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The "Obese Insulin-Sensitive" Adolescent: Importance of Adiponectin and Lipid Partitioning

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There is a wide interindividual variation in peripheral insulin sensitivity at any given body mass index or percent body fat among obese adolescents with normal glucose tolerance. The goals of this study were to determine whether variability in insulin sensitivity is associated with differences in patterns of lipid partitioning or substrate use under fasting and hyperinsulinemic conditions.

We compared 14 obese insulin-resistant adolescents with 14 obese insulin-sensitive controls, pair matched for age, gender, pubertal stage and body composition. Insulin sensitivity was assessed by the hyperinsulinemic-euglycemic clamp, intramyocellular lipid content by ^{1}H-nuclear magnetic resonance and visceral fat by magnetic resonance imaging.

Obese insulin-sensitive subjects had lower intramyocellular (1.64 ± 0.68 *vs.* 2.26 ± 0.62% of water peak, $P = 0.017$) and visceral lipid deposition (45 ± 23 *vs.* 77 ± 52 cm^2, $P = 0.04$) and a higher level of adiponectin, compared with their obese-resistant counterparts (8.8 ± 3.6 *vs.* 6.5 ± 1.8 μg/dl, $P = 0.015$). Glycerol fluxes were similar between the two obese groups yet occurred in the face of different concentrations of insulin. Intramyocellular lipid and visceral fat were negatively related to insulin sensitivity.

Obese insulin-sensitive adolescents are characterized by lower lipid deposition in the intramyocellular and visceral compartments and greater levels of adiponectin, despite similar degree of adiposity. **(*J Clin Endocrinol Metab* 90: 3731–3737, 2005)**

CHILDHOOD OBESITY IS one of the most serious and urgent public health problems in both developed and developing countries (1). Many of the metabolic and cardiovascular complications associated with obesity, namely impaired glucose tolerance, type 2 diabetes, hypertension, and dyslipidemia, are already present during childhood and are closely linked to the concomitant insulin resistance/hyperinsulinemia (2, 3) and the degree of adiposity (4).

Studies from our childhood obesity cohort demonstrated that obese children with impaired glucose tolerance (IGT) were much more insulin resistant than obese children with normal glucose tolerance (NGT) (5). Furthermore, obese children with IGT had greater lipid deposition in the muscle and visceral compartments (6), compared with their counterparts with NGT. Although most obese children with NGT are insulin resistant to some degree, our studies also indicate that there is a wide interindividual variation in peripheral insulin sensitivity at any given body mass index (BMI) or percent body fat among these youngsters (7). This observation suggests that factors other than total body fat contribute to the variation in insulin sensitivity, even in the absence of abnormal glucose tolerance. Identifying and understanding the metabolic phenotype of the obese child or adolescent who is at greatest risk for progression from NGT to IGT and ultimately to type 2 diabetes mellitus may help to focus prevention programs in those who will benefit the most.

This study was undertaken to examine whether alterations in lipid partitioning in skeletal muscle and abdominal fat tissues differentiate insulin-sensitive from insulin-resistant obese children with NGT, as they do obese IGT from obese NGT subjects. To examine this question, we studied two groups of obese children with NGT who had a similar degree of overall adiposity but a wide variation in their degree of insulin sensitivity. Differences in the profile of adiponectin and IL-6 levels, along with substrate use under fasting and hyperinsulinemic conditions, were also explored.

Subjects and Methods

The obese participants of this study are part of a cohort of children and adolescents taking part in a longitudinal study aimed at defining the pathophysiology of prediabetes in obese youth. To be eligible for the present study, subjects had to have a BMI greater than the 95th percentile for age and gender (8), be taking no medications that may affect glucose metabolism, be otherwise healthy, and not be participating in organized physical activity. All participants who were enrolled in our cohort had a detailed medical history, a complete physical examination including assessment of Tanner stage of development, and a standard oral glucose tolerance test (OGTT) to determine carbohydrate tolerance. Forty obese children with NGT also underwent a hyperinsulinemic-euglycemic clamp to determine insulin sensitivity and a dual-energy x-ray absorptiometry (DEXA) to assess body composition. These 40 obese NGT children were then divided into two groups according to the median M (or glucose disposal) values from the insulin clamp: insulin-sensitive NGT (M

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Abbreviations: BMI, Body mass index; DEXA, dual-energy x-ray absorptiometry; EMCL, extramyocellular lipid; FFA, free fatty acid; IGT, impaired glucose tolerance; IMCL, intramyocellular lipid; lbm, lean body mass; M, glucose disposal value; NGT, normal glucose tolerance; NMR, nuclear magnetic resonance; OGTT, oral glucose tolerance test.

value > 8.50 mg/kg-lbm·min) and insulin-resistant NGT (M value < 8.50 mg/kg-lbm·min). Fourteen resistant subjects were pair matched to 14 sensitive others. Pair matching was based on similarities of gender, lean body mass (lbm; within 4 kg), percent body fat (within 4%), body weight (within 8 kg), and pubertal status (two prepubertal children and 12 pubertal adolescents in each group). The remaining six nonmatched resistant subjects were significantly more obese than their six sensitive nonmatched counterparts. The nature and purpose of the study were explained to the parent/guardian and child before written consent from the parent and written assent from the child were obtained. The study protocol was approved by the Human Investigation Committee of the Yale University School of Medicine.

Procedures

Participants were instructed by our dietitian to consume a diet consisting of about 250 g of carbohydrates and refrain from strenuous physical activity on the day before the study. After an overnight fast, an OGTT was performed in the outpatient facility of the Yale Clinical Research Center beginning at 0730 h, as previously described (5). To be included in the study, all obese children and adolescents had to have NGT, according to the American Diabetes Association guidelines (2-h plasma glucose lower than 140 mg/dl) (9).

Hyperinsulinemic-euglycemic clamp

Participants arrived at the Yale Clinical Research Center at 0730 h after an overnight fast. Two iv catheters, one for blood drawing and one for infusion of glucose, insulin, and tracers, were inserted in the antecubital vein of each arm after local infiltration with lidocaine. The arm used for blood drawing was kept in a heated box for arterialization of blood. Insulin sensitivity was measured by a hyperinsulinemic-euglycemic clamp (10) by infusing insulin as a primed continuous infusion 80 mU/m^2·min for 120 min. A primed continuous infusion of [6,6-^{2}H]-glucose at a rate of 2 mg/m^2·min and a continuous infusion of [$^2H_5$]-glycerol at a rate of 0.02 mg/m^2·min were used to quantify insulin's effects on glucose and glycerol turnover (11). Arterialized blood samples were collected every 10 min during the last 30 min of the basal period and during the last 30 min of the insulin infusion period for determination of glucose and glycerol enrichments, hormones, and substrates. To estimate net rates of carbohydrates and lipid oxidation, indirect calorimetry was employed at the last 30 min of the baseline and clamp period (12).

Hyperglycemic clamp

To quantify insulin secretion, blood glucose was rapidly raised to 200 mg/dl by infusing 20% dextrose at variable rates, and plasma glucose was kept at that level for 120 min, as previously described (10).

^{1}H-nuclear magnetic resonance (NMR) spectroscopy of the intramyocellular triglyceride content

Localized ^{1}H-NMR spectra of the soleus muscle were acquired on a 2.1T Biospec system (Bruker Instruments, Inc., Billerica, MA), as previously described (13). ^{1}H-NMR spectroscopy was performed on all of the sensitive NGT subjects and 12 of 14 of the resistant NGT subjects. The investigator who performed the scans and analyzed the data was blinded to the sensitivity status of the obese subjects. Although we have not yet studied the reproducibility of intramyocellular lipid (IMCL)/extramyocellular lipid (EMCL) measurements in our obese youngsters, we have found a coefficient of variation of 10% for EMCL and 5% for IMCL in young nonobese adults.

Assessment of abdominal fat distribution and total body composition

Magnetic resonance imaging was employed to quantify visceral and sc fat depots as previously described (14). This procedure was performed in all of the sensitive NGT subjects and 13 of 14 of the resistant NGT subjects. Total body composition was measured by DEXA (15) using a Hologic (Boston, MA) scanner on all subjects. The investigators who performed the scans were blinded to the clinical status of the subjects.

Analytical procedures and calculations

Plasma and urine glucose levels were measured by the glucose oxidase method with a glucose analyzer (Beckman Instruments, Brea, CA). Plasma insulin, C-peptide, leptin, and adiponectin levels were measured by a double-antibody RIA (Linco). Free fatty acids (FFAs) were assayed by a colorimetric method. IL-6 levels were measured with the use of highly sensitive solid-phase ELISA kits (R&D Systems, Minneapolis, MN) (lower limit of detection, 0.1 pg/ml; intraassay and interassay coefficients of variation, 3.3 and 3.6%, respectively).

Calculations

The glucose infusion rates were calculated during the last 30 min of the hyperinsulinemic-euglycemic clamp and expressed as glucose per kilogram of lean body mass per minute, as previously reported (16). Nonoxidative glucose disposal was calculated as the difference between M and the glucose oxidation rates measured by indirect calorimetry during the hyperinsulinemic-euglycemic clamp. Glycerol turnover and endogenous hepatic glucose production were calculated as previously described (6). First-phase insulin and C-peptide secretion during the hyperglycemic clamp were calculated as the mean of samples at 2, 4, 6, 8, and 10 min. Second-phase secretion was calculated as the mean insulin/C-peptide level from min 20 to 120.

Statistical analysis

Data are presented as means ± SD. Positively skewed variables were log transformed for analysis. The two obese groups were compared by paired *t* tests. *Post hoc* Bonferroni corrections for multiple comparisons were employed. Spearman correlation coefficients were estimated to describe associations between continuous variables. All analyses were performed using SPSS (12.0 for Windows, SPSS Inc., Chicago, IL).

Results

Clinical and biochemical characteristics of the study groups

As shown in Table 1, the ethnic composition was comparable in the two obese groups. Because obese subjects were pair matched, gender distribution, physical dimensions, percent body fat, and lean body mass were virtually identical between obese insulin-resistant and -sensitive subjects. Fasting plasma glucose and FFA levels were similar in the two obese groups (Table 2). Fasting insulin was significantly higher in the resistant NGT compared with the sensitive NGT group ($P = 0.008$). Hemoglobin A_1c was comparable between the two groups. Adiponectin was higher in the obese-sensitive subjects, compared with their resistant counterparts ($P = 0.01$). IL-6 levels were comparable between the obese-resistant and the obese-sensitive group.

TABLE 1. Demographic and anthropometric data (mean ± SD)

	Obese resistant NGT (n = 14)	Obese sensitive NGT (n = 14)
Male/female	7/7	7/7
Age (yr)	13.9 ± 2.0	13.7 ± 2.1
Pre/pubertal	2/12	2/12
Ethnicity (Black/White/Hispanic)	3/5/6	5/3/6
Height (cm)	164 ± 8	165 ± 10
Weight (kg)	101.6 ± 18	103.3 ± 19
BMI	37.7 ± 5.8	37.8 ± 5.5
% body fat	40.4 ± 4.9	41.2 ± 3.7
Lean body mass (kg)	56.3 ± 10.8	57.0 ± 3.7

TABLE 2. Baseline parameters

	Obese resistant NGT (n = 14)	Obese sensitive NGT (n = 14)
Fasting glucose (mg/dl)	90 ± 5	91 ± 6
Fasting insulin (μU/ml)	36 ± 14	27 ± 9[a]
HbA1C (%)	5.2 ± 0.3	5.2 ± 0.4
Triglycerides (mg/dl)	132 ± 80	98 ± 43[b]
HDL-C (mg/dl)	40 ± 12	38 ± 7
Total cholesterol (mg/dl)	164 ± 48	142 ± 28
Fasting FFA (μM)	632 ± 80	565 ± 151
Adiponectin (μg/ml)	6.5 ± 1.8	8.6 ± 3.6[c]
Leptin (μg/liter)	34.8 ± 14.1	29.9 ± 15.2
IL-6 (pg/ml)	2.3 ± 2	1.5 ± 1.2

[a] $P = 0.008$; [b] $P < 0.001$; and [c] $P = 0.015$ *vs.* NGT resistant.

Insulin action on glucose metabolism

Plasma glucose levels during the hyperinsulinemic-euglycemic clamp were comparable between the groups. The steady-state plasma insulin levels during the hyperinsulinemic-euglycemic clamp were higher in the obese-resistant group (246 ± 64 μU/ml), compared with the obese-sensitive group (201 ± 45 μU/ml, $P < 0.05$) despite similar priming and insulin infusion rates. This discrepancy may be attributed to the difference in the basal insulin levels among the groups, differences in insulin clearance, or a lack of suppression of endogenous insulin production during the clamp in obese insulin-resistant subjects. In support of the latter possibility, steady-C-peptide levels were 793 ± 350 (14 ± 23% suppression from basal) and 562 ± 286 pmol/liter (28 ± 16% suppression from basal) in the resistant and sensitive participants respectively. Despite differences in the insulin levels during the clamp, glucose uptake expressed per kilogram of lean body mass was markedly different among the obese subjects, allowing a clear separation into a sensitive and resistant group. These differences in peripheral glucose uptake can be attributed mostly to differences in nonoxidative glucose disposal, as shown in Fig. 1. Nonoxidative glucose disposal in the sensitive obese subjects (9.07 ± 3.74 mg/kg-lbm·min) was higher than in the resistant group (3.14 ± 1.22 mg/kg-lbm·min, $P < 0.001$). Expressing insulin sensitivity as the insulin-stimulated glucose metabolism (M) over the mean steady-state glucose concentration multiplied by the insulin increment (GIR/(ΔI·Glu), as suggested by Bergman *et al.* (17), did not alter the differences observed in glucose metabolism between the two obese groups [13.30 ± 3.51 *vs.* 23.16 ± 6.30 (mg/kg-lbm·min) per mg·μU/ml for obese resistant and obese sensitive, respectively, $P < 0.001$]. Fasting hepatic glucose production was similar in both groups (2.90 ± 0.37 *vs.* 2.65 ± 0.29 mg/kg-lbm·min for resistant and sensitive, respectively) and was completely suppressed during the clamp.

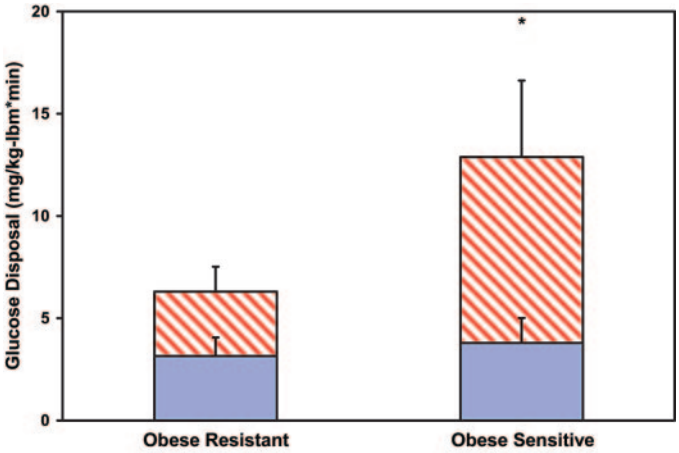

FIG. 1. Carbohydrate oxidation (*blue*) and nonoxidative glucose disposal (*hatched*) derived from the hyperinsulinemic-euglycemic clamp. *, $P = 0.001$ *vs.* obese resistant.

Insulin action on lipid metabolism

Fasting levels of FFAs were not different in the two obese groups (632 ± 80 and 566 ± 150 mmol/liter). Despite higher steady-state insulin levels during the clamp, obese-resistant subjects tended to have slightly higher levels of FFAs than their counterparts (44 ± 22 *vs.* 29 ± 8 mmol/liter for obese resistant and sensitive, respectively, $P = 0.09$ for resistant *vs.* sensitive).

Rates of glycerol turnover at baseline were comparable among the obese subjects (17.09 ± 3.98 *vs.* 17.54 ± 5.91 mg/m^2·min for obese resistant and sensitive, respectively). Similarly, under different hyperinsulinemic conditions, glycerol turnover was comparable between the obese subjects (7.46 ± 2.10 *vs.* 7.83 ± 4.18 mg/kg·min for obese resistant and sensitive, respectively).

Substrate use and energy expenditure

Both groups had a similar respiratory quotient at baseline. Indeed, baseline carbohydrate and lipid oxidation rates were similar in both groups (Table 3). Under hyperinsulinemic conditions, the sensitive subjects significantly increased their respiratory quotient, compared with the resistant group ($P = 0.04$). The sensitive subjects suppressed their lipid oxidation rates by 59 ± 22% of baseline, compared with a smaller suppression of 36 ± 25% of baseline in the resistant group ($P = 0.07$ for sensitive *vs.* resistant). Energy expenditure under hyperinsulinemic conditions increased 6.6% in the sensitive group, whereas it remained stable with a minimal

TABLE 3. Respiratory quotient, substrate oxidation, and energy expenditure during the hyperinsulinemic-euglycemic clamp

	Obese resistant	Obese sensitive
Respiratory quotient		
Baseline	0.79 ± 0.03	0.79 ± 0.07
Hyperinsulinemia	0.87 ± 0.05	0.91 ± 0.06
Δ RQ	0.077 ± 0.04	0.12 ± 0.05[a]
Glucose oxidation (mg/kg-lbm·min)		
Baseline	1.73 ± 0.70	1.61 ± 1.15
Hyperinsulinemia	3.15 ± 0.91	3.79 ± 1.22
Lipid oxidation (mg/kg-lbm·min)		
Baseline	1.58 ± 0.43	1.67 ± 0.62
Hyperinsulinemia	0.99 ± 0.49	0.76 ± 0.53
Energy expenditure (kcal/kg-lbm·24 h)		
Baseline	37 ± 6	36 ± 5
Hyperinsulinemia	36 ± 5	38 ± 6
% increase from baseline	−2.4 ± 5.0	6.5 ± 12[b]

[a] $P = 0.046$ *vs.* obese resistant; [b] $P = 0.05$ *vs.* obese resistant.

decrease in the resistant group ($P = 0.05$ for sensitive *vs.* resistant).

Muscle and abdominal fat partitioning

Figure 2, A and B, shows the IMCL and visceral lipid levels in the two groups. The obese-sensitive group had significantly lower IMCL and visceral fat levels, compared with the obese resistant ($P = 0.04$). The sc fat area was similar between the two obese groups (565 ± 166 *vs.* 588 ± 160 cm^2), yet the ratio of visceral to sc fat was significantly different (0.13 ± 0.5 *vs.* 0.08 ± 0.04 for resistant and sensitive, respectively, $P = 0.01$). EMCL was similar in the two groups (2.48 ± 1.21 *vs.* 2.22 ± 0.60% of water peak, $P = 0.53$).

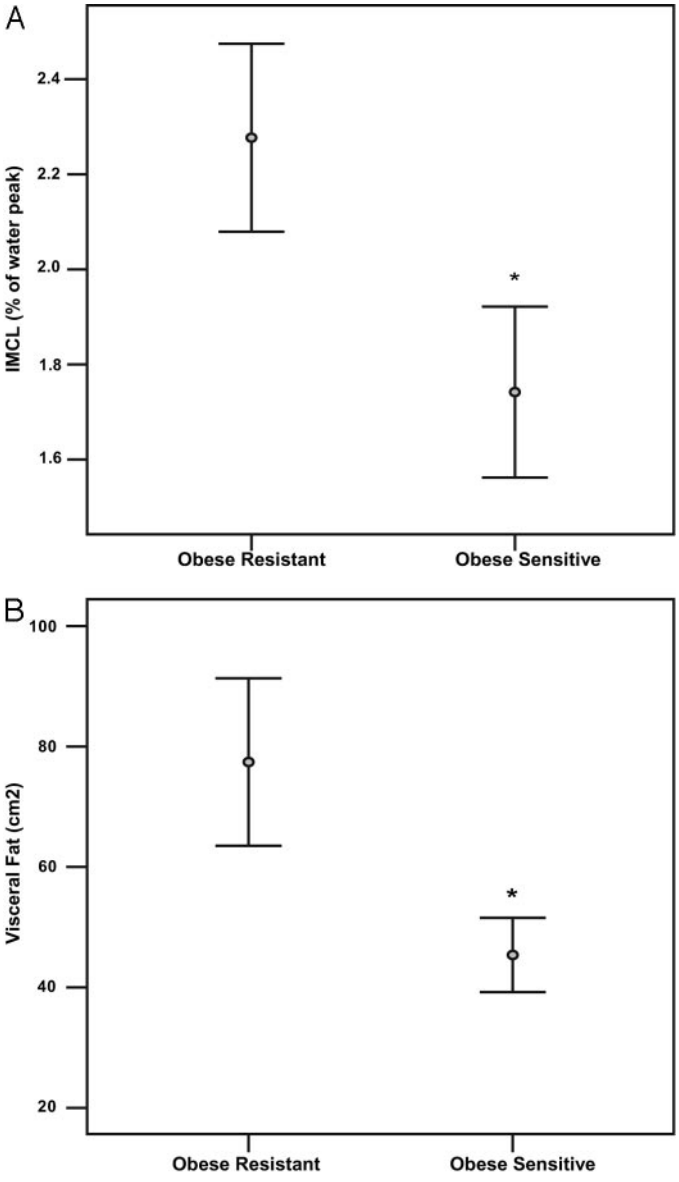

FIG. 2. Levels of IMCL (A) and visceral lipid (B) in the groups. *, $P = 0.017$ *vs.* obese resistant for IMCL and *, $P = 0.04$ *vs.* obese resistant for visceral fat.

Relationship of IMCL, visceral lipid, and adiponectin to insulin sensitivity (Fig. 3)

When using only the 28 obese subjects for the analysis, IMCL negatively correlated with insulin sensitivity ($r = -0.56$, $P = 0.006$) as did visceral fat ($r = -0.46$, $P = 0.02$). Adiponectin was positively related to insulin sensitivity ($r = 0.37$, $P = 0.02$) and to baseline and hyperinsulinemic nonoxidative glucose disposal ($r = 0.64$, $P = 0.03$ and $r = 0.46$, $P = 0.01$, respectively). Adiponectin was negatively related to visceral fat ($r = -0.47$, $P = 0.01$) and fasting carbohydrate oxidation ($r = -0.50$, $P = 0.008$). Including all obese subjects in the correlation analysis did not significantly affect any of the correlation coefficients.

Insulin secretion

The magnitude of the acute insulin and C-peptide release during the hyperglycemic clamp tended to be greater in the obese-resistant compared with the obese-sensitive group (Table 4). The trend for greater insulin release observed during the hyperglycemic clamp was also seen during the OGTT in the obese-resistant compared with the obese-sensitive group (data not shown). To analyze insulin secretion in the context of insulin resistance, we related the first-phase in-

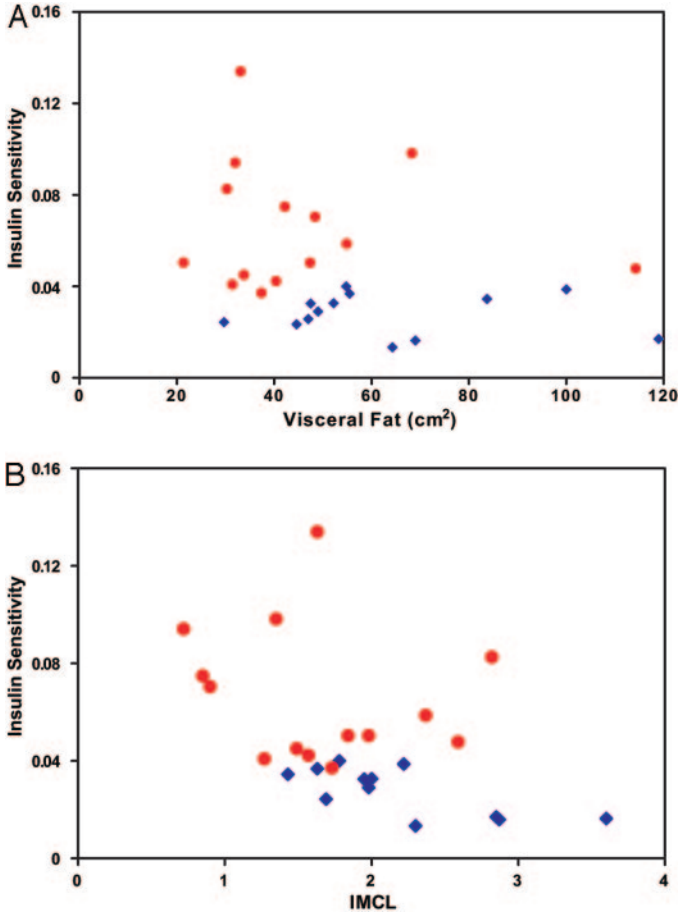

FIG. 3. Relation of IMCL (B) and visceral lipid (A) to insulin sensitivity. Obese sensitive, *light red circles*; obese resistant, *dark diamonds*. Insulin sensitivity expressed as M/I in (mg/kg-lbm·min) per microunits per milliliter.

sulin release to insulin sensitivity (disposition index) in obese subjects. As can be seen in Fig. 4, the hyperbolic relationship between insulin secretion and sensitivity was maintained in the participants. Increased insulin resistance was accompanied by a greater first-phase insulin response; thus, the obese insulin-resistant group was able to adequately increase insulin secretion and maintain normal glucose tolerance.

Discussion

This cross-sectional study demonstrated the wide range in insulin action in obese children and adolescents with a similar degree of adiposity and NGT. Using the median value of the distribution of insulin-mediated glucose disposal, determined during the hyperinsulinemic-euglycemic clamp, we identified two metabolically distinct subgroups of obese subjects: one sensitive and the other resistant. Differences between these two groups in lipid partitioning, biochemical markers of insulin resistance, substrate use, and insulin secretion were measured and related to insulin action. The major findings of this study are that the obese-sensitive group had lower intramyocellular and intra-abdominal visceral fat depots, higher adiponectin levels and greater tissue flexibility of substrate use than the obese-resistant group.

The main factor that explained the disparity of peripheral insulin sensitivity between our resistant and sensitive obese subjects was the difference in the nonoxidative glucose disposal pathway, which most likely represents muscle glycogen synthesis (18). A similar finding was demonstrated by our group when comparing obese youngsters with IGT with their normal counterparts. Thus, the obese-resistant subjects demonstrate metabolic characteristics comparable with those of youth with IGT. In contrast to subjects with IGT with similar insulin resistance, the resistant subjects in this study had adequate β-cell compensation for the degree of insulin resistance, thus maintaining normal glucose homeostasis, an observation similar to our previous findings using a large cohort of obese children and adolescents (7). Future follow-up will determine the long-term capability of the β-cells of these obese insulin-resistant youngsters to compensate for the marked peripheral resistance over time.

Accurate assessment of total body fat by DEXA, abdominal fat depots by magnetic resonance imaging, and IMCL content by ^{1}H-NMR provided the means for analyzing the complex relationships between these parameters and insulin action. The results of these analyses indicate that, independent of the overall mass of adipose tissue, IMCL and visceral fat depots have a critical role in shaping insulin resistance in childhood obesity. The relationship demonstrated here between the aberrant lipid deposits (IMCL and visceral fat depots) and insulin sensitivity demonstrates that lower levels of fat deposition in these two anatomically different compartments allow the maintenance of relatively normal insulin sensitivity. Larger levels of lipid in these compartments contribute less to the further decrease in glucose disposal, whereas at lower levels, the impact on insulin sensitivity is pronounced. We chose to divide our cohort based on the median of insulin sensitivity to allow us to perform stringent matching of subjects, yet the median of M values is not a true determinant of sensitivity. Indeed, our results show, similar to our previous findings using a large cohort (7), that among obese children with NGT, some have similar patterns of lipid partitioning and insulin sensitivity reminiscent of normal nonobese youth, whereas others demonstrate IMCL and visceral lipid levels similar to the obese with IGT. The participants with lower IMCL content were not necessarily the ones with lower visceral fat, thus emphasizing that, although both lipid depots are significant contributors to overall insulin sensitivity, several other factors have an impact as well. An important implication of our data is that selective changes in visceral and IMCL depots occurring in the critical ranges may have a large and significant impact on insulin resistance. Studies in obese nondiabetic adult subjects found that, in terms of body composition, a decrease in visceral adiposity best predicted the improvement in insulin sensitivity after weight loss (19). In animal studies, surgical removal of visceral adipose tissue was associated with dramatic changes in insulin resistance, even in the context of the maintenance of adiposity (20).

IMCL lipid content has emerged as a critical modulator of insulin resistance, even in obese and lean adolescents (16). How such a lipid deposit induces insulin resistance is not entirely clear and is the focus of intense work by several groups. Rather than triglycerides *per se*, the accumulation of long chain acyl coenzyme A, diacylglycerol, or other lipid moieties (21) has been found to induce alterations in the insulin signaling cascade and consequently interfere with the propagation of insulin signaling (22). It is, however, impor-

TABLE 4. First- and second-phase secretion of insulin and C-peptide, derived from the hyperglycemic clamp

	Obese resistant	Obese sensitive
First-phase insulin (μU/ml)	166 ± 74	116 ± 68[a]
First-phase C-peptide (pmol/liter)	2569 ± 713	2324 ± 1117
Second-phase insulin (μU/ml)	229 ± 112	171 ± 79
Second-phase C-peptide (pmol/liter)	3949 ± 765	3472 ± 906

[a] $P = 0.05$ *vs.* obese resistant.

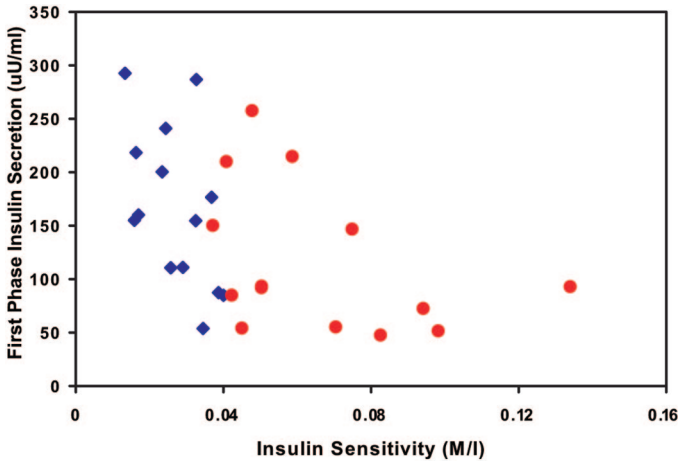

FIG. 4. Relation of insulin sensitivity and secretion among study participants. Obese sensitive, *red circles*; obese resistant, *blue diamonds*.

tant to note that highly trained athletes have a relatively high content of IMCL, yet these individuals are highly insulin sensitive (23). This paradoxical observation may be due to the fact that fatty acyl coenzyme A and diacylglycerol and not triglycerides *per se* are the fatty derivates that impact muscle insulin resistance (22). IMCL may thus be a marker but not the major determinant of muscle insulin resistance. Another putative explanation for this paradox is the different capacity of skeletal muscle to oxidize fat. Studies by Kelley *et al.* (24) indicate that the metabolic capacity of skeletal muscle in obese adults appears to be organized toward fat storage rather than oxidation. Our data demonstrate a trend toward higher rates of lipid oxidation at baseline and under hyperinsulinemic conditions in the obese sensitive subjects, similar to the findings of Perseghin *et al.* (25) in overweight insulin-sensitive adults. All obese youth had a relatively reduced suppression of lipid oxidation during hyperinsulinemia. An explanation for this discrepancy may be our assessments of total body substrate oxidation, which may be less sensitive to tissue-specific differences in the large muscle beds. Other possible explanations for preferential intramyocellular storage of lipid may be related to increased triglyceride transport into the myocyte or increased *de novo* synthesis of triglycerides within the myocyte.

Although the two obese groups had similar total fat and lean body mass and were matched for gender and pubertal status, there were some differences, albeit small, in the ethnic distribution. Therefore, our findings regarding the imbalance in fat partitioning in the abdominal region and its relationship to insulin resistance warrant further studies in larger groups that are well matched for ethnicity. Lack of regular physical activity was determined in this study by history and not by direct assessment of fitness. Because physical fitness has an impact on substrate oxidation, the relation of these factors should be studied further.

Although obese subjects in this study were matched for their overall adiposity, the level of adiponectin, an adipocyte-derived adipocytokine, was significantly higher in obese insulin-sensitive participants. It is unclear whether elevated adiponectin levels have an active effect on lipid partitioning or are merely a marker of the insulin-sensitive milieu. Our study demonstrates a negative correlation between levels of visceral fat and adiponectin. These results are in agreement with the finding of reduced adiponectin mRNA in visceral compared with sc adipocytes (26). The presence of adiponectin-specific receptors in muscle, liver (27), and pancreas suggests that this adipocytokine may have a role in mediating tissue substrate use, possibly through activation of AMP kinase (28). Indeed, adiponectin negatively correlated with fasting carbohydrate oxidation rates and positively correlated with baseline and stimulated nonoxidative glucose disposal.

Normal metabolism in hyperinsulinemic conditions favors carbohydrate use, thus increasing the respiratory quotient. The switch from lipid to carbohydrate oxidation is due to tissue flexibility in substrate use. Although we measured whole-body respiratory quotient and not across the muscle bed, we were able to detect a significant decrease in the ability of resistant NGT subjects to switch to carbohydrate use under hyperinsulinemic conditions. Moreover, the energy expenditure across a tissue bed tends to rise in hyperinsulinemic conditions due to the anabolic processes of storage and synthesis. Although we used indirect calorimetry, thus evaluating a whole-body response, we did detect a 6% increase in energy use in the sensitive NGT without any changes in the resistant NGT subjects. The 6% change we detected in the sensitive group needs further investigation because it approximates the coefficient of variation of the measurement. Further studies are needed to evaluate these subtle differences in tissue flexibility in metabolic processes.

The burgeoning epidemic of type 2 diabetes in children and adolescents in the past decade emphasizes the urgent need to identify subjects at high-risk for this condition before their presentation with full-blown diabetes. Our study emphasizes that not all severely obese youngsters are necessarily insulin resistant, and, indeed, some of them display normal peripheral insulin sensitivity despite their severe adiposity. In contrast, other severely obese youngsters with seemingly normal glucose tolerance have a similar metabolic phenotype similar to youth with prediabetes. Our cross-sectional design prevents us from predicting whether the insulin-resistant subjects with NGT will eventually develop altered glucose metabolism or whether the increase in aberrant lipid deposits precedes the deterioration in glucose metabolism. Nevertheless, the strong relationship between visceral and intramyocellular lipid deposits and insulin resistance indicates that prevention or reversal of such deposits may be a favorable early intervention in obese youth at risk for developing type 2 diabetes.

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