistance was decreased in patients with impaired glucose tolerance compared with normal glucose tolerance (32). However, the similarity of correlations of insulin to fasting glucose ratio and fasting insulin with S_i strongly suggests the young people in this study did not progress to β-cell failure. Second, the relatively small and homogeneous sample of obese children and adolescents did not permit subgroup analyses based on race/ethnicity, sex, or maturational stage. Validation studies are needed in other population groups because differences in insulin sensitivity and compensatory insulin secretion have been demonstrated in children of different racial/ethnic backgrounds (27,28). Lastly, while the combination of hyperglycemic and hyperinsulinemic clamp studies is described as the traditional gold standard for quantifying the in vivo action, secretion, and disposal of insulin, insulin sensitivity assessed by Bergman's modified minimal model FSIVGTT has been shown to be strongly correlated with the euglycemic glucose clamp (8) and has been used as a criterion measure in other pediatric studies (9,39–43).

In summary, indexes of insulin sensitivity derived from fasting plasma glucose and insulin (HOMA-IR, QUICKI, FGIR, and fasting insulin) correlate strongly with S_i assessed by the FSIVGTT in this cohort of obese children and adolescents. HOMA-β% (a derived index of insulin secretion), FGIR, and fasting insulin correlated less strongly with AIR. Consequently, indexes derived from fasting samples appear to be a valid tool for estimating insulin sensitivity in obese children and adolescents.

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