Are Obesity-Related Metabolic Risk Factors Modulated by the Degree of Insulin Resistance in Adolescents?

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OBJECTIVE — Obesity is often associated with insulin resistance and the components of the metabolic syndrome. However, wide variations in insulin sensitivity are noted in obese youth. It is not clear if greater insulin resistance confers a higher risk of cardiovascular comorbidities and risk for type 2 diabetes.

RESEARCH DESIGN AND METHODS — We investigated physical and metabolic features of 54 obese adolescents. Subsequently, we pair matched 17 moderately insulin-resistant (MIR group) to 17 severely insulin-resistant (SIR group) youth based on cut points for insulin sensitivity (MIR group insulin sensitivity within 2 SDs and SIR group <2 SDs of normal-weight adolescent values). We evaluated differences in body composition (dual-energy X-ray absorptiometry), abdominal fat (computed tomography scan), cardiorespiratory fitness (CRF) ($V\text{O}_{2\text{max}}$ on a treadmill), insulin sensitivity and secretion (hyperinsulinemic-euglycemic and hyperglycemic clamps), substrate utilization (indirect calorimetry), and fasting adiponectin and lipid profile.

RESULTS — SIR youth had higher visceral adiposity (78.3 ± 6.9 vs. 60.3 ± 6.9 cm^2, $P = 0.017$) and waist-to-hip ratio (0.91 ± 0.01 vs. 0.86 ± 0.02, $P = 0.026$) and lower HDL (1.0 ± 0.03 vs. 1.16 ± 0.06 mmol/l, $P = 0.015$) than pair-matched MIR subjects. There was a tendency for adiponectin (6.1 ± 0.5 vs. 8.6 ± 1.1 μg/ml, $P = 0.079$) and CRF (49.9 ± 3.2 vs. 55.2 ± 3.5 $ml \cdot min^{-1} \cdot kg^{-1}$ fat-free mass, $P = 0.09$) to be lower in SIR subjects. SIR youth also had an impaired balance between insulin sensitivity and β-cell compensation with a lower glucose disposition index.

CONCLUSIONS — Despite similar BMI, the degree of insulin resistance impacts the risk for obesity-related metabolic comorbidities. The SIR youth are at greater risk for type 2 diabetes and cardiovascular disease.

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Although obesity is often associated with insulin resistance and the components of the metabolic syndrome, there is a subgroup of obese individuals who do not fit this metabolic profile (1). With wide variations in insulin sensitivity, it is not clear what distinguishes obese moderately insulin-resistant children from obese severely insulin-resistant peers and whether they are at lower risk of obesity-related comorbidities. With the current obesity epidemic in children (2), it is important to be able to identify these individuals so that therapeutic efforts can be concentrated on the more at-risk category.

In adults, obese and nonobese insulin-sensitive versus insulin-resistant individuals have higher HDL and adiponectin levels, lower fasting insulin and triglycerides, but no significant difference in blood pressure (3). Similarly, obese metabolically normal postmenopausal women have 49% less visceral fat, lower fasting and post–oral glucose tolerance test insulin levels, lower triglycerides, and higher HDL levels than their insulin-resistant counterparts (4). In a recent study (5), obese insulin-sensitive adolescents were found to have lower visceral and intramyocellular fat. Because physical activity and cardiorespiratory fitness (CRF) independent of body weight are associated with better health outcomes (6), we hypothesized that obese youth who are less insulin resistant are more likely to have higher CRF in addition to lower abdominal adiposity, better cardiovascular disease (CVD) profile, and less risk of type 2 diabetes. Therefore, we investigated physical and metabolic features that distinguish obese but moderately insulin-resistant youth (MIR group) from severely insulin-resistant youth (SIR group).

RESEARCH DESIGN AND METHODS

— Fifty-four obese (mean BMI 34.9 ± 5.5 kg/m^2) otherwise-healthy African-American and American white adolescents were studied. Subjects had exogenous obesity with no clinical evidence of endocrinopathy or syndromes. They were not involved in any regular physical activity or weight reduction programs and were not on medications that affect glucose metabolism. Female subjects were evaluated in the follicular phase of their menstrual cycle. All studies were approved by the institutional review board of the University of Pittsburgh. Study participants were recruited through newspaper advertisements in the community. Parental informed consent and child assent were obtained. Clinical characteristics of the study subjects are summarized in Table 1. All subjects were at Tanner stage II–V of puberty on examination, as confirmed by plasma testosterone in male and estradiol in female subjects.

Clamp studies

Each participant underwent a hyperinsulinemic-euglycemic clamp and a hyperglycemic clamp study after 10–12 h of fasting, at 1- to 3-week intervals, in ran-

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Abbreviations: CRF, cardiorespiratory fitness; CVD, cardiovascular disease; FFM, fat-free mass; VAT, visceral adipose tissue.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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Table 1—*Characteristics of 54 MIR and SIR adolescents compared with normal NW adolescents*

	NW	MIR	SIR
n	76	23	31
Age (years)	13.1 ± 0.2	13.3 ± 0.4	13.6 ± 0.3
Sex (male/female)*	35/41	10/13	17/14
Ethnicity			
African American*	33	11	14
American white	43	12	17
Tanner stage*			
II–III	34	9	20
IV–V	42	14	11
FH of type 2 diabetes*			
Absent	33	9	7
Present	42	13	23
BMI (kg/m^2)	20.1 ± 0.3	32.6 ± 1.1	36.6 ± 0.9†‡§
Percent body fat	20.3 ± 1.0	42.5 ± 1.2	44.2 ± 0.7†‡
Fat mass (kg)	10.1 ± 0.6	35.2 ± 1.8	39.0 ± 1.3†‡
FFM (kg)	37.6 ± 1.0	44.8 ± 1.5	47.4 ± 1.9†‡
Waist-to-hip ratio	0.82 ± 0.006	0.85 ± 0.02	0.92 ± 0.02‡§
Subcutaneous fat (cm^2)	100.3 ± 7.1	485.0 ± 36.6	557.8 ± 23.8†‡§
Visceral fat (cm^2)	21.2 ± 1.4	57.6 ± 5.5	82.7 ± 6.9†‡§
Insulin sensitivity (μmol · kg^{-1} · min^{-1} per pmol/l)	8.8 ± 0.37	3.4 ± 0.22	1.5 ± 0.08†‡§
Adiponectin (μg/ml)	12.7 ± 0.7	8.6 ± 0.9	6.7 ± 0.6†‡
Cholesterol (mmol/l)	3.9 ± 0.09	4.3 ± 0.16	4.4 ± 0.17‡
HDL (mmol/l)	1.2 ± 0.03	1.1 ± 0.04	1.0 ± 0.03‡
LDL (mmol/l)	2.2 ± 0.08	2.6 ± 0.12	2.8 ± 0.13‡
Triglycerides (mmol/l)	0.98 ± 0.05	1.24 ± 0.19	1.35 ± 0.09‡

Data are means ± SD. *The χ^2 analysis revealed no significant differences among groups with respect to ethnicity, sex, Tanner stage, and family history (FH) of type 2 diabetes. The following symbols indicate ANOVA *P* values for post hoc analysis (Bonferroni correction): †$P < 0.05$ in NW vs. MIR subjects; ‡$P < 0.05$ in NW vs. SIR subjects; §$P < 0.05$ in MIR vs. SIR subjects. One individual in the NW group, one in the MIR group, and another one in the SIR group had no information on family history of type 2 diabetes. Waist-to-hip ratio data was available on 63 NW, 18 MIR, and 25 SIR subjects.

dom order. Participants were admitted to the General Clinical Research Center the afternoon before the day of the testing.

In vivo insulin sensitivity

A fasting blood sample was obtained for determination of cholesterol, LDL, HDL, VLDL, triglycerides, HbA_{1c} (A1C), proinsulin, C-peptide, and adiponectin. Fasting endogenous glucose production was measured with a primed constant rate infusion of [6,6-$^2H_2$] glucose (0.306 ± 0.009 μmol · kg^{-1} · min^{-1}) (Isotech, Miamisburg, OH) (7,8). Blood was sampled at the start of the 2-h isotope infusion and every 10 min from −30 to 0 times (basal period) for determination of plasma glucose, insulin, and isotopic enrichment of glucose. Fasting turnover calculations were made during the last 30 min of the basal period. Insulin-mediated glucose metabolism and insulin sensitivity were evaluated during a 3-h hyperinsulinemic-euglycemic clamp (7,8). Intravenous crystalline insulin (Humulin; Lilly, Indianapolis, IN) was infused at a rate of 80 mU/m^2 per min (7). Plasma glucose was clamped at 5.6 mmol/l with a variable rate infusion of 20% dextrose, based on arterialized plasma glucose determinations every 5 min. Continuous indirect calorimetry by a ventilated hood (Deltatrac metabolic monitor; Sensormedics, Anaheim, CA) was used to measure CO_2 production, O_2 consumption, and respiratory quotient. Measurements were made for 30 min at baseline and at the end of the euglycemic clamp (9).

In vivo insulin secretion

First- and second-phase insulin secretion was evaluated during a 2-h hyperglycemic clamp (8). Plasma glucose was rapidly increased to 12.5 mmol/l and maintained by a variable rate infusion of 20% dextrose. The night before the clamp, blood pressure was measured between 10 and 11 P.M. and the next morning between 6 and 7 A.M. in the resting supine position (8).

Body composition

Body composition was determined by dual-energy X-ray absorptiometry and subcutaneous abdominal adipose tissue and visceral adipose tissue (VAT) by a single-slice computed tomography scan at L_4-L_5 (8).

CRF

Maximal O_2 uptake was measured using the Bruce multistage treadmill protocol reported by us in children before (10). $V_{O_{2max}}$ was indexed to total body mass (ml · kg^{-1} · min^{-1}) and fat-free mass (FFM; ml · min^{-1} · kg FFM^{-1}).

Biochemical measurements

Plasma glucose was measured with a glucose analyzer (Yellow Springs Instrument, Yellow Springs, OH), insulin by radioimmunoassay (8), adiponectin by a radioimmunoassay kit (Linco Research) (7), A1C by high-performance liquid chromatography (Tosoh Medics), and lipids using the standards of the Centers for Disease Control and Prevention (7). Deuterium enrichment of glucose in the plasma was determined on a Hewlett-Packard 5971 mass spectrometer (Hewlett-Packard, Palo Alto, CA) coupled to a 5890 series II gas chromatograph as before (7).

Calculations

Fasting hepatic glucose production was calculated during the last 30 min of the 2-h isotope infusion according to steady-state tracer dilution equations (7). Insulin-stimulated glucose disposal rate (R_d) was calculated during the last 30 min of the euglycemic clamp to be equal to the rate of exogenous glucose infusion. Peripheral insulin sensitivity was calculated by dividing the R_d by the steady-state (SS_{EU}) clamp insulin level (8). Metabolic clearance rate of insulin was calculated by dividing the insulin infusion rate by the Δ increase in circulating insulin during the SS_{EU} (8). Insulin-stimulated carbohydrate and lipid oxidation rates were calculated according to the formulas of Frayn (11) from the indirect calorimetry data. Nonoxidative glucose disposal was estimated by subtracting the rate of glucose oxidation from the total R_d.

During the hyperglycemic clamp, the first-phase insulin concentration was calculated as the mean of five determinations from 2.5 to 12.5 min after the dextrose

Table 2—*Physical characteristics and fasting metabolic profile of the 17 pair-matched obese subjects*

	MIR	SIR	*P* value
n	17	17	
Age (years)	13.0 ± 0.4	12.8 ± 0.3	NS
Race			
African American	9	9	NS
American white	8	8	
Sex			
Male	8	8	NS
Female	9	9	
Tanner stage			
II–III	6	12	NS
IV–V	11	5	
Estradiol (pmol/l)*	204.5 ± 72.3	152.3 ± 117.1	NS
Testosterone (nmol/l)†	798.1 ± 231.2	651.4 ± 150.8	NS
BMI (kg/m^2)	32.6 ± 0.8	33.6 ± 0.9	NS
Percent body fat	42.6 ± 1.5	43.8 ± 0.7	NS
Fat mass (kg)	36.0 ± 2.0	36.1 ± 1.4	NS
FFM (kg)	46.0 ± 1.8	44.7 ± 2.3	NS
Waist-to-hip ratio	0.86 ± 0.02	0.91 ± 0.01	0.026
Subcutaneous fat (cm^2)	472.8 ± 34.6	483.9 ± 26.2	NS
Visceral fat (cm^2)	60.3 ± 6.9	78.3 ± 6.9	0.017
Vo_{2max} (ml · min^{-1} · kg FFM^{-1})	55.2 ± 3.5	49.9 ± 3.2	0.09
Insulin (pmol/l)	165.1 ± 12.0	307.3 ± 25.2	<0.001
C-peptide (nmol/l)	0.7 ± 0.07	1.04 ± 0.09	0.002
Proinsulin (pmol/l)	28.8 ± 4.6	53.5 ± 6.2	0.007
Adiponectin (μg/ml)	8.6 ± 1.2	6.1 ± 0.5	0.079
HDL (mmol/l)	1.16 ± 0.06	1.0 ± 0.03	0.015
Triglycerides (mmol/l)	1.13 ± 0.17	1.24 ± 0.11	NS
Cholesterol (mmol/l)	4.32 ± 0.2	3.93 ± 0.2	NS
Triglyceride-to-HDL ratio	2.3 ± 0.4	2.8 ± 0.2	0.076
LDL (mmol/l)	2.66 ± 0.15	2.38 ± 0.14	NS
Morning systolic BP (mmHg)	112.1 ± 3.0	113.7 ± 2.7	NS
Morning diastolic BP (mmHg)	63.7 ± 2.2	63.7 ± 1.6	NS

Data are means ± SD. Data on abdominal adiposity was missing in two pairs. Vo_{2max} data was available for 10 of 17 pairs. Waist-to-hip ratio was available for 11 pairs. *Estradiol only in female subjects; †testosterone only in male subjects. BP, blood pressure.

bolus. The second phase was calculated as the mean of eight determinations from 15 to 120 min (8). Glucose disposition index was calculated as the product of insulin sensitivity times first-phase insulin.

Statistics

Statistical analyses were performed using ANOVA followed by post hoc Bonferroni correction for three group comparisons. We used paired *t* test or Wilcoxon rank-sum analysis to compare the obese pair-matched groups, Spearman's correlation and multiple regression analyses for bivariate and multivariate relationships, and curve estimation regression statistics to evaluate the relationship of insulin secretion to insulin sensitivity. Data are presented as means ± SE. Two-tailed *P* value ≤0.05 was considered statistically significant.

RESULTS

Study subjects (Table 1)

The obese adolescents were divided into two groups based on cut points for insulin sensitivity in normal-weight adolescents (NW group). The NW and obese adolescents were part of our ongoing investigations of determinants of insulin sensitivity and secretion during childhood. The insulin sensitivity of the MIR group was within 2 SDs below the mean of the NW subjects, and the insulin sensitivity of the SIR group was <2 SDs (<2.35 μmol · kg^{-1} · min^{-1} per pmol/l) of the mean insulin sensitivity of NW adolescents. Table 1 depicts the characteristics of the two obese groups (MIR versus SIR) versus NW adolescents. Of 54 obese adolescents, 23 (43%) were categorized as MIR and 31 (57%) as SIR subjects. The SIR group had higher BMI, waist-to-hip ratio, and visceral and subcutaneous fat compared with the MIR and NW groups. There were no differences in waist-to-hip ratio and lipid profile between the MIR and NW groups.

Physical characteristics and metabolic profile of pair-matched SIR versus MIR subjects (Table 2)

To control for differences in BMI, race, and sex between the SIR and MIR groups, we pair matched 17 MIR and 17 SIR subjects with respect to these variables. All subjects were pubertal (Tanner II–V). Despite similar BMI, percent body fat, fat mass, and subcutaneous abdominal fat, SIR adolescents had significantly greater VAT and higher waist-to-hip ratio, fasting insulin, C-peptide, proinsulin, and triglyceride-to-HDL ratio and lower HDL and a tendency for lower adiponectin levels than MIR subjects. The MIR and SIR adolescents had similar fasting glucose (5.4 ± 0.06 vs. 5.5 ± 0.09 mmol/l), A1C (5.3 ± 0.1% in both), and systolic and diastolic blood pressure (Table 2).

Multiple regression analysis

Because there were significant differences between the pair-matched MIR versus SIR subjects in HDL, VAT, and waist-to-hip ratio despite similar BMI, we proceeded to investigate if differences in insulin sensitivity among these obese children determine cardiovascular outcome measures (HDL, LDL, triglyceride-to-HDL ratio, and systolic and diastolic blood pressure) independent of BMI. We performed multiple regression analysis with each outcome as the dependent variable and BMI and insulin sensitivity as independent variables. Insulin sensitivity independent of BMI explained ~8% of the variance in HDL ($R^2 = 0.08$, $P = 0.03$) but not in the other dependent variables. On the other hand, VAT independent of BMI and of insulin sensitivity explained ~20% of the variance in triglyceride-to-HDL ratio ($R^2 = 0.198$, $P < 0.001$). Similarly, waist-to-hip ratio independent of insulin sensitivity explained ~15% of the variance in the triglyceride-to-HDL ratio ($R^2 = 0.15$, $P = 0.04$). The variance in LDL ($R^2 = 0.10$, $P = 0.02$) and systolic ($R^2 = 0.10$, $P = 0.03$) and diastolic ($R^2 = 0.12$, $P = 0.001$) blood pressure was attributable to BMI independent of insulin sensitivity.

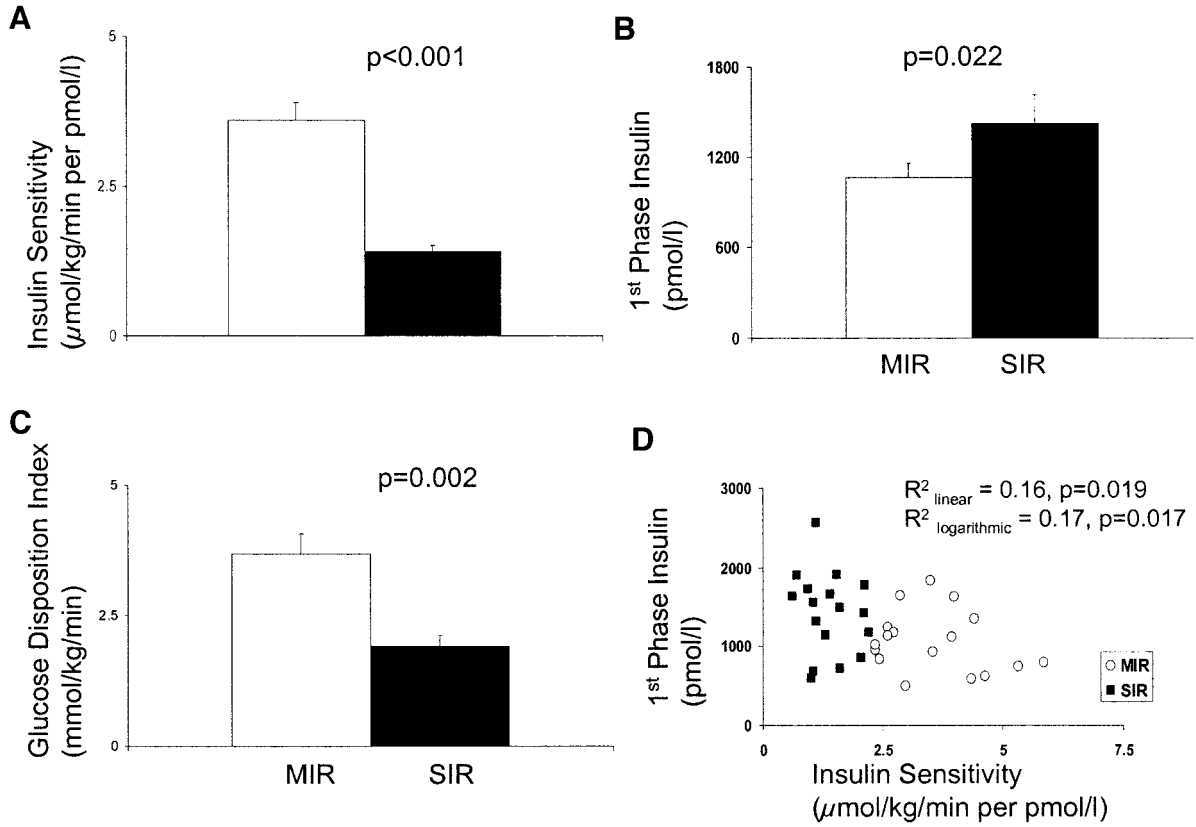

Figure 1—*Insulin sensitivity* (A)*, first-phase insulin* (B)*, and glucose disposition index* (C) *in MIR* (□) *versus SIR* (■) *subjects.* D: *Relationship of insulin sensitivity to first-phase insulin levels in MIR* (○) *versus SIR* (■) *subjects.*

Clamp data in pair-matched MIR versus SIR (Figs. 1 and 2)

Per design, insulin sensitivity was lower in the SIR versus MIR pair-matched children (1.4 ± 0.1 vs. 3.6 ± 0.3 μmol · kg^{-1} · min^{-1} per pmol/l, $P < 0.001$). This remained true when insulin sensitivity was expressed per kilogram FFM (2.6 ± 0.2 vs. 6.7 ± 0.5 μmol · min^{-1} · kg FFM^{-1} per pmol/l, $P < 0.001$). Similarly, metabolic clearance rate of insulin was lower in the SIR group (6.5 ± 0.3 vs. 9.6 ± 0.6 ml · kg^{-1} · min^{-1}, $P = 0.001$). Glucose disposition index was lower in the SIR group (1.91 ± 0.22 vs. 3.70 ± 0.37 mmol · min^{-1} · kg^{-1}, $P = 0.002$), despite higher first-phase insulin (1,422.4 ± 194.3 vs. 1,066.2 ± 94.0 pmol/l, $P = 0.022$) (Fig. 1). Hepatic glucose production was not different between the two groups (13.4 ± 0.85 vs. 13.0 ± 0.70 μmol · kg^{-1} · min^{-1}). Total, oxidative, and nonoxidative glucose disposal were lower in SIR subjects. During hyperinsulinemia, the suppression in fat oxidation was lower in SIR adolescents (1.29 ± 0.19 vs. 1.94 ± 0.26 μmol · kg^{-1} · min^{-1}, $P = 0.039$) (Fig. 2).

CRF, energy expenditure, and substrate utilization in pair-matched MIR versus SIR subjects

$V_{O_{2max}}$, a measure of CRF, tended to be lower in SIR adolescents (Table 2). Resting energy expenditure, respiratory quotient, glucose, and fat oxidation were not different between the two groups (data not shown). However, during insulin-stimulated conditions of the hyperinsulinemic clamp, respiratory quotient (0.89 ± 0.01 vs. 0.93 ± 0.01, $P = 0.017$), energy expenditure (22.3 ± 0.67 vs. 23.9 ± 0.75 kcal · kg^{-1} · min^{-1}, $P = 0.05$), and glucose oxidation (14.3 ± 0.9 vs. 17.6 ± 0.6 μmol · kg^{-1} · min^{-1}, $P = 0.005$) were lower, while fat oxidation was higher (1.58 ± 0.19 vs. 0.90 ± 0.17 μmol · kg^{-1} · min^{-1}, $P = 0.022$) in the SIR versus MIR group.

CONCLUSIONS — The present study demonstrates that despite similar BMI, there are obese adolescents who are only moderately insulin resistant and at lower risk for obesity-associated comorbidities compared with severely insulin-resistant ones. These MIR adolescents have higher physical fitness, lower VAT, higher adiponectin levels, and better substrate utilization and energy consumption compared with the SIR group. Moreover, they have a preserved balance of β-cell secretory compensation to insulin resistance, lessening their risk of progression to type 2 diabetes. Furthermore, their lower triglyceride-to-HDL ratio and higher HDL profile would suggest lower risk of CVD. This study adds to the limited existing literature by providing *1*) a comparison between two groups of obese adolescents, severely versus moderately insulin resistant, strictly defined based on data in normal-weight youth and pair matched for BMI, ethnicity, sex, and puberty; *2*) information on CRF; *3*) information on energy and substrate utilization; and *4*) in vivo evaluation of insulin sensitivity and secretion simultaneously.

In recent years, researchers became aware of the existence of "fat-fit" individuals (12). In population studies, based on measurement of insulin sensitivity with the hyperinsulinemic-euglycemic clamp in 1,146 healthy Caucasians, aged 18–85 years, it was shown that insulin resistance

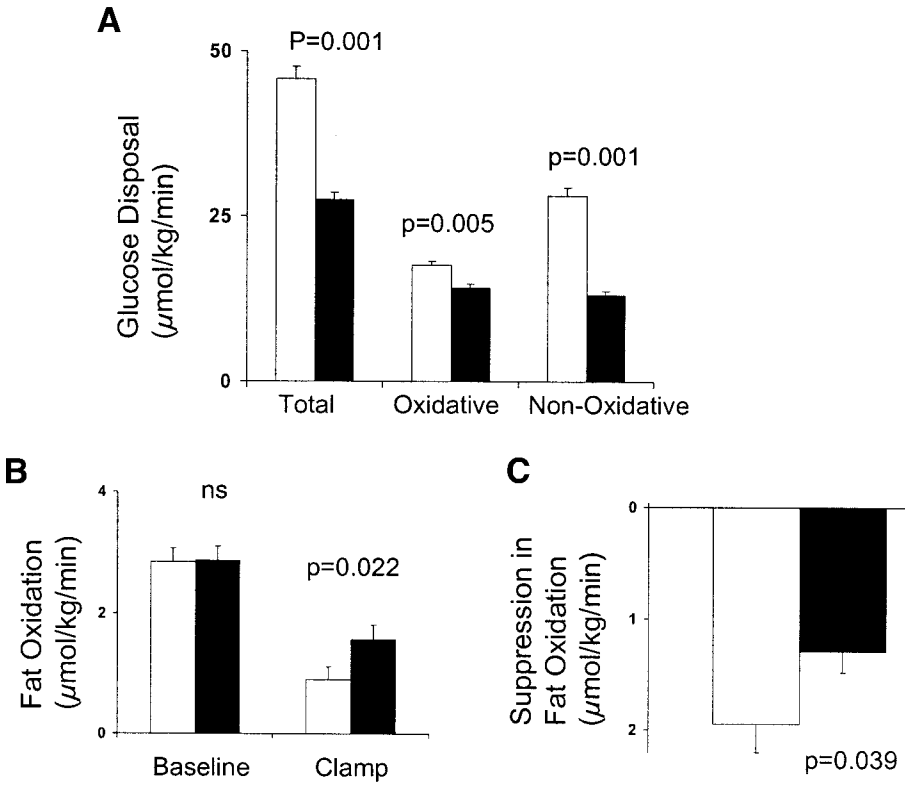

Figure 2—A*: Total, oxidative, and nonoxidative glucose disposal in MIR versus SIR subjects.* B*: Fat oxidation at baseline and during the hyperinsulinemic-euglycemic clamp in MIR versus SIR subjects.* C*: Suppression in fat oxidation in MIR versus SIR subjects.* □*, MIR;* ■*, SIR.*

(defined as <10% of the M value of lean subjects) in "simple obesity" is not as prevalent as previously thought (1). Accordingly, only 26% of all obese subjects were insulin resistant. Bonora et al. (13) similarly reported that insulin resistance, estimated by the homeostasis model, was present in 42% of overweight subjects with no metabolic disorders.

In our current study, 57% of obese adolescents were severely insulin resistant, while 43% had insulin sensitivity within 2 SDs of that of the NW group. Adiposity and insulin sensitivity independently appear to modulate different CVD risk factors. In our multiple regression analysis, insulin sensitivity determined HDL independent of BMI, while LDL and blood pressure were determined by BMI. This is consistent with adult data showing a decrease in HDL with an increase in the tertile of insulin resistance, while LDL worsened with an increase in BMI tertile (14). Another observation is that despite similar BMI, MIR subjects had lower VAT, waist-to-hip ratio, and a tendency for higher adiponectin than SIR subjects. This is consistent with adult data of lower VAT in metabolically normal obese postmenopausal women (4) and lower adiponectin levels in obese and nonobese insulin-resistant versus insulin-sensitive men and women (3). Lower visceral and intramyocellular fat and higher adiponectin was reported (5) in obese insulin-sensitive youth. However, subjects were of three different ethnicities, potentially impacting the outcome measures, particularly race-related differences in visceral adiposity (15).

The difference in insulin sensitivity between the MIR and SIR groups was related to both oxidative and nonoxidative (storage) glucose disposal, which were lower in the SIR group. They also had less suppression of fat oxidation and lower respiratory quotient in response to hyperinsulinemia, indicative of insulin resistance in suppressing fat oxidation. This is consistent with the higher VAT in the SIR group. Our results differ from those of Weiss et al. (5), in which lipid and glucose oxidations were not significantly different between the insulin-sensitive and -resistant groups. This could again stem from including different racial groups in their study despite reports of race-related differences in lipolysis, substrate oxidation (16,17), and energy expenditure (18). Lower glucose oxidation and higher fat oxidation were observed in insulin-resistant subjects and were proposed as one of the mechanisms for limiting additional weight gain in insulin-resistant versus insulin-sensitive obese Pima Indians in a longitudinal study (19).

In addition, SIR youth have evidence of suboptimal insulin compensation resulting in a lower glucose disposition index compared with their MIR peers. This finding, along with hypoadiponectinemia, which was associated with the future development of type 2 diabetes (20), suggests a higher propensity to progress to an impaired glucose-tolerant state and diabetes (21).

Another observation is the tendency of MIR subjects to have higher CRF. CRF, which is influenced by physical activity, has been associated with lower rates of CVD and all-cause mortality in adult populations (22–24). In female adolescents with a wide range of BMI, $V_{O_{2max}}$ was a more critical determinant of insulin sensitivity than percent body fat (25). In the study by Brochu et al. (4), the insulin-sensitive versus -resistant obese women had similar CRF. It remains to be determined whether the tendency for higher CRF in the MIR group will become more significant if more subjects are studied.

From the practical clinical perspective, the SIR children had significantly higher waist-to-hip ratio, higher fasting insulin, lower HDL, and a tendency for worse CRF and lower adiponectin levels. Similar findings were reported by the few studies addressing the metabolic risk of obesity in adults (3,4) and children (5). However, more research is needed in children to derive specific cut points for the different variables with careful assessment of sensitivity and specificity to enable the distinction between moderately versus severely insulin-resistant children.

In summary, we conclude that despite similar BMI in obese youth, there are differences in the degree of insulin sensitivity and metabolic consequences. The severely insulin-resistant youth are at greater risk for obesity-related comorbidities, including the risk of type 2 diabetes and dyslipidemia. Whether differences in insulin sensitivity stem from higher visceral adiposity or lead to abdominal obesity remains to be determined. Also, it remains to be determined whether this risk phenotype is genetically programmed yet environmentally modulated to allow for therapeutic interventions.

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