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Estimation of insulin sensitivity in children: methods, measures and controversies

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Abstract

Insulin resistance is defined as a state where insulin produces a diminished biological response, primarily in its capacity as a glucose-regulating hormone. Insulin resistance is commonly diagnosed by pediatric clinicians, but is rarely measured directly in children or adolescents. This review provides an overview of the techniques that can be used to assess insulin sensitivity in children, summarizing the methods involved, the assumptions, pitfalls, and appropriate uses of each technique, as well as their validation and reproducibility in pediatric samples.

Keywords

Insulin sensitivity; Glucose Clamp Technique; frequently sampled intravenous glucose tolerance test; HOMA; Quicki; glucose tolerance; surrogate measures

Introduction

Insulin resistance, clinically defined as a state where insulin produces a diminished glucoregulatory response, is clearly recognized as one of the risk factors for the development of type 2 diabetes, a disease that, as pediatric obesity becomes more common, is increasingly diagnosed among children. There are no widely accepted clinical diagnostic criteria available to separate insulin sensitive from insulin resistant children, and there are no approved pharmaceuticals for the treatment of pediatric insulin resistance unaccompanied by dysglycemia. However, accurate and reproducible estimates of children's insulin sensitivity are of interest from a research perspective, even if measurement of insulin sensitivity is very seldom clinically indicated. The gold standard research technique to determine whole-body insulin sensitivity is the hyperinsulinemic-euglycemic clamp (1, 2). Because this method requires considerable time and expertise to perform, numerous surrogate measures have

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been developed to estimate insulin sensitivity. This review provides an overview of the techniques used to assess insulin sensitivity in children, summarizing the methods involved, the assumptions, pitfalls, and appropriate use of each technique, and their validation and reproducibility in pediatric samples.

Insulin action

Insulin acts via its cognate receptor to increase glucose transporter 4 translocation to the cell surface and therefore increases glucose uptake in many body tissues. Notable exceptions are most neural cells, red blood cells, the renal tubules, the liver, and the intestinal mucosa, each of which can take up glucose via other glucose transporter molecules that are permanently located in their cell membranes (3). There are three major insulin responsive organs that are commonly studied: the muscle, the liver, and the adipose tissue. The adipose tissue is the most sensitive to insulin, with stimulation of glucose uptake and lipogenesis, and suppression of lipolysis, occurring at relatively low insulin concentrations. The liver is slightly less sensitive than the adipocyte; somewhat higher insulin levels are required to promote hepatic glucose uptake, by increasing glucose phosphorylation and glucose utilization, and to suppress hepatic gluconeogenesis. Still higher concentrations of insulin are required to stimulate glucose uptake maximally in muscle. Muscle insulin response is particularly important because skeletal muscle is responsible for over 75% of insulin-stimulated whole body glucose uptake (4). Insulin's ability to stimulate whole body glucose uptake should be conceptualized as a summing of insulin's action at many independently regulated tissues.

Measurement of insulin and glucose

Techniques for assessing insulin sensitivity require accurate measurement of insulin. Insulin assays have changed over time, and show considerable inter-laboratory variation (5). It is important to avoid assays that have significant cross-reactivity with proinsulin or other insulinomimetic compounds. The standards used for insulin assay calibration also may vary among assays (6). Thus, any numerical value for insulin (and therefore for measures of insulin sensitivity) cannot necessarily be directly compared between laboratories, but only among patients studied in a single lab using the same assay with known standards. For this reason, universal numerical definitions of insulin resistance do not exist for clinical use, and measurement of insulin sensitivity remains a research technique. In addition to variation between laboratories, falsely low insulin readings may be caused when blood specimens are hemolyzed, because insulin degrading enzymes are released (7).

Almost all assessments of insulin sensitivity also require accurate measurement of blood glucose. When whole blood samples are permitted to remain at room temperature for prolonged periods of time prior to processing, continued glycolysis will lower the concentration of glucose in the sample. To avoid this problem, common practice is to draw blood for measurement of glucose into gray-top tubes, which contain sodium fluoride, an inhibitor of glycolysis. Less recognized is that sodium fluoride fails to inhibit glycolysis fully during the first few hours after sample collection, as sodium fluoride inhibits enolase, an enzyme that acts late in the glycolytic pathway, but does not inhibit early glycolytic enzymes (8). The problem of glucose lowering due to glycolysis can be effectively

minimized either by acidification of the sample with a citrate buffer, or by immediately placing samples in an ice-water slurry and separating plasma from cells within 30 minutes of collection (9).

Preparation for testing

It has been recommended that assessment of glucose metabolism be performed after 72 hours of high-carbohydrate diet (250–350g per day). Although this recommendation has not been evaluated in children, adult studies suggest the carbohydrate content of the diet in the 3 days prior to testing has relatively little effect on assessment of glucose metabolism in healthy (10) or pregnant individuals (11). Some elevation of post-prandial blood glucose may be seen with malnutrition or after low carbohydrate diets (50–100g per day) (10).

Techniques to estimate insulin sensitivity

Many approaches to estimate insulin sensitivity have been promulgated, from single blood sample tests to investigational procedures requiring frequent sampling for many hours. The consensus “gold standard” technique for whole body insulin sensitivity assessment is the hyperinsulinemic-euglycemic clamp study (1). Because all other methods are compared in their ability to approximate data from this complex research procedure, we present the hyperinsulinemic-euglycemic clamp test first, before exploring simpler measures.

The hyperinsulinemic-euglycemic clamp

The hyperinsulinemic-euglycemic clamp is a direct measure of insulin stimulated glucose disposal (primarily by the muscle) at a given level of hyperinsulinemia. It has been used extensively in children and adolescents, including lean and obese Caucasians and African Americans (12–20), those with prediabetes (18, 21), those with type 1 (18, 22, 23) and type 2 diabetes (18, 24), survivors of childhood cancer (25) and those with critical illness (26). The hyperinsulinemic clamp in pediatrics has allowed greatly improved understanding of the causes of insulin resistance in childhood and during adolescence, including the role of growth hormone in mediating pubertal insulin resistance, how competition between oxidation of glucose and free fatty acids can help explain pubertal insulin resistance, and the associations of factors such as race and intra-abdominal adipose tissue with pathologic insulin resistance and type 2 diabetes (27).

The basic principle of the technique is simple: measure glucose uptake while exogenous insulin is given via intravenous infusion to raise blood insulin concentration above baseline to a new, steady-state, “hyperinsulinemic” level. As a result of the hyperinsulinemic state, glucose disposal increases in insulin sensitive tissues that take up glucose, and endogenous glucose production from the liver is suppressed. Simultaneously, glucose is infused at a variable rate to maintain a constant, or “clamped” blood glucose in the normal, or “euglycemic” range, typically 90–100 mg/dL ± 5%.

The original description of the hyperinsulinemic-euglycemic clamp (1) involved measurement of arterial blood glucose concentrations. Arterial catheterization for measurement of insulin sensitivity is generally considered more risky than venous sampling in adults (and clearly in children), thus an attempt is made to “arterialize” venous blood

samples. This is done by increasing arterio-venous shunting through the capillary beds by warming the extremity in a hot box or heating blanket, and drawing blood from an IV placed in a distal location (e.g. the hand). Ideally, the IV should be placed in a retrograde fashion, but this is seldom done in pediatric studies.

Once a steady state is attained during which blood glucose, blood insulin, and glucose infusion rate are constant (usually after 2–3 hours of insulin infusion), the glucose infusion rate (GIR), after adjusting for changes in glucose concentration over the evaluated period and subtracting out any urine glucose excreted during the test, is equal to the rate of glucose disposal (often referred to as "M"). An individual who is sensitive to the blood glucose lowering effects of insulin will require a high GIR in order to maintain euglycemia, while an insulin-resistant individual will require a lower GIR to maintain euglycemia. M is usually expressed relative to body size (total weight or lean mass) and time (mg dextrose disposed/kg/min), although there has been little study of how correction for body size should be done for children. M must be interpreted in relation to the level of hyperinsulinemia achieved during the clamp: a GIR of 8 mg/kg/min at a sub-maximal insulin level of 50 mcIU/mL is not equivalent to a GIR of 8 mg/kg/min at an insulin level of 100 mcIU/mL, a concentration at which maximal glucose uptake is generally observed. The insulin dose should be matched to the anticipated insulin sensitivity of the study population, such that a range of glucose disposal rates is observed, allowing the investigator to distinguish differences among subjects. If too low a dose is chosen, M will be clustered in a low range, too high a dose will produce high M values even in more insulin-resistant subjects. Thus, investigators planning hyperinsulinemic-euglycemic clamp studies should carefully review the literature to pick an insulin dose that will maximize variation in observed insulin sensitivity. For example, investigators studying lean, prepubertal children might choose a low dose (e.g. 20 mcU/m^2/minute), while those studying obese adolescents might choose a higher dose (e.g. 40–80 mcU/m^2/minute) due to physiologic insulin resistance of puberty (28) combined with pathologic insulin resistance associated with obesity. However, even at the same rate of insulin infusion, individuals may have varying steady-state insulin levels due to differences in insulin clearance; thus insulin concentrations must be measured during each study.

One of the critical assumptions of the hyperinsulinemic-euglycemic clamp is that measured GIR equals glucose disposal (M) in the steady state; however, this is true only if steady state conditions are achieved. Although many investigators report M values during a predefined time period during the clamp (e.g. the final 30 or 60 minutes), steady state conditions may not have been achieved during this time frame for all subjects. Some recommend defining the steady state period individually, as a 30 minute time period occurring at least one hour after beginning the insulin infusion, during which the GIR, insulin concentration, and blood glucose do not vary by more than 5% (29). However, glucose disposal generally increases with increasing duration of insulin infusion, even when serum insulin remains constant. Thus, it is important to attempt to keep the duration of insulin infusion similar among study subjects. In addition, GIR will not equal M if hepatic glucose production (HGP) is not completely suppressed by the hyperinsulinemic state. HGP may not be suppressed in insulin-resistant individuals if the dose of insulin chosen is not high enough (30, 31). Suppression of HGP may be verified by using glucose tracers during the study.

Numerous variants of the hyperinsulinemic-euglycemic clamp exist that can add to the scientific information gained. These include use of multiple insulin doses to investigate insulin sensitivity at different target tissues (adipose, liver, and muscle), somatostatin analogs to suppress incretin hormone production as well as pancreatic insulin or glucagon secretion (with or without the addition of basal pancreatic hormone infusions), isotope tracers to measure endogenous glucose or lipid production, and indirect calorimetry to measure energy expenditure and substrate oxidation (32, 33).

The major limitation for use of the hyperinsulinemic-euglycemic clamp as a research tool is that it is non-trivial to perform: it requires a minimum of 2–3 hours of time per subject, and experienced operators must be present to manage the infusions, draw blood, measure blood glucose every 5 minutes, and adjust glucose infusion rates. As bedside glucometers do not have sufficient precision or accuracy for use during hyperinsulinemic-euglycemic clamps, a more accurate glucose measurement device such as the Yellow Springs Instrument or Beckman analyzer must be used. Although algorithms exist to assist in decision-making regarding adjustment of glucose infusion rates, an experienced operator will typically do better than a computer in maintaining steady state glucose concentrations (29, 34). Finally, subjects must be mature enough to cooperate; in the experience of the authors, this may be challenging in children less than eight years of age.

Even though blood glucose is monitored frequently, there is a risk for hypoglycemia during hyperinsulinemic-euglycemic clamps. Care must be taken to ensure continued patency of the intravenous line through which dextrose is infused, and to avoid infiltration of the line, as infiltration with high-concentrations of dextrose may cause tissue damage. Most groups have two glucose analyzers available during each study in case of equipment malfunction, and a bedside glucometer should be present as well in case of IV failure. Especially with higher doses of insulin, hypokalemia may result from intracellular shifts of potassium, and serum potassium should be monitored and replaced as needed. For these reasons, the hyperinsulinemic-euglycemic clamp remains a research test performed at relatively few pediatric centers and the vast majority of pediatric studies report other, simpler, measures of insulin sensitivity.

Alternatives to the Hyperinsulinemic-Euglycemic Clamp to Assess Insulin Sensitivity

Alternative indices of insulin sensitivity include steady-state (usually fasting) and dynamic measures. Dynamic indices measure the change in glucose and/or insulin during a perturbation. Formulas for surrogate measures of insulin sensitivity and their correlations with the hyperinsulinemic-euglycemic clamp in pediatrics are summarized in Table 1.

The Insulin Tolerance Test

Perhaps the simplest test of insulin action to understand is the insulin tolerance test (ITT). It provides a direct measure of glucose disappearance in response to an exogenous insulin bolus. An insulin bolus of 0.1 units/kg is given intravenously, and blood samples are obtained for 15 minutes following the injection for measurement of glucose (35). The rate of glucose disappearance (K_{ITT}) from time 3 to 15 minutes is used a measure of insulin action. The ITT assumes that the rate of glucose disappearance is linear over time and is solely

attributable to the effects of insulin. Rises in counterregulatory hormones in response to falling glucose concentrations may blunt the decline in glucose (36), particularly among normoglycemic, insulin sensitive individuals. The short (15 minute) ITT has largely replace prior versions that included measurement of glucose for 30–60 minutes after insulin injection, as the counterregulatory hormone surge appears between 15 and 30 minutes after the insulin dose (35). The ITT carries with it a non-negligible risk of symptomatic hypoglycemia, particularly in insulin sensitive subjects. A lower dose version (0.05 units/kg of insulin) has been tested in lean adults, and appeared to be safe, with fair correlation with the hyperinsulinemic-euglycemic clamp (R=0.68) (37). Higher dose versions (0.2 unit/kg of insulin) have been safely used in populations with extreme insulin resistance, including adults and children with lipodystrophy or insulin receptor mutations (38, 39). Because the ITT requires only a single IV with serial blood draws over 15 minutes, it is far less resource intensive than the hyperinsulinemic-euglycemic clamp.

Studies validating the ITT to assess insulin sensitivity in children, however, are almost nonexistant. In 8 adolescents with type 1 diabetes, the validity of the ITT was poor compared to the clamp ($r=-0.33$, $P=0.43$) (40), suggesting this is not an appropriate test of insulin sensitivity in this population. More thorough study of the safety and validity of the ITT in children is necessary before recommending this test for pediatric studies.

The Hyperglycemic Clamp

The hyperglycemic clamp is used primarily to measure beta-cell function, but an indirect measure of insulin sensitivity may be calculated using this technique. The principle of the hyperglycemic clamp is that glucose is raised using intravenous dextrose infusion to a hyperglycemic steady-state level, typically at or above 200 mg/dL. The hyperglycemic clamp maximally stimulates endogenous insulin secretion, allowing measurement of first- and second-phase beta-cell response to hyperglycemia and measurement of glucose disposal in response to endogenous insulin. After an overnight fast, the patient is given a bolus of 25–50% dextrose over 2 minutes to acutely raise the blood glucose to ~225 mg/dL. Arslanian and colleagues calculate the bolus dose of dextrose as (225 minus fasting plasma glucose) times body weight (kg) times a glucose distribution factor (1.5 in lean and 1.1 in overweight or obese children) (34). The bolus is followed by a variable rate 20% dextrose infusion, adjusted based on glucose measurements every 2.5 minutes for the first 15 minutes, and every 5 minutes for the remaining 105 minutes. Insulin and C-peptide are typically measured with each blood draw during the first 15 minutes, and every 15 minutes thereafter. During the final 30–60 minutes of the study, an index of insulin sensitivity may be calculated as the rate of glucose utilization (equal to GIR minus urinary glucose loss plus adjustment for any change in blood glucose concentration) divided by the mean insulin concentration. Like the hyperinsulinemic-euglycemic clamp, the hyperglycemic clamp requires two well-functioning IV lines, two accurate glucose measurement devices, and frequent blood draws. Because dextrose infusion rates vary according to endogenous insulin secretion (which is phasic and pulsatile), maintaining a hyperglycemic clamped state is technically quite difficult and even experienced operators find it difficult to achieve better than ±20 mg/dL around the intended target blood glucose concentration.

Among the identified limitations to the use of the hyperglycemic clamp to estimate insulin sensitivity are: 1) subjects must have fasting blood glucose below the concentration at which the glucose is clamped during the study; 2) the clamped glucose level should be below the renal threshold or one must correct glucose infusion rates for large urine glucose losses; 3) use of the hyperglycemic clamp method requires that subjects have significant insulin secretory capacity (thus not useful in those with diabetes); and 4) because the hyperglycemic clamp uses endogenous insulin production for its estimates, the assay used for its insulin measurements must have minimal cross-reactivity with proinsulin or other insulinomimetic compounds (41). In children, greater apparent insulin sensitivity has been observed during hyperglycemic clamps than during hyperinsulinemic-euglycemic clamps, likely due to increased glucose effectiveness (the ability of glucose to induce its own entry into cells) in the setting of hyperglycemia (42). The correlation of the insulin sensitivity index derived from the hyperglycemic clamp with that obtained from the hyperinsulinemic-euglycemic clamp in pediatrics has ranged from r=0.45 to 0.92 (34, 42, 43), suggesting that this test is not completely equivalent, but may be a reasonable alternative to the hyperinsulinemic-euglycemic clamp, especially if estimation of beta-cell function is desired in addition to determination of insulin sensitivity.

The Insulin-Modified Frequently Sampled Intravenous Glucose Tolerance Test (FSIGT)

Like the hyperglycemic clamp, the FSIGT procedure can be used to produce estimates of both first-phase insulin secretory capacity and insulin sensitivity; it is technically much simpler to perform, but more challenging to interpret than clamp studies. After an overnight fast, basal samples are obtained for measurement of glucose and insulin. Dextrose (300 mg/kg) is then infused intravenously over 2 minutes. Subsequently, insulin (0.02 to 0.05 units/kg) is acutely injected or infused over 5 minutes starting 20 minutes after the glucose infusion. Blood samples for glucose and insulin are obtained frequently, for example at 2, 4, 6, 8, 10, 12, 14, 16, 20, 22, 23, 24, 25, 27, 30, 40, 50, 60, 70, 80, 90, 100, and 120, and 180 minutes. The data obtained are analyzed assuming a minimal model for insulin action, applied to the frequently sampled intravenous glucose tolerance test (FSIGT) by Bergman and colleagues (44, 45). This model solves two differential equations to describe the dynamic changes in glucose and insulin over time. From these equations, an index of insulin sensitivity, S_I, is calculated. S_I essentially equals the effect of insulin to reduce glucose concentration over time. A reduced-sample FSIGT method (using samples obtained at 0, 2, 4, 8, 19, 22, 30, 40, 50, 70, 90, and 180 min) has also been validated by the Bergman group (46), and may be more appropriate for use in young children. The full 30 sample FISGT requires a minimum of about 35 mL of blood, while the reduced 12 sample version may be completed using only about 14 mL. Like the clamp, the FSIGT requires two well-functioning intravenous lines during a 3-hour test, but involves less time from skilled personnel after the first hour of the test (after the injections have been completed and the risk of hypoglycemia lessens). The frequency of hypoglycemia in children undergoing the FSIGT ranges from one report of 32% in relatively lean prepubertal children given 0.03 U/kg insulin (47) to less than 3% in obese, insulin-resistant children given 0.02 U/kg (48).

The minimal model makes numerous assumptions and has significant limitations. The dextrose bolus is assumed to be rapidly distributed in a single “glucose space” or

compartment; thus rapid injection of dextrose via a well-functioning IV is necessary. The analysis approach is considered a "minimal model" because insulin is assumed to act when it leaves the blood stream and reaches a single, "remote compartment," which is conceptualized physiologically as the interstitial space. The disappearance of glucose due either to insulin action or glucose effectiveness is assumed to be monoexponential, which some studies suggest leads to systematic underestimation of S_I in humans (29). Finally, the model requires glucose concentration at the end of the test (180 minutes) to return to the initial fasting level, a condition not always observed. Limitations include that the level of insulin achieved following the glucose bolus must be above a threshold in order to fit a valid model for S_I. Further, in humans, peak endogenous insulin secretion overlaps the period of maximal glucose effectiveness, so exogenous insulin (or in some versions of the test, an insulin secretagogue) need to be given 20 minutes after the glucose bolus (at which time the period of maximal glucose effectiveness has passed) in order to isolate the effect of insulin to lower glucose. The minimal model cannot distinguish between the effect of insulin to promote glucose disposal at the muscle (muscle insulin sensitivity), versus the effect of insulin to suppress hepatic glucose production (hepatic insulin sensitivity). In addition, the model does not always work well in patients with both insulin resistance and insulinopenia (e.g. type 2 diabetes with advanced beta-cell failure); some studies report physiologically impossible estimates of S_I (either negative or zero) (49–51) in patients with type 2 diabetes, although others have not reported this problem (52). The FISGT has been used in multiple pediatric studies (53–55), and has yielded important insight into, for examples, racial differences in insulin sensitivity, hepatic insulin extraction, and insulin secretion (56) and sex-associated differences in free fatty acid flux (57). However, there are surprisingly few investigations that directly compare the FSIGT to the hyperinsulinemic-euglycemic clamp in children. Henderson et al. studied 20 healthy children aged 6 to 18 years, including a spectrum from lean to obese (58). S_I from the FSIGT correlated well with hyperinsulinemic-euglycemic clamp M (R=0.74). In adults, correlation coefficients from as low as 0.44 to as high as 0.92 have been reported (50). The FSIGT, like the hyperglycemic clamp, is a less-intensive alternative to hyperinsulinemic-euglycemic clamp that also supplies a measure of beta cell function (first-phase insulin secretion).

The Oral Glucose Tolerance Test (OGTT)

There are several categories of insulin sensitivity indices that make use of glucose and insulin measured both before and after administration of oral glucose (Table 1). The first category includes theoretically-derived equations based on the principle that whole-body insulin sensitivity during the OGTT is inversely proportional to the product of mean or integrated insulin and glucose values during the test (i.e. Belfiore (59) and Matsuda (60) indices). The second category includes empirically derived formulas based on OGTT data that were designed to maximize correlation with the euglycemic clamp (i.e. Stumvoll (61), Gutt (62), and Insulin Sensitivity Index [ISI] (63) indices). Finally, the minimal model may be applied to data derived from the OGTT, analogous to its use with the FSIGT (64).

All tests are based on a standard OGTT with an oral glucose load of 1.75 g/kg, up to a maximum of 75g. Thus, one major advantage of OGTT-derived indices is that the investigator makes use of a test that can provide clinical diagnostic information about

diabetes status as well as research information about insulin sensitivity. In addition to the clinical measures of glucose in the fasting state and 2 hours after the oral glucose load, OGTT-derived indices require measurement of fasting and 120 minute insulin, and several of the indices require measurement of glucose and insulin at intermediate or later time points (e.g. 30, 60, 90, 150, and 180 minutes after the glucose load). If sampling at multiple time points is to be done, IV access for the purpose of blood draws is desirable. Although the OGTT is considered a benign test, some children will refuse to drink the glucose solution, and some will complain of nausea.

Oral ingestion of glucose more closely mimics the normal physiology activated to handle a meal than the other tests described here; however, the oral route adds considerable complexity to interpretation of the results. In addition to insulin secretion and sensitivity, variability in test results may be introduced by differences in gastric emptying, splanchnic glucose uptake, and incretin hormone secretion. The test-retest reproducibility of the OGTT for the diagnosis of impaired fasting glucose and impaired glucose tolerance is poor in overweight youth (65, 66) and the correlation between glucose measurements from two OGTTs was remarkably low: 0.73 for fasting glucose, and only 0.37 for 2h glucose measurements (65), suggesting that subtle changes in test conditions (including unknown factors) may significantly influence the results. Good correlations with the hyperinsulinemic-euglycemic clamp (R=0.74–0.78) have been observed between some OGTT-derived indices (Matsuda index and ISI) in two pediatric studies (67, 68). The OGTT can also provide data for indices of insulin secretory capacity, although these do not seem very well correlated to insulin secretion after intravenous dextrose, probably due to incretin effects.

Fasting surrogates

Fundamentally, almost all fasting surrogates are based on measuring a steady state (fasting) insulin concentration, and operate on the principle that, in the context of euglycemia, insulin secretion will compensate for insulin resistance (Table 1). Thus, higher fasting insulin indicates greater insulin resistance, while lower fasting insulin indicates insulin sensitivity. Because insulin concentrations are relatively low in the fasted state, insulin is primarily acting at the level of the adipose tissue and the liver, rather than the muscle. Thus, many investigators consider fasting surrogates as primarily reflecting hepatic insulin sensitivity (69). In contrast, the hyperinsulinemic-euglycemic clamp (at the typical doses of insulin used) primarily measures muscle insulin sensitivity. When patients are truly fasting, simply measuring the insulin concentration produces very high correlations with M from hyperinsulinemic-euglycemic clamps (70) (Table 1).

Most fasting measures take into account both insulin and glucose concentrations in an effort to account for different expected amounts of insulin secretion when glucose is maintained at different levels within the range of euglycemia. The simplest of these is fasting glucose divided by fasting insulin. The HOMA-IR model was based physiologically on the idea that a feedback loop exists between the glucose production by the liver and insulin production by the beta-cell that works in concert to maintain euglycemia. This index also solely depends on fasting glucose and insulin concentrations. The original and most widely used model, the

HOMA1, approximates the true physiologic model using a simple arithmetic calculation (Table 1) and can be expressed either as a resistance index, so that higher values indicate greater insulin sensitivity, or, by calculating the inverse, as a sensitivity index, where higher values indicate greater insulin resistance. The HOMA2 model has non-linear solutions, and thus must be calculated using computer software, but is more comparable to the minimal model of S_I based on the FSIGT (69). The equation for HOMA1 was originally calibrated to give an output of 1 for normal insulin sensitivity based on insulin assays from the 1970s, and thus will overestimate insulin sensitivity using current insulin assays; the HOMA2 computer software, in contrast, has been recalibrated using modern insulin assays (69). The quantitative insulin sensitivity check index (QUICKI) is slightly more complicated to calculate because it log-transforms insulin and glucose, but is mathematically related to HOMA1 (Table 1) and does not appear to offer obvious advantages to HOMA1 (70).

The major value of fasting surrogates is their simplicity, as they require measurement only of insulin (and, in most cases, glucose) after an 8 to 10 hour fast. Ideally, because insulin is secreted in pulses, 2 to 3 fasting samples should be drawn, 5 to 10 minutes apart, and the mean of the samples should be used for calculations. Several studies have examined the correlation between fasting surrogates of insulin sensitivity and the hyperinsulinemic-euglycemic clamp in children. Correlations have varied considerably among studies, ranging from poor (R=0.25) to excellent (R=0.92) (43, 67, 68, 70, 71). This variability may depend, in part, on the rigor with which testing conditions (particularly, fasting) were controlled. In the majority of large-scale studies, fasting blood draws are performed on an outpatient basis, and thus the patient must be relied upon to maintain a fasted state. This assumption is frequently violated, and can be avoided by admitting patients to hospital the night before the blood sample is obtained. This adds substantially to the cost of studies, but may be less expensive than performing hyperinsulinemic-euglycemic clamps. As with all measures of insulin sensitivity, insulin and glucose must be measured accurately, in accordance with the considerations discussed above.

In diabetic subjects with reduced beta-cell function, insulin secretion can no longer appropriately compensate for insulin resistance, and thus when fasting hyperglycemia is present, any surrogate measure based on measurement of insulin will not be valid. This is of particular concern in patients with type 1 diabetes, or those with type 2 diabetes with advanced disease. To deal with this issue, Dabelea and colleagues developed a fasting surrogate measure of insulin sensitivity specifically for use in diabetic children that does not incorporate insulin into the calculation (72). This measure of insulin sensitivity is sometimes referred to as estimated insulin sensitivity score (eIS), and is based on waist circumference, hemoglobin A1c, and triglycerides (Table 1). The eIS had reasonable correlation with insulin sensitivity measured as the glucose disposal rate obtained from a medium-dose insulin (80 mU m_2 min^{1}) hyperinsulinemic-euglycemic clamp (R=0.65) after overnight normalization of blood glucose by insulin infusion, regardless of diabetes type (type 1 or type 2). A similar “insulin resistance score” (IRS) was developed in 24 adults with type 1 diabetes, incorporating waist to hip ratio, presence of hypertension, and hemoglobin A1c concentration (Table 1) (73). However, this index has not been tested in children, and may have reduced utility in pediatrics due to the inclusion of hypertension as one of the predictive factors.

Fasting surrogate markers of insulin sensitivity have been used effectively in large-scale pediatric clinical trials, for which more complex techniques would have been impractical. For example, the Treatment Options for type 2 Diabetes in Adolescents and Youth (TODAY) trial used fasting surrogates to suggest that the addition of rosiglitazone to metformin resulted in greater improvements in insulin sensitivity than metformin alone (74).

Conclusions

The hyperinsulinemic-euglycemic clamp is considered the gold-standard test of insulin sensitivity in children, but it requires considerable resources and expertise to perform. In addition to providing a direct measure of insulin sensitivity, the hyperinsulinemic-euglycemic clamp can give information about tissue-specific insulin action (using different insulin doses), insulin clearance, and, when combined with isotopic tracers, endogenous glucose production. Hyperinsulinemic-euglycemic clamps are thus exceptionally valuable for small, mechanistic studies.

Surrogate measures of insulin sensitivity, including fasting measures, OGTT measures, the hyperglycemic clamp, and the minimal model of the FSIGT give distinct views of insulin sensitivity that are certainly not equivalent to the hyperinsulinemic-euglycemic clamp, but still have importance and validity. The extant data suggest that, in pediatric-age subjects who are definitely known to be fasting, simple surrogate indices of insulin sensitivity have very high correlation with hyperinsulinemic-euglycemic clamp results. Thus if hyperinsulinemic-euglycemic clamps cannot be performed, only measurement of insulin sensitivity is needed, fasting can be assured, and insulin and glucose are accurately measured, it is not clear that testing more involved than measuring fasting glucose and insulin is required. Fasting measures are especially to be preferred for large scale studies, in which performing more intensive metabolic testing would require prohibitive resources. Ensuring that children are fasting is the major challenge – this may be best ensured by admitting them to the hospital overnight. Although this is expensive, it may still be less resource intensive than performing hyperinsulinemic-euglycemic clamps.

Even for surrogates with strong correlation to the hyperinsulinemic-euglycemic clamp, there is considerable variation in clamp insulin sensitivity for any given value of the surrogate. Thus, researchers and clinicians should not infer that a specific value for insulin sensitivity from a surrogate, such as fasting insulin or HOMA, in a specific child, may be used to calculate whole-body insulin sensitivity for that child. Rather, estimates of insulin sensitivity from surrogates may be compared among different populations. Likewise, surrogate measures of insulin sensitivity, and even the hyperinsulinemic-euglycemic clamp itself, should not be used for clinical diagnostic purposes, but only for research.

In conclusion, there are many measures of insulin sensitivity available that supply different views of insulin action; some require significant technical skills that make them unsuited for most pediatric investigations and most others have relatively limited validation in pediatric samples and assumptions that must be carefully evaluated before being applied to a pediatric sample. Determination of insulin sensitivity is not currently clinically-indicated. Until the diagnosis of pediatric insulin resistance – independent of abnormalities in glucose

metabolism - has been demonstrated to have clinical consequences and effective treatment is available, its measurement should remain restricted to research studies.

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References

1. DeFronzo RA, Tobin JD, Andres R. Glucose clamp technique: a method for quantifying insulin secretion and resistance. Am J Physiol. 1979; 237:E214–23. [PubMed: 382871]
2. Levy-Marchal C, Arslanian S, Cutfield W, Sinaiko A, Druet C, Marcovecchio ML, et al. Insulin resistance in children: consensus, perspective, and future directions. J Clin Endocrinol Metab. 2010; 95:5189–98. [PubMed: 20829185]
3. Bell GI, Kayano T, Buse JB, Burant CF, Takeda J, Lin D, et al. Molecular biology of mammalian glucose transporters. Diabetes care. 1990; 13:198–208. [PubMed: 2407475]
4. DeFronzo RA. Pathogenesis of type 2 (non-insulin dependent) diabetes mellitus: a balanced overview. Diabetologia. 1992; 35:389–97. [PubMed: 1516769]
5. Robbins DC, Andersen L, Bowsher R, Chance R, Dinesen B, Frank B, et al. Report of the American Diabetes Association's Task Force on standardization of the insulin assay. Diabetes. 1996; 45:242–56. [PubMed: 8549870]
6. Miller WG, Thienpont LM, Van Uytfanghe K, Clark PM, Lindstedt P, Nilsson G, et al. Toward standardization of insulin immunoassays. Clinical chemistry. 2009; 55:1011–8. [PubMed: 19325009]
7. Chevenne D, Letailleur A, Trivin F, Porquet D. Effect of hemolysis on the concentration of insulin in serum determined by RIA and IRMA. Clin Chem. 1998; 44:354–6. [PubMed: 9474041]
8. Gambino R. Sodium fluoride: an ineffective inhibitor of glycolysis. Ann Clin Biochem. 2013; 50:3–5. [PubMed: 23129725]
9. Sacks DB, Arnold M, Bakris GL, Bruns DE, Horvath AR, Kirkman MS, et al. Executive summary: guidelines and recommendations for laboratory analysis in the diagnosis and management of diabetes mellitus. Clin Chem. 2011; 57:793–8. [PubMed: 21617153]
10. Wilkerson HL, Hyman H, Kaufman M, Mc CA, Francis JO. Diagnostic evaluation of oral glucose tolerance tests in nondiabetic subjects after various levels of carbohydrate intake. N Engl J Med. 1960; 262:1047–53. [PubMed: 13844739]
11. Buhling KJ, Elsner E, Wolf C, Harder T, Engel B, Wascher C, et al. No influence of high- and low-carbohydrate diet on the oral glucose tolerance test in pregnancy. Clin Biochem. 2004; 37:323–7. [PubMed: 15003736]
12. Arslanian SA, Saad R, Lewy V, Danadian K, Janosky J. Hyperinsulinemia in african-american children: decreased insulin clearance and increased insulin secretion and its relationship to insulin sensitivity. Diabetes. 2002; 51:3014–9. [PubMed: 12351441]
13. Arslanian SA, Kalhan SC. Correlations between fatty acid and glucose metabolism. Potential explanation of insulin resistance of puberty. Diabetes. 1994; 43:908–14. [PubMed: 8013756]
14. Arslanian S, Suprasongsin C. Insulin sensitivity, lipids, and body composition in childhood: is "syndrome X" present? J Clin Endocrinol Metab. 1996; 81:1058–62. [PubMed: 8772576]
15. Arslanian S, Suprasongsin C, Janosky JE. Insulin secretion and sensitivity in black versus white prepubertal healthy children. J Clin Endocrinol Metab. 1997; 82:1923–7. [PubMed: 9177407]
16. Lee S, Bacha F, Hannon T, Kuk JL, Boesch C, Arslanian S. Effects of aerobic versus resistance exercise without caloric restriction on abdominal fat, intrahepatic lipid, and insulin sensitivity in obese adolescent boys: a randomized, controlled trial. Diabetes. 2012; 61:2787–95. [PubMed: 22751691]

17. Lee S, Kim Y, White DA, Kuk JL, Arslanian S. Relationships between insulin sensitivity, skeletal muscle mass and muscle quality in obese adolescent boys. Eur J Clin Nutr. 2012; 66:1366–8. [PubMed: 23073260]

18. Sjaarda LG, Bacha F, Lee S, Tfayli H, Andreatta E, Arslanian S. Oral disposition index in obese youth from normal to prediabetes to diabetes: relationship to clamp disposition index. J Pediatr. 2012; 161:51–7. [PubMed: 22325254]

19. Giannini C, Weiss R, Cali A, Bonadonna R, Santoro N, Pierpont B, et al. Evidence for early defects in insulin sensitivity and secretion before the onset of glucose dysregulation in obese youths: a longitudinal study. Diabetes. 2012; 61:606–14. [PubMed: 22315322]

20. Moran A, Jacobs DR Jr, Steinberger J, Hong CP, Prineas R, Luepker R, et al. Insulin resistance during puberty: results from clamp studies in 357 children. Diabetes. 1999; 48:2039–44. [PubMed: 10512371]

21. Sjaarda LA, Michaliszyn SF, Lee S, Tfayli H, Bacha F, Farchoukh L, et al. HbA(1c) diagnostic categories and beta-cell function relative to insulin sensitivity in overweight/obese adolescents. Diabetes Care. 2012; 35:2559–63. [PubMed: 22912428]

22. Davey RJ, Howe W, Paramalingam N, Ferreira LD, Davis EA, Fournier PA, et al. The effect of midday moderate-intensity exercise on postexercise hypoglycemia risk in individuals with type 1 diabetes. J Clin Endocrinol Metab. 2013; 98:2908–14. [PubMed: 23780373]

23. Rathsman B, Rosfors S, Sjoholm A, Nystrom T. Early signs of atherosclerosis are associated with insulin resistance in non-obese adolescent and young adults with type 1 diabetes. Cardiovascular diabetology. 2012; 11:145. [PubMed: 23185996]

24. Bacha F, Gungor N, Lee S, Arslanian SA. Progressive deterioration of beta-cell function in obese youth with type 2 diabetes. Pediatr Diabetes. 2013; 14:106–11. [PubMed: 22913617]

25. Petryk A, Baker KS, Frohnert B, Moran A, Chow L, Sinaiko AR, et al. Blunted response to a growth hormone stimulation test is associated with unfavorable cardiovascular risk factor profile in childhood cancer survivors. Pediatric blood & cancer. 2013; 60:467–73. [PubMed: 23002034]

26. Verbruggen SC, Coss-Bu J, Wu M, Schierbeek H, Joosten KF, Dhar A, et al. Current recommended parenteral protein intakes do not support protein synthesis in critically ill septic, insulin-resistant adolescents with tight glucose control. Crit Care Med. 2011; 39:2518–25. [PubMed: 21765361]

27. Arslanian SA. Clamp techniques in paediatrics: what have we learned? Horm Res. 2005; 64 (Suppl 3):16–24. [PubMed: 16439840]

28. Hannon TS, Janosky J, Arslanian SA. Longitudinal study of physiologic insulin resistance and metabolic changes of puberty. Pediatr Res. 2006; 60:759–63. [PubMed: 17065576]

29. Muniyappa R, Lee S, Chen H, Quon MJ. Current approaches for assessing insulin sensitivity and resistance in vivo: advantages, limitations, and appropriate usage. Am J Physiol Endocrinol Metab. 2008; 294:E15–26. [PubMed: 17957034]

30. Del Prato S, Bonadonna RC, Bonora E, Gulli G, Solini A, Shank M, et al. Characterization of cellular defects of insulin action in type 2 (non-insulin-dependent) diabetes mellitus. The Journal of clinical investigation. 1993; 91:484–94. [PubMed: 8432857]

31. Matsuda, M.; DeFronzo, RA. In vivo measurement of insulin sensitivity in humans. In: Draznin, B.; Rizza, RA., editors. Clinical Research in Diabetes and Obesity, Part I: Methods, Assessment, and Metabolic Regulation. Humana Press, Inc; Totowa, NJ: 1997. p. 23-65.

32. Krentz AJ, Boyle PJ, Macdonald LM, Schade DS. Octreotide: a long-acting inhibitor of endogenous hormone secretion for human metabolic investigations. Metabolism: clinical and experimental. 1994; 43:24–31. [PubMed: 8289671]

33. Matsuda, M.; DeFronzo, R. In vivo measurement of insulin sensitivity in humans. In: Draznin, B.; Rizza, R., editors. Clinical Research in Diabetes and Obesity, Part I: Methods, Assessment, and Metabolic Regulation. Humana Press; Totowa, NJ: 1997. p. 23-65.

34. Arslanian SA. Clamp techniques in paediatrics: what have we learned? Hormone research. 2005; 64 (Suppl 3):16–24. [PubMed: 16439840]

35. Bonora E, Moghetti P, Zancanaro C, Cigolini M, Querena M, Cacciatori V, et al. Estimates of in vivo insulin action in man: comparison of insulin tolerance tests with euglycemic and

hyperglycemic glucose clamp studies. J Clin Endocrinol Metab. 1989; 68:374–8. [PubMed: 2645308]

36. Reaven GM. Insulin resistance in noninsulin-dependent diabetes mellitus. Does it exist and can it be measured? Am J Med. 1983; 74:3–17. [PubMed: 6337484]
37. Gelding SV, Robinson S, Lowe S, Niththyananthan R, Johnston DG. Validation of the low dose short insulin tolerance test for evaluation of insulin sensitivity. Clin Endocrinol (Oxf). 1994; 40:611–5. [PubMed: 8013142]
38. Javor ED, Cochran EK, Musso C, Young JR, Depaoli AM, Gorden P. Long-term efficacy of leptin replacement in patients with generalized lipodystrophy. Diabetes. 2005; 54:1994–2002. [PubMed: 15983199]
39. Cochran E, Young JR, Sebring N, DePaoli A, Oral EA, Gorden P. Efficacy of recombinant methionyl human leptin therapy for the extreme insulin resistance of the Rabson-Mendenhall syndrome. J Clin Endocrinol Metab. 2004; 89:1548–54. [PubMed: 15070911]
40. Sarnblad S, Kroon M, Aman J. The short insulin tolerance test lacks validity in adolescents with Type 1 diabetes. Diabet Med. 2002; 19:51–6. [PubMed: 11869303]
41. Mitrakou A, Vuorinen-Markkola H, Raptis G, Toft I, Mokan M, Strumph P, et al. Simultaneous assessment of insulin secretion and insulin sensitivity using a hyperglycemia clamp. The Journal of clinical endocrinology and metabolism. 1992; 75:379–82. [PubMed: 1639939]
42. Uwaifo GI, Parikh SJ, Keil M, Elberg J, Chin J, Yanovski JA. Comparison of insulin sensitivity, clearance, and secretion estimates using euglycemic and hyperglycemic clamps in children. The Journal of clinical endocrinology and metabolism. 2002; 87:2899–905. [PubMed: 12050270]
43. Uwaifo GI, Fallon EM, Chin J, Elberg J, Parikh SJ, Yanovski JA. Indices of insulin action, disposal, and secretion derived from fasting samples and clamps in normal glucose-tolerant black and white children. Diabetes Care. 2002; 25:2081–7. [PubMed: 12401760]
44. Bergman RN, Phillips LS, Cobelli C. Physiologic evaluation of factors controlling glucose tolerance in man: measurement of insulin sensitivity and beta-cell glucose sensitivity from the response to intravenous glucose. J Clin Invest. 1981; 68:1456–67. [PubMed: 7033284]
45. Bergman RN, Ider YZ, Bowden CR, Cobelli C. Quantitative estimation of insulin sensitivity. Am J Physiol. 1979; 236:E667–77. [PubMed: 443421]
46. Steil GM, Volund A, Kahn SE, Bergman RN. Reduced sample number for calculation of insulin sensitivity and glucose effectiveness from the minimal model. Suitability for use in population studies. Diabetes. 1993; 42:250–6. [PubMed: 8425661]
47. Tompkins CL, Cefalu W, Ravussin E, Goran M, Soros A, Volaufova J, et al. Feasibility of intravenous glucose tolerance testing prior to puberty. Int J Pediatr Obes. 2010; 5:51–5. [PubMed: 19579147]
48. Cruz ML, Weigensberg MJ, Bergman RN, Goran MI. Frequency of hypoglycaemia during the intravenous glucose tolerance test in overweight children. Int J Pediatr Obes. 2007; 2:122–5. [PubMed: 17763019]
49. Saad MF, Anderson RL, Laws A, Watanabe RM, Kades WW, Chen YD, et al. A comparison between the minimal model and the glucose clamp in the assessment of insulin sensitivity across the spectrum of glucose tolerance. Insulin Resistance Atherosclerosis Study. Diabetes. 1994; 43:1114–21. [PubMed: 8070611]
50. Katz A, Nambi SS, Mather K, Baron AD, Follmann DA, Sullivan G, et al. Quantitative insulin sensitivity check index: a simple, accurate method for assessing insulin sensitivity in humans. J Clin Endocrinol Metab. 2000; 85:2402–10. [PubMed: 10902785]
51. Pillonetto G, Sparacino G, Magni P, Bellazzi R, Cobelli C. Minimal model S(I)=0 problem in NIDDM subjects: nonzero Bayesian estimates with credible confidence intervals. American journal of physiology Endocrinology and metabolism. 2002; 282:E564–73. [PubMed: 11832358]
52. Coates PA, Luzio SD, Brunel P, Owens DR. Comparison of estimates of insulin sensitivity from minimal model analysis of the insulin-modified frequently sampled intravenous glucose tolerance test and the isoglycemic hyperinsulinemic clamp in subjects with NIDDM. Diabetes. 1995; 44:631–5. [PubMed: 7789626]

53. Brandou F, Brun JF, Mercier J. Limited accuracy of surrogates of insulin resistance during puberty in obese and lean children at risk for altered glucoregulation. J Clin Endocrinol Metab. 2005; 90:761–7. [PubMed: 15546909]
54. Rossner SM, Neovius M, Montgomery SM, Marcus C, Norgren S. Alternative methods of insulin sensitivity assessment in obese children and adolescents. Diabetes Care. 2008; 31:802–4. [PubMed: 18202247]
55. Cutfield WS, Jefferies CA, Jackson WE, Robinson EM, Hofman PL. Evaluation of HOMA and QUICKI as measures of insulin sensitivity in prepubertal children. Pediatr Diabetes. 2003; 4:119–25. [PubMed: 14655269]
56. Goran MI, Bergman RN, Cruz ML, Watanabe R. Insulin resistance and associated compensatory responses in african-american and Hispanic children. Diabetes Care. 2002; 25:2184–90. [PubMed: 12453958]
57. Adler-Wailes DC, Periwal V, Ali AH, Brady SM, McDuffie JR, Uwaifo GI, et al. Sex-associated differences in free fatty acid flux of obese adolescents. J Clin Endocrinol Metab. 2013; 98:1676–84. [PubMed: 23450055]
58. Henderson M, Rabasa-Lhoret R, Bastard JP, Chiasson JL, Baillargeon JP, Hanley JA, et al. Measuring insulin sensitivity in youth: How do the different indices compare with the gold-standard method? Diabetes Metab. 2011; 37:72–8. [PubMed: 21126900]
59. Belfiore F, Iannello S, Volpicelli G. Insulin sensitivity indices calculated from basal and OGTT-induced insulin, glucose, and FFA levels. Mol Genet Metab. 1998; 63:134–41. [PubMed: 9562967]
60. Matsuda M, DeFronzo RA. Insulin sensitivity indices obtained from oral glucose tolerance testing: comparison with the euglycemic insulin clamp. Diabetes Care. 1999; 22:1462–70. [PubMed: 10480510]
61. Stumvoll M, Van Haeften T, Fritsche A, Gerich J. Oral glucose tolerance test indexes for insulin sensitivity and secretion based on various availabilities of sampling times. Diabetes Care. 2001; 24:796–7. [PubMed: 11315860]
62. Gutt M, Davis CL, Spitzer SB, Llabre MM, Kumar M, Czarnecki EM, et al. Validation of the insulin sensitivity index (ISI(0,120)): comparison with other measures. Diabetes Res Clin Pract. 2000; 47:177–84. [PubMed: 10741566]
63. Soonthornpun S, Setasuban W, Thamprasit A, Chayanunnukul W, Rattarasarn C, Geater A. Novel insulin sensitivity index derived from oral glucose tolerance test. J Clin Endocrinol Metab. 2003; 88:1019–23. [PubMed: 12629079]
64. Breda E, Cavaghan MK, Toffolo G, Polonsky KS, Cobelli C. Oral glucose tolerance test minimal model indexes of beta-cell function and insulin sensitivity. Diabetes. 2001; 50:150–8. [PubMed: 11147781]
65. Libman IM, Barinas-Mitchell E, Bartucci A, Robertson R, Arslanian S. Reproducibility of the oral glucose tolerance test in overweight children. J Clin Endocrinol Metab. 2008; 93:4231–7. [PubMed: 18713820]
66. Gustafson JK, Yanoff LB, Easter BD, Brady SM, Keil MF, Roberts MD, et al. The stability of metabolic syndrome in children and adolescents. J Clin Endocrinol Metab. 2009; 94:4828–34. [PubMed: 19837941]
67. George L, Bacha F, Lee S, Tfayli H, Andreatta E, Arslanian S. Surrogate estimates of insulin sensitivity in obese youth along the spectrum of glucose tolerance from normal to prediabetes to diabetes. J Clin Endocrinol Metab. 2011; 96:2136–45. [PubMed: 21508130]
68. Yeckel CW, Weiss R, Dziura J, Taksali SE, Dufour S, Burgert TS, et al. Validation of insulin sensitivity indices from oral glucose tolerance test parameters in obese children and adolescents. J Clin Endocrinol Metab. 2004; 89:1096–101. [PubMed: 15001593]
69. Wallace TM, Levy JC, Matthews DR. Use and abuse of HOMA modeling. Diabetes Care. 2004; 27:1487–95. [PubMed: 15161807]
70. Gungor N, Saad R, Janosky J, Arslanian S. Validation of surrogate estimates of insulin sensitivity and insulin secretion in children and adolescents. J Pediatr. 2004; 144:47–55. [PubMed: 14722518]

71. Schwartz B, Jacobs DR Jr, Moran A, Steinberger J, Hong CP, Sinaiko AR. Measurement of insulin sensitivity in children: comparison between the euglycemic-hyperinsulinemic clamp and surrogate measures. Diabetes Care. 2008; 31:783–8. [PubMed: 18174496]

72. Dabelea D, D'Agostino RB Jr, Mason CC, West N, Hamman RF, Mayer-Davis EJ, et al. Development, validation and use of an insulin sensitivity score in youths with diabetes: the SEARCH for Diabetes in Youth study. Diabetologia. 2011; 54:78–86. [PubMed: 20886205]

73. Williams KV, Erbey JR, Becker D, Arslanian S, Orchard TJ. Can clinical factors estimate insulin resistance in type 1 diabetes? Diabetes. 2000; 49:626–32. [PubMed: 10871201]

74. Group TS. Effects of metformin, metformin plus rosiglitazone, and metformin plus lifestyle on insulin sensitivity and beta-cell function in TODAY. Diabetes Care. 2013; 36:1749–57. [PubMed: 23704674]

Table 1

Simple surrogate measures of insulin sensitivity

Surrogate	Formula	Correlation with hyperinsulinemic-euglycemic clamp in children[1]	References	Sample Size	Population	Age (years)
Fasting measures						
Insulin	I_f	0.82	(67)	188	NGT/IGT/T2D/T1D/PCOS, OW	10–19
	$1/I_f$	0.92	(70)	156	NGT/IGT/PCOS	8–19
		.48–.52	(71)	323	Lean/OW	13–15
Glucose to insulin ratio	G_f/I_f	0.78	(43)	31	OW	6–11
		0.92	(67)	188	NGT/IGT/T2D/T1D/PCOS, OW	10–19
		.25–.48	(70)	156	NGT/IGT/PCOS	8–19
		.37	(71)	323	Lean/OW	13–15
HOMA-1	$I_f x G_f/22.5$	0.81	(43)	31	OW	6–11
HOMA-IS	$22.5/I_f x G_f$	0.91	(67)	188	NGT/IGT/T2D/T1D/PCOS, OW	10–19
		.49–.53	(68)	38	NGT/IGT, OW	8–18
		.51	(70)	156	NGT/IGT/PCOS	8–19
		0.57	(71)	323	Lean/OW	13–15
HOMA-2	Calculated using computer software	No studies				
QUICKI	$1/[\log I_f + \log(G_f x 18)]$	0.80	(43)	31	OW	6–11
		0.91	(67)	188	NGT/IGT/T2D/T1D/PCOS, OW	10–19
		.43–.54	(70)	156	NGT/IGT/PCOS	8–19
		.69	(71)	323	Lean/OW	13–15
eIS	Loge[eIS] = 4.64725 − 0.02032 x waist − 0.09779 x A1c − 0.00235 x TG	0.62–0.65	(72)	107	NGT/T1D/T2D	12–19
IRS	IRS = 24.31 − 12.22 x WHR − 3.29 x HTN − 0.57 x A1c	No studies				

Surrogate	Formula	Correlation with hyperinsulinemic-euglycemic clamp in children[1]	References	Sample Size	Population	Age (years)
OGTT-derived measures						
Matsuda index	$10^4/([G_f x 18] \times I_f \times [\text{mean } G_{OGTT} x 18] \times \text{mean } I_{OGTT})^{0.5}$	0.77 0.78	(67) (68)	188 38	NGT/IGT/T2D/T1D/PCOS, OW NGT/IGT, OW	10–19 8–18
Belfiore index	$2/(I_{AUC} \times G_{AUC} + 1)$	No studies				
Stumvoll index	$18.8 - 0.271 \times BMI - 0.0052 \times I_{120} - 0.27 \times G_{90}$	No studies				
Gutt index	$(75000 + (G_f - G_{120}) \times 0.19 \times \text{body weight})/(120 \text{ min} \times [(G_f + G_{120})/2] \times \log [(I_f + I_{120})/2])$	No studies				
Insulin sensitivity index (ISI)	$[1.9/6 \times \text{body weight} \times G_f + 520 - 1.9/18 \times \text{body weight} \times G_{AUC}) - \text{urinary glucose}]/[I_{AUC} \times \text{body weight}]$	0.74	(68)	38	NGT/IGT, OW	8–18

[1] Absolute value of Pearson correlation coefficient

Body weight is measured in kg; Height is measured in meters; Waist, circumference measured in centimeters; BMI, body mass index (body weight/height^2).

G_f, fasting glucose (mmol/L); G_{90}, glucose at 90 minutes after oral glucose load; G_{120}, glucose at 120 minutes after oral glucose load; G_{AUC}, area under the curve for glucose during oral glucose tolerance testing (calculated using trapezoidal method); Mean G_{OGTT}, mean glucose during 120 minute oral glucose tolerance test; I_f, fasting insulin (microunits per mL); I_{120}, insulin at 120 minutes after oral glucose load; I_{AUC}, area under the curve for glucose during oral glucose tolerance testing (calculated using trapezoidal method); Mean I_{OGTT}, mean insulin during 120 minute oral glucose tolerance test

A1c, hemoglobin A1c (%)

HTN, hypertension (1=yes, 0=no)

TG, triglyceride (mg/dL)

WHR, waist to hip circumference ratio

eIS, estimated insulin resistance score

IRS, insulin resistance score

NGT, normal glucose tolerance; IGT, impaired glucose tolerance; T1D, type 1 diabetes; T2D, type 2 diabetes

OW, overweight or obese

PCOS, polycystic ovarian syndrome