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Use of a simple liquid meal test to evaluate insulin sensitivity and beta-cell function in children

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Abstract

Insulin sensitivity and β -cell function are useful indices of metabolic disease risk but are difficult to assess in young children because of the invasive nature of commonly-used methodology. A meal-based method for assessing insulin sensitivity and β -cell function may at least partially alleviate concerns. Objectives of this study were to: 1) determine the association of insulin sensitivity assessed by liquid meal test with that determined by an insulin-modified frequently sampled intravenous glucose tolerance test (FSIGT); 2) examine the association of insulin sensitivity derived from each test with measures of body composition, fat distribution, and metabolic health (lipids, fasting insulin and glucose, and surrogate indices of insulin sensitivity); and 3) examine the associations of indices of β -cell function derived from each test with total and regional adiposity. Forty-seven children (7–12 yr) underwent both a liquid meal test and an FSIGT. The insulin sensitivity index derived from the meal test (SI-meal) was positively associated with that from the FSIGT (SI-FSIGT; $r=0.63$; $P<0.001$), and inversely with all measures of insulin secretion derived from the meal test. Both SI-meal and SI-FSIGT were associated with measures of total and regional adiposity. SI-meal, but not SI-FSIGT, was associated with triglycerides and fasting insulin, after adjusting for ethnicity, gender, pubertal stage, and fat mass. Basal insulin secretion measured during the meal test was positively associated with all measures of adiposity, independent of insulin sensitivity. In conclusion, a liquid meal offers a valid and sensitive means of assessing insulin sensitivity and β -cell responsiveness in young children.

Keywords

Adiposity; Children; Insulin secretion; Insulin sensitivity; Lipid; Metabolic Health

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Introduction

The prevalence of pediatric type 2 diabetes is increasing. Pediatric type 2 diabetes has been diagnosed in children less than 10 years of age, with the highest frequency of new diagnoses occurring during the pubertal years, primarily among obese individuals (1; 2). Data from adults suggest that obesity leads to insulin resistance, which places stress on the beta-cell, eventually leading to insufficient beta cell function. The etiology of type 2 diabetes, including the contribution of obesity, has been less well characterized in children.

Insulin sensitivity and β -cell function are difficult to assess in young children however, because of the invasive nature of commonly-used methodology. The euglycemic clamp (3) and the insulin-modified frequently-sampled intravenous glucose tolerance test (FSIGT) (4; 5) are two of the most commonly used tests and are considered to be robust measures of insulin sensitivity in adults. These tests assess whole-body insulin sensitivity that reflects both insulin stimulation of glucose uptake and insulin suppression of hepatic glucose production. The “gold standard” euglycemic clamp involves continuous infusion of exogenous insulin over ~3 hours while “clamping” circulating glucose at basal levels by way of continuous glucose infusion. One limitation of the euglycemic clamp however, is that it provides no information about insulin secretion. The FSIGT is a commonly used alternative that permits simultaneous assessment of both insulin sensitivity and insulin secretion using circulating concentrations of insulin, glucose, and C-peptide collected over 3 to 4 h following injection of a single bolus of glucose. The FSIGT is fundamentally different from the clamp in that the dynamic physiological response to glucose is incorporated in the derived indices. Both tests require frequent blood samples and the intravenous administration of glucose and insulin, processes that may not be readily accepted and tolerated by parents and their children. Although surrogate indices of insulin sensitivity and secretion based on fasting concentrations of insulin and glucose have been developed (6; 7), these indices do not consider the dynamic response to glucose elevation, and primarily reflect hepatic metabolism (8). Consequently, there is a need to identify strong and less invasive methods for assessing whole-body insulin sensitivity and β -cell response that can be used in a pediatric population.

The use of oral glucose or mixed macronutrient meal tests to accurately assess insulin sensitivity and insulin secretion may provide a simpler and more acceptable test for children, and also provide the advantage of being more physiologically relevant in comparison to an FSIGT because nutrient absorption and incretin action are not bypassed. For this test, children consume glucose or a solid or liquid meal, and 7–25 blood samples are collected over 2–7 h, depending upon the protocol used. Insulin sensitivity is derived from mathematical modeling of glucose and insulin data (9; 10), and has been validated against clamp in adults (11; 12), and compared to FSIGT in adults (13; 14). In children and adolescents, estimates of insulin sensitivity from oral glucose and mixed meal tests correlate well with those derived from clamp studies (15; 16), and with that derived using a triple tracer approach (17). Furthermore, the oral glucose test has been shown to be a useful predictor of conversion to type 2 diabetes among obese adolescents (18). Another advantage of the oral glucose or meal test is the ability to simultaneously measure indices of β -cell

function through mathematical modeling of glucose and C-peptide (9), which is secreted in equimolar amounts with insulin but not cleared by the liver.

To our knowledge, no previous study has compared the insulin sensitivity index derived from the FSIGT to that derived from a meal challenge among peripubertal children. Given the association of obesity and metabolic health with insulin sensitivity and secretion, it would also be of interest to examine associations of indices of insulin sensitivity and secretion derived from FSIGT and meal test with measures of adiposity and metabolic health in children.

The objectives of this study were to: 1) determine the association of insulin sensitivity assessed with liquid meal test (SI-meal) with that determined by FSIGT (SI-FSIGT); 2) examine the association of insulin sensitivity derived from each test with measures of body composition (total fat mass, % fat, intra-abdominal fat, and sub-cutaneous fat) and metabolic health (lipids, fasting insulin and glucose, and surrogate indices of insulin sensitivity); and 3) examine the associations of indices of β -cell function derived from the FSIGT and meal test with total and regional adiposity. We tested the hypotheses that SI-meal would be significantly associated with SI-FSIGT; that the two insulin sensitivity indices would be similarly associated with measures of adiposity and metabolic health; and that, irrespective of whether meal or FSIGT was used, adiposity would be positively associated with basal β -cell response and inversely associated with glucose-stimulated insulin secretion after adjusting for insulin sensitivity.

Methods

Participants and protocol

Children were recruited from a larger parent study, details of which have been published (19). Children involved in this ancillary study (N=54) agreed to undergo one additional test, the liquid meal tolerance test. Other results from this ancillary study have been published (20; 21). Inclusion/exclusion criteria were age between 7 and 12 years, no major illness, not taking prescription medications known to affect glucose metabolism or body composition, and normal glucose tolerance. The Institutional Review Board of the University of Alabama at Birmingham (UAB) approved all procedures. Parents and children provided written informed consent and assent, respectively, before entry to this ancillary study.

Testing was conducted during two overnight inpatient evaluations at UAB's General Clinical Research Center (GCRC). The first visit involved a physical examination, assessment of pubertal status (22; 23), assessment of body fat distribution by computed tomography scanning, and a frequently sampled FSIGT. The second visit, which occurred approximately one week after the first visit, involved a liquid meal tolerance test and body composition analysis. For both visits, participants arrived between 4:00 pm and 6:00 pm, and received a standardized meal, which was consumed by 8:00 pm, after which no caloric or caffeinated beverages or snacks were consumed. Each parent-child pair was assigned a private room and instructed to minimize physical activity.

Anthropometrics

Participants were weighed (Scale-tronix 6702W; Scale-tronix, Carol Stream, IL) in minimal street clothing and without shoes, to the nearest 0.1 kg. Height, without shoes, was measured using a digital stadiometer (Heightronic 235; Measurement Concepts, Snoqualmie, WA). Waist circumference was measured at the narrowest part of the torso and hip circumference measured at the widest part of the buttock, to the nearest 0.1 cm using a flexible tape measure (Gulik II; Country Technology, Gays Mills, WI). The same registered dietitian obtained anthropometric measures on all children.

Body composition and fat distribution

Body composition was assessed with dual-energy X-ray absorptiometry (DXA; GE-Lunar Prodigy; Madison, WI). Cross-sectional areas of intra-abdominal adipose tissue (IAAT) and subcutaneous abdominal adipose tissue (SAAT) were assessed with computed tomography scanning. A single slice was taken at the level of the umbilicus as previously described (24).

Insulin sensitivity and β -cell response to glucose

Insulin sensitivity and β -cell response to glucose were assessed by both an insulin-modified frequently-sampled intravenous glucose tolerance test (FSIGT) and a liquid meal test. For the FSIGT, flexible intravenous catheters were placed in the antecubital spaces of both arms. Two blood samples were drawn over 20 minutes for determination of basal glucose and insulin, and values averaged. At time “0”, glucose (50% dextrose at 300 mg/kg) was administered intravenously. Insulin (0.02 U/kg) was infused over a 5-min period from 20–25 min post glucose injection. Subsequent blood samples were drawn at 2, 3, 4, 5, 6, 8, 10, 12, 15, 19, 20, 21, 22, 24, 26, 28, 30, 35, 40, 50, 60, 70, 180, and 240 min post glucose injection. Sera were stored at -85°C until analysis for glucose, insulin and C-peptide. Insulin sensitivity (SI-FSIGT) was determined using the Millennium version of the minimal model; MINMOD Millennium 5.18, 2000 (25). Indices of insulin secretion were derived by mathematical modeling of C-peptide and glucose data collected during the FSIGT (26–28). As described by Cobelli and colleagues (13), these indices are: basal (PhiB); first-phase (Phi1); second-phase (Phi2); total (PhiTOT). In addition, given that β -cell function should be interpreted relative to the individuals’ insulin sensitivity, the Disposition Index (DI) was calculated as the product of SI and the Acute Insulin Response (AIR), which was calculated as the incremental area under the curve for the first 10 minutes of the FSIGT.

For the liquid meal test, a flexible intravenous catheter was placed in the antecubital space of the left arm. Two blood samples were taken over a 15 min period for determination of basal glucose and insulin (the average of the two values). At time “0”, a liquid meal was administered (240 ml Ensure, Ross Laboratories, IL, USA; 250 kcal, 6g fat, 40g carbohydrate, and 9g of protein). Children were instructed to consume the meal within 5 min. Additional blood samples were drawn at 5, 10, 15, 20, 25, 30, 45, 60, 90, 120, 150, and 180 min after the start of meal ingestion. Sera were separated and stored at -85°C until assayed for insulin, glucose, and C-peptide. Insulin sensitivity and β -cell responsivity to glucose were determined as described (9). These models use insulin and glucose data to generate an insulin sensitivity index (SI-meal), and glucose and C-peptide data to generate indices of β -cell responsivity to glucose. The β -cell indices are basal β -cell response (PhiB),

static β -cell response (PhiS), dynamic β -cell response (PhiD), and total β -cell response (PhiTOT). DI-meal was calculated as the product of SI and PhiD.

Surrogate indices of insulin resistance (HOMA-IR, (6)) and insulin sensitivity (QUICKI (7)) also were calculated in order to examine associations of these commonly-used indices with SI-meal and SI-FSIGT. Both indices are based on fasting insulin and glucose values and are thought to primarily reflect hepatic metabolism (8).

Laboratory analyses

All analyses were performed in the Core Laboratory of the GCRC, DRTC, and NORC. Insulin was determined using RIA reagents from Linco/Millipore (St. Charles, MO); C-peptide with RIA materials from Diagnostic Products Corporation/Siemens (Los Angeles); glucose and lipids via SIRRUS analyzer (Stanbio Laboratory, Boerne, TX). Intra- and inter-assay cvs were 10% for all analytes.

Statistical analyses

Means, standard deviations, and distributions of participant characteristics and outcome variables were determined. The association between SI-meal and SI-FSIGT, and between each comparable index of insulin secretion from the meal and FSIGT were determined using simple Pearson correlation analysis. Associations of the two SI indices with total and regional adiposity were determined using partial correlation analysis, adjusting for ethnicity, sex, and pubertal stage. Associations of the two SI indices with indices of metabolic health (insulin, glucose, and the lipid profile) were determined using partial correlation analysis, adjusting for ethnicity, sex, pubertal stage, and total body fat mass. Associations of the indices of insulin secretion with measures of adiposity were determined using partial correlation analysis, adjusting for ethnicity, sex, pubertal stage, and SI from the meal test or FSIGT, as appropriate. Data for SI, insulin, Phi values, DI, triglycerides, HDL-C, HOMA-IR, IAAT, SAAT were log transformed prior to correlational analyses to ensure a normal distribution. All analyses were conducted using SPSS software version 18.0 (SPSS Inc., Chicago, IL).

Results

Final analyses were conducted on 47 children with complete data for both the liquid meal test and FSIGT. Children were excluded from the final analyses if they had insufficient or hemolyzed sera (6 individuals) or if SI for meal or FSIGT was an outlier (1 individual). In addition, two children had insufficient sera to measure C-peptide following the FSIGT, and so were excluded from the analyses involving indices of β -cell secretion from the FSIGT. Characteristics of the study population are shown in Table 1. The sample included 28 boys (19 girls) and 32 African Americans (15 European Americans).

SI-meal was positively associated with SI-FSIGT ($r=0.63$; $P<0.001$; Fig. 1). SI-meal was inversely associated with each measure of β -cell responsivity derived from the meal test, after adjusting for ethnicity, gender, and pubertal stage: PhiB, $r = -0.38$, $P<0.05$; PhiS, $r = -0.33$, $P<0.05$; PhiD, $r = -0.38$, $P<0.05$; PhiTOT, $r = -0.52$, $P<0.001$. Similarly, SI-FSIGT was inversely associated with PhiB and Phi2 from the FSIGT, after adjusting for ethnicity,

gender, and pubertal stage (PhiB: $r = -0.44$, $P < 0.01$; Phi2: $r = -0.44$, $P < 0.01$). SI-FSIGT was not significantly associated with Phi1 ($r = -0.15$) or PhiTOT ($r = -0.21$). DI-FSIGT and DI-meal were not correlated with each other ($r = -0.032$, $P = 0.83$; not shown).

PhiB-meal was positively associated with PhiB-FSIGT ($r = 0.514$, $P < 0.001$; Fig. 2), and there was a trend for PhiS-meal and Phi2-FSIGT to be positively associated ($r = 0.273$, $P = 0.07$). PhiD-meal and Phi1-FSIGT were not associated with each other ($r = -0.129$, $P > 0.3$), and neither were PhiTOT from each test ($r = 0.226$, $P = 0.14$).

Associations of SI-meal and SI-FSIGT with measures of body composition are shown in Table 2. Both SI measures were associated with all measures of adiposity, with the exception of SI-FSIGT and %fat, which failed to achieve statistical significance. Neither measure of DI was associated with any measure of body composition to a statistically significant level (not shown).

Associations of SI-meal and SI-FSIGT with measures of metabolic health are shown in Table 3. After adjusting for ethnicity, sex, pubertal stage, and fat mass, SI-meal was inversely associated with TG and fasting insulin. SI-FSIGT was not associated with any measure of metabolic health. Neither measure of DI was associated with any measure of metabolic health (not shown).

PhiB-meal was positively associated with all measures of adiposity, independent of insulin sensitivity (Table 4). In contrast, PhiB-FSIGT was not associated with any measure of adiposity. Phi1 was found to be inversely associated with IAAT, independent of insulin sensitivity ($P < 0.05$). There were no statistically significant associations between other meal or FSIGT-derived indices of β -cell responsivity and measures of adiposity.

Discussion

The major objective of this study was to determine the association of SI-meal with SI-FSIGT in children, and to examine how these two measures related to body composition and metabolic risk. We found that the relatively less-invasive meal test produced an index of insulin sensitivity that was well correlated with that derived from the FSIGT. Further, SI-meal was inversely associated with measures of adiposity, reflecting its sensitivity to detect the adverse effects of adiposity on insulin action. Measures of β -cell responsivity derived from the meal test also provided information regarding the potential influence of adiposity on diabetes risk, with more overweight children having augmented basal insulin secretion. These results indicated that meal-derived SI and indices of β -cell responsivity are likely to be useful measures for studies of adiposity and metabolic risk in healthy children.

We found that, in a sample of children aged 7–12 years, SI-meal was correlated with SI-FSIGT ($r = 0.63$; $P < 0.001$; Fig. 1), suggesting that SI-meal is a valid means of assessing insulin sensitivity in children. Insulin sensitivity is an important determinant of metabolic health, but has been relatively difficult to determine accurately in children due to the invasive nature of commonly used tests. The liquid meal test used in this study reduces or removes many of the ethical challenges and invasive elements of the clamp and the FSIGT. Further, the meal test provides simultaneous measures of insulin sensitivity and secretion,

thereby maximizing the insight into metabolism that can be gained from a single test. An additional benefit of the liquid meal test is that it is more physiologically relevant, as it incorporates processes such as incretin secretion that may affect the outcomes of interest. Thus, the observation that SI-meal appears well-correlated with SI-FSIGT offers pediatric investigators a powerful tool for assessing insulin sensitivity in children.

Although statistically significant, the correlation coefficient between SI-FSIGT and SI-meal was not as large as might be expected. Previous studies among obese children have found higher correlations (0.77–0.78) between an oral glucose tolerance test (OGTT)-based index of insulin sensitivity and that measured by hyperinsulinemic-euglycemic clamp (15; 16). Possible explanations for the differences among studies include inherent error in the derived indices and differences in the characteristics of the study populations. It may be that surrogate whole-body indices of insulin sensitivity are not as robust among a younger, leaner sample of children as compared to obese older children and adolescents. Nonetheless, the liquid meal test has a low subject burden and high physiological relevance, as it allows for concurrent measurement of the incretin response. Thus it may be of interest in future research to conduct validation studies of the liquid meal test-derived SI measure in comparison to the clamp technique.

In this cohort, we also compared DI estimates derived from the meal test and from the FSIGT, and found that they were not associated with each other. Although each provides an estimate of β -cell function relative to SI, the measures are not analogous. DI-meal uses PhiD, which reflects C-peptide response in relation to glucose, whereas DI-FSIGT uses an incremental AUC measure of insulin.

Because adiposity, particularly central adiposity, is a strong determinant of insulin sensitivity in both adults and children (29–31), we were interested to determine if total and regional adiposity were adversely associated with SI-meal in our sample of children. Results of this study showed that both SI-meal and SI-FSIGT were inversely associated with most measures of adiposity. Therefore, the meal-based index of insulin sensitivity is just as sensitive to the association with adiposity as is the FSIGT-based index of insulin sensitivity. In adults, insulin resistance is associated with hyperinsulinemia and dyslipidemia (32). In this study, we examined independent associations of SI-meal and SI-FSIGT with fasting insulin and the lipid profile in children. We found that SI-meal was inversely associated with concentrations of both triglycerides and fasting insulin, after adjusting for adiposity. In contrast, SI-FSIGT was not associated with lipids or insulin, suggesting that SI-meal may be a more sensitive indicator of risk for metabolic disease. It was somewhat surprising that SI-FSIGT was not associated with HOMA or QUICKI, and that only marginal associations of these surrogate indices of insulin sensitivity were found with SI-meal. It is possible that the small sample size of the current study limited our ability to detect meaningful associations between these measures. In addition, weight status of the children might also have contributed to the poor strength of associations between SI-FSIGT or SI-meal and HOMA and QUICKI. In previous studies among obese children and adolescents, HOMA and QUICKI were strongly correlated with whole body estimates of insulin sensitivity (16; 33). Previous work from our laboratory, however, has shown that associations between SI-FSIGT and HOMA or QUICKI were stronger among overweight versus normal weight

women (34). Therefore, in this sample of primarily normal weight children, associations of these estimates may be weaker. It is also possible that differences in sensitivity of each measure to hepatic versus skeletal muscle insulin sensitivity contributed to the lack of associations shown in this study. As mentioned previously, FSIGT is thought to primarily reflect insulin sensitivity in skeletal muscle, and because HOMA and QUICKI are derived from fasting insulin and glucose, they are more likely to reflect hepatic insulin sensitivity (8; 35). Together with the existing literature, findings of the current study suggest that HOMA and QUICKI may lack sensitivity as a whole-body measure of insulin sensitivity among normal weight, normoglycemic children.

An additional aim of this study was to determine if C-peptide-based measures of insulin secretion from the FSIGT were associated with analogous measures from the meal test, and how these measures related to insulin sensitivity, body composition, and fat distribution. In this cohort, we found that PhiB from the FSIGT was associated with PhiB from the meal test. In contrast, FSIGT-derived measures of β -cell response reflecting first- and second-phase and total insulin secretion were not associated with analogous measures from the meal test. In a previous study among young and old adults, Basu and colleagues (28) found positive associations of PhiTOT from each test, along with Phi1-FSIGT with PhiD-meal, and Phi2-FSIGT with PhiS-meal. It is possible that both the small sample size and the relative homogeneity of the sample in the current study precluded the detection of comparable associations.

We found that all measures of insulin secretion derived from the meal test were inversely associated with SI-meal. Similarly, basal and second phase insulin secretion from the FSIGT was inversely associated with SI-FSIGT. These results agree with data from adults indicating that β cells compensate for insulin resistance by increasing insulin secretion (36). In this study, we observed that PhiB-meal was positively associated with all indices of total and regional adiposity, an observation that agrees with data from adults showing greater basal insulin secretion in obese vs normal-weight individuals (37). The associations of PhiB-meal with adiposity were independent of insulin sensitivity, supporting direct effects of adiposity on the β -cell. Data from adults suggest that adiposity also promotes β -cell hyperplasia, with resultant increased basal insulin secretion and increased fasting insulin concentration (37). Consequently, similar to the finding in adults, excess adiposity in children may contribute to fasting hyperinsulinemia both as compensation for relative insulin resistance, and as a result of β -cell hyperplasia.

Strengths of the study were the use of robust measures of insulin sensitivity and body composition in a sample of young children. Limitations were the relatively small sample size that did not permit sub-analyses by gender or ethnicity, and the uniform dose of liquid meal (one 8-oz container of Ensure) provided to all children. Finally, no children younger than 7 years were tested in this study. We recruited children aged 7–12 years for this study because we have established previously that children in this age range are able to tolerate an FSIGT (29). It would also be of interest in future studies to perform the same comparison among older children, given that insulin sensitivity commonly decreases during adolescence.

In conclusion, the insulin sensitivity index derived from the meal test was positively associated with that derived from FSIGT, suggesting that the relatively less-invasive meal test can be used in children to provide an accurate assessment of whole-body insulin sensitivity. Further, the meal-derived indices of insulin action were associated with a number of measures of adiposity and metabolic health, suggesting that the liquid meal test provides a useful indicator of the adverse effects of adiposity on insulin sensitivity and metabolic health. Finally, insulin secretion measures derived from the meal test indicated that more overweight children showed an enhanced basal insulin response to glucose, and tended to show a suppressed first-phase insulin response. Ultimately, this pattern of insulin secretion may contribute to the development of impaired glucose tolerance and type 2 diabetes (38; 39).

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Fig. 1. SI-FSIGT [$\times 10^{-4} \text{ min}^{-1}/(\mu\text{IU/ml})$] vs SI-meal ($10^{-4} \text{ dl/kg per min per } \mu\text{IU/ml}$). Correlation coefficient (r) = 0.63; $P < 0.001$.

Fig. 2.
PhiB-meal (10^9 min^{-1}) vs PhiB-FSIGT (10^9 min^{-1}). Correlation coefficient (r) = 0.51;
 $P < 0.001$.

Table 1

Characteristics of the participant population.

Measure	Mean $\pm$ SD	Median	Interquartile Range
Age (yr)	10.0 $\pm$ 1.5	10.0	2
Sex (M/F)	28/19		
Ethnicity (AA/EA)	32/15		
Pubertal stage	1.5 $\pm$ 0.7	1.0	1
Weight (kg)	38.8 $\pm$ 9.6	36.0	13.0
Body mass index (kg/m ²)	19.1 $\pm$ 3.6	17.9	3.5
Waist circumference (cm)	65.1 $\pm$ 9.2	62.8	10.1
Hip circumference (cm)	77.3 $\pm$ 8.2	75.5	11.2
Total body fat mass (kg)	10.0 $\pm$ 6.5	8.5	8.0
Total body lean mass (kg)	26.7 $\pm$ 5.2	25.9	5.3
%fat	25.6 $\pm$ 10.9	25.6	15.1
Fasting glucose (mg/dL)	92.6 $\pm$ 7.1	92.0	11
Fasting insulin (μ IU/ml)	14.3 $\pm$ 4.8	14.0	8
SI-meal ($\times 10^{-4}$ dl/kg min ⁻¹ /(μ IU/ml))	5.5 $\pm$ 4.0	4.7	4.5
PhiB-meal (10^9 min ⁻¹)	5.8 $\pm$ 2.3	5.4	2.8
PhiS-meal (10^9 min ⁻¹)	64.0 $\pm$ 32.7	62.7	44.6
PhiD-meal (10^9)	623.2 $\pm$ 281.7	580.8	267.1
PhiTOT-meal (10^{-9} min ⁻¹)	42.4 $\pm$ 26.0	36.4	28.2
DI-meal (SI $\times$ PhiD)	197.0 $\pm$ 140.9	156.1	136.4
SI-FSIGT ($\times 10^{-4}$ min ⁻¹ /(μ IU/ml))	4.3 $\pm$ 2.1	4.1	2.6
PhiB-FSIGT (10^9 /min ⁻¹)	4.9 $\pm$ 1.7	4.6	2.4
Phi1-FSIGT (10^9)	236.7 $\pm$ 106.6	217.1	182.0
Phi2-FSIGT (10^9 /min ⁻¹)	5.2 $\pm$ 4.1	3.8	3.8
PhiTOT-FSIGT (10^9 /min ⁻¹)	6.6 $\pm$ 5.1	4.5	6.0
DI-FSIGT (SI $\times$ AIR)	4329.8 $\pm$ 2374.8	3571.5	2728.2
Total cholesterol (mg/dL)	151.0 $\pm$ 24.6	146.0	28.0
HDL-cholesterol (mg/dL)	54.8 $\pm$ 14.8	53.0	23.0
Triglycerides (mg/dL)	62.2 $\pm$ 38.9	49.0	38.0

Table 2

Associations of SI-meal and SI-FSIGT with measures of body composition. Data shown are partial correlations (r), adjusted for ethnicity, sex, and pubertal stage.

	SI-meal	SI-FSIGT
BMI	-0.47**	-0.42**
Waist circ	-0.49**	-0.40*
Hip circ	-0.49**	-0.41**
Fat mass	-0.54***	-0.41**
%fat	-0.43**	-0.24
IAAT	-0.45**	-0.41**
SAAT	-0.43**	-0.33*

*
P<0.05,

**
P<0.01,

P<0.001

Table 3

Associations of SI-meal and SI-FSIGT with measures of metabolic health. Data shown are partial correlations (r), adjusted for ethnicity, sex, pubertal stage, and fat mass.

	SI meal	SI FSIGT
Total cholesterol	-0.15	-0.17
HDL-cholesterol	0.15	-0.14
Triglycerides	-0.37*	-0.09
Fasting insulin	-0.33*	-0.21
Fasting glucose	-0.05	-0.04
HOMA-IR	-0.31 [†]	-0.20
QUICKI	0.31 [†]	0.18

[†] 0.05>P>0.10,

* P<0.05,

** P<0.01,

*** P<0.001

Table 4

Associations of indices of insulin secretion from the meal and FSIGT tests with measures of adiposity. Data shown are partial correlations (r), adjusted for ethnicity, sex, pubertal stage, and SI (from meal or FSIGT as appropriate).

	Total fat	%fat	IAAT	SAAT
PhiB-meal	0.49**	0.44**	0.45**	0.47**
PhiS-meal	0.24	0.25	−0.05	0.18
PhiD-meal	−0.26	−0.26	−0.05	−0.07
PhiTOT-meal	0.09	0.10	−0.07	0.04
PhiB-FSIGT	0.15	0.13	0.13	0.16
Phi1-FSIGT	0.04	0.08	−0.36*	−0.17
Phi2-FSIGT	−0.10	−0.18	−0.05	−0.08
PhiTOT-FSIGT	0.17	0.18	0.11	0.23

**
P<0.01;

*
P<0.05