Oral Disposition Index in Obese Youth from Normal to Prediabetes to Diabetes: Relationship to Clamp Disposition Index

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Objective We sought to assess the glucose disposition index using an oral glucose tolerance test (OGTT; oDI) compared with the glucose disposition index measured from the combination of the euglycemic-hyperinsulinemic and hyperglycemic clamps (cDI) in obese pediatric subjects spanning the range of glucose tolerance.

Study design Overweight/obese adolescents (n = 185) with varying glucose tolerance (87 normal, 54 impaired, 31 with type 2 diabetes, and 13 with type 1 diabetes) completed an OGTT and both a hyperinsulinemic-euglycemic and a hyperglycemic clamp study. Indices of insulin sensitivity and β-cell function were calculated, and 4 different oDI estimates were calculated as the products of insulin and C-peptide-based sensitivity and secretion indices.

Results Mirroring the differences across groups by cDI, the oDI estimates were greatest in normal glucose tolerance adolescents and lowest in type 2 diabetes mellitus and obese with type 1 diabetes mellitus adolescents. The insulin-based oDI estimates correlated with cDI overall ($r \geq 0.74$, $P < .001$) and within each glucose tolerance group ($r \geq 0.40$, $P < .001$). Also, oDI and cDI predicted 2-hour OGTT glucose similarly.

Conclusions The oDI is a simple surrogate estimate of β-cell function relative to insulin sensitivity that can be applied to obese adolescents with varying glucose tolerance in large-scale epidemiological studies where the applicability of clamp studies is limited due to feasibility, cost, and labor intensiveness. *(J Pediatr 2012;161:51-7)*.

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Conditions associated with impairment in glucose homeostasis in pediatrics, including obesity, insulin resistance, type 2 diabetes mellitus (T2DM), and polycystic ovary syndrome (PCOS), are on the rise.[1-4] Because these disorders involve impairment of both insulin sensitivity and insulin secretion, which are tightly coupled,[5-7] reliable measures of insulin sensitivity and pancreatic β-cell function are needed. Even though the hyperinsulinemic-euglycemic clamp and the hyperglycemic clamp are considered the gold standards for measuring insulin sensitivity and secretion,[8,9] respectively, they are labor intensive, costly, and not suitable for large-scale epidemiologic or interventional studies. Furthermore, to evaluate β-cell function relative to insulin sensitivity, two separate clamps are needed; one, a hyperinsulinemic-euglycemic clamp for insulin sensitivity measurement, and another, the hyperglycemic clamp for insulin secretion measurement.[7,10] Therefore, due to the importance of simultaneously assessing insulin sensitivity and insulin secretion,[5,7,11] simple estimates of the disposition index (DI) to describe insulin secretion relative to insulin sensitivity have been proposed for use in large-scale studies that preclude the use of clamp studies and the frequently sampled intravenous glucose tolerance test (IVGTT).[12,13] These estimates can be calculated from fasting and oral glucose tolerance test (OGTT) data and have been dubbed the oral disposition index (oDI).[12] In longitudinal cohorts of adults without diabetes, baseline oDI is shown to be the strongest metabolic predictor of future diabetes and appears to differentiate those who progress from normal to abnormal glucose metabolism from nonprogressors.[14,15] We previously demonstrated that fasting surrogate estimates of insulin sensitivity, namely 1/fasting insulin,

BMI	Body mass index	I_F	Fasting insulin concentration
cDI	Disposition index measured from the combination of the euglycemic-hyperinsulinemic and hyperglycemic clamps	IGT	Impaired glucose tolerance
		ISSI-2	Insulin secretion-sensitivity index-2
		IVGTT	Intravenous glucose tolerance test
C_F	Fasting C-peptide concentration		
DI	Glucose disposition index	NGT	Normal glucose tolerance
GAD65	Glutamic acid decarboxylase 65-kDa	oDI	Disposition index measured with oral glucose tolerance test
G_F	Fasting glucose concentration	OGTT	Oral glucose tolerance test
HbA1c	Glycated hemoglobin	OT1DM	Obese with type 1 diabetes mellitus
HOMA-IS	Homeostasis model assessment for insulin sensitivity	PCOS	Polycystic ovary syndrome
IA2	Insulinoma-associated protein-2	T2DM	Type 2 diabetes mellitus

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Supported by US Public Health Service grant R01 HD-27503 (to S.A.), K24 HD-01357 (to S.A.), Richard L. Day Endowed Chair (to S.A.), Department of Defense (to S.A., L.G., F.B., S.L. and H.T.), American Diabetes Association Junior Faculty Award (to S.L.), Thrasher Research Fund (to F.B.), and UL1 RR024153 CTSA (previously M01 RR-00084). The authors declare no conflicts of interest.

 10.1016/j.jpeds.2011.12.050

correlated strongly with in vivo insulin sensitivity measured with the hyperinsulinemic-euglycemic clamp in obese youth.[16] The aim of the current investigation was to assess simple estimates of oDI, based on fasting and OGTT-derived insulin sensitivity and secretion, in relation to clamp-measured DI (cDI) in overweight/obese adolescents with varying glucose tolerance, including diabetes.

Methods

All procedures were approved by the Institutional Review Board of the University of Pittsburgh, and parental consent and child assent were obtained prior to any research procedure. A total of 185 overweight/obese youth (70 African American, 109 Caucasian, and 6 biracial; 65 girls with untreated PCOS; ages 8 to <20 years old; Tanner II-V) who had participated in our ongoing "Childhood Metabolic Markers of Adult Morbidity in Blacks" and "Childhood Insulin Resistance" grants and had complete OGTT and hyperinsulinemic-euglycemic and hyperglycemic clamp data were included. Some of these participants were reported previously.[10,16-18] There were 87 with normal glucose tolerance (NGT) including 38 with PCOS, 54 with impaired glucose tolerance (IGT) including 27 with PCOS, 31 with a diagnosis of T2DM and negative glutamic acid decarboxylase 65-kDa (GAD65) and insulinoma-associated protein-2 (IA2) antibodies, and 13 obese with type 1 diabetes mellitus (OT1DM) and positive GAD65 and IA2 antibodies. Among patients with T2DM, there were 7 on lifestyle therapy alone, 15 on metformin alone, 2 on insulin alone, and 4 on metformin and insulin combined. Among OT1DM patients, there were 1 on lifestyle therapy alone, 3 on insulin alone, 2 on metformin alone and 7 on insulin and metformin combined. A glycated hemoglobin (HbA1c) >8.5% was an exclusion criterion for subjects with diabetes for patient safety reasons in undergoing the experimental procedures. Participants were recruited through advertisements in newspapers, buses, and fliers posted on the medical campus and the outpatient clinics in the Weight Management and Wellness Center and the Division of Pediatric Endocrinology. Participants' health status was assessed by history, physical examination, and routine hematologic and biochemical tests. Stage of pubertal development was determined by physical examination according to Tanner criteria[19] and confirmed with measurement of plasma testosterone in males, estradiol in females, and dehydroepiandrosterone sulfate in both males and females. Overweight was defined as body mass index (BMI; kg/m^2) ≥85th and <95th percentile and obesity was BMI ≥95th percentile according to age- and sex-specific percentiles of BMI.[20] Tests were conducted at the Pediatric Clinical and Translational Research Center of the Children's Hospital of Pittsburgh, University of Pittsburgh Medical Center.

A 3-hour hyperinsulinemic-euglycemic clamp was performed after a 10- to 12-hour overnight fast following admission to the Pediatric Clinical and Translational Research Center the previous afternoon. The details of the clamp procedures have been described previously.[17,21] Briefly, participants were advised to consume a standard diet of 55% carbohydrate, 30% fat, and 15% protein the week before the clamp study. In patients with diabetes, regardless of type, metformin and long- and/or intermediate-acting insulin were discontinued 48 hours before the clamp procedures and 24 hours before the OGTT studies, as described.[10,22] Subcutaneous injections of rapid-acting insulin were used to manage glycemia during this withdrawal period, day and night, with the last dose given 6-8 hours before study procedures. Clamp constant-rate insulin infusion (80 μU/m^2/min) was initiated following collection of 4 baseline blood samples every 10 minutes on the morning of the clamp study. Blood glucose was clamped at 100 mg/dL (5.5 mmol/L) with a variable rate infusion of 20% dextrose in water. Peripheral insulin sensitivity was calculated during the last 30 minutes of the clamp to be equal to the rate of exogenous glucose infusion divided by the steady-state clamp insulin concentration and expressed per kilogram of body weight (mg/kg/min per μU/mL).

On a separate occasion, 1-3 weeks apart, and in a random order, a 2-hour hyperglycemic clamp (225 mg/dL) was performed after a 10- to 12-hour overnight fast. The details of the clamp procedures have been described previously.[8,17,23] Diet and glycemia management was the same as given for the euglycemic clamp. Briefly, plasma glucose concentration was rapidly increased to approximately 225 mg/dL with a bolus dextrose infusion and maintained with a variable rate infusion of 20% dextrose in water. First-phase insulin (μU/mL) was calculated as the mean insulin concentration of 5 measurements at times 2.5, 5, 7.5, 10, and 12.5 minutes of the clamp.

Either the day preceding one of the clamp procedures or on a separate visit within a 1- to 3-week period, assigned at random, a 120-minute OGTT (1.75 g/kg glucola, maximum 75 g) was performed in the morning after a 10- to 12-hour overnight fast. Diet and glycemia management was the same as described earlier. Blood samples were obtained at −15, 0, 15, 30, 60, 90, and 120 minutes for determination of glucose, insulin, and C-peptide as described previously.[22,24]

Plasma glucose was measured by the glucose oxidase method (Yellow Springs Instrument Co, Yellow Springs, Ohio). Plasma insulin was analyzed by a commercial radioimmunoassay (catalog No. 1011; Linco, St Charles, Missouri) as previously done.[17] C-peptide concentration was measured using a double-antibody radioimmunoassay (Siemens Medical Solutions Diagnostics, Tarrytown, New York). Pancreatic autoantibodies (GAD65 and IA2) were measured to distinguish obese youth with autoimmune type 1 diabetes from type 2 diabetes as reported previously.[10]

Fasting glucose (G_F), insulin (I_F), and C-peptide (C_F) concentrations were derived from the baseline measurements of the OGTT. From I_F and G_F, the homeostasis model assessment for insulin sensitivity (HOMA-IS) was calculated using the HOMA2 calculator at http://www.dtu.ox.ac.uk.[25,26] The insulinogenic index and comparable C-peptide index ($\Delta I_{30}/\Delta G_{30}$, $\Delta C_{30}/\Delta G_{30}$) were calculated as the ratio of the incremental change of insulin, glucose, or C-peptide from 0 to 30 minutes of the OGTT as previously reported.[24,27,28]