

High Visceral and Low Abdominal Subcutaneous Fat Stores in the Obese Adolescent

A Determinant of an Adverse Metabolic Phenotype

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OBJECTIVE—To explore whether an imbalance between the visceral and subcutaneous fat depots and a corresponding dysregulation of the adipokine milieu is associated with excessive accumulation of fat in the liver and muscle and ultimately with insulin resistance and the metabolic syndrome.

RESEARCH DESIGN AND METHODS—We stratified our multi-ethnic cohort of 118 obese adolescents into tertiles based on the proportion of abdominal fat in the visceral depot. Abdominal and liver fat were measured by magnetic resonance imaging and muscle lipid (intramyocellular lipid) by proton magnetic resonance spectroscopy.

RESULTS—There were no differences in age, BMI *Z* score, or fat-free mass across tertiles. However, as the proportion of visceral fat increased across tertiles, BMI and percentage of fat and subcutaneous fat decreased, while hepatic fat increased. In addition, there was an increase in 2-h glucose, insulin, c-peptide, triglyceride levels, and insulin resistance. Notably, both leptin and total adiponectin were significantly lower in tertile 3 than 1, while C-reactive protein and interleukin-6 were not different across tertiles. There was a significant increase in the odds ratio for the metabolic syndrome, with subjects in tertile 3 5.2 times more likely to have the metabolic syndrome than those in tertile 1.

CONCLUSIONS—Obese adolescents with a high proportion of visceral fat and relatively low abdominal subcutaneous fat have a phenotype reminiscent of partial lipodystrophy. These adolescents are not necessarily the most severely obese, yet they suffer from severe metabolic complications and are at a high risk of having the metabolic syndrome. *Diabetes* 57:367–371, 2008

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¹H-MRS, proton magnetic resonance spectroscopy; CRP, C-reactive protein; FFA, free fatty acid; HFF, hepatic fat fraction; IL, interleukin; IMCL, intramyocellular lipid; MRI, magnetic resonance imaging.

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Controversy remains regarding the contribution of abdominal visceral and subcutaneous fat to the development of insulin resistance (1–4). A previous study by our group showed that obese adolescents with impaired glucose tolerance had increased visceral and decreased subcutaneous fat (5). This pattern of abdominal fat distribution was associated with increased intramyocellular lipid (IMCL) deposition and low adiponectin, which together explained the greater insulin resistance. This earlier study suggests that, in some obese adolescents, insulin resistance may be a result of altered abdominal fat partitioning. The hypothesis that inadequate subcutaneous fat results in lipid overflow into the visceral depot and nonadipose tissues, thereby modulating insulin sensitivity, was proposed by Schulman (6) and Danforth (7). It is noteworthy that the two fat depots are distinct in their endocrine and paracrine secretion profiles of hormones and cytokines relevant for glucose homeostasis. In the present study, we tested the hypothesis that, in obese adolescents, an imbalance between the visceral and subcutaneous fat depots and a corresponding dysregulation of the adipokine milieu would be associated with excessive accumulation of fat in the liver and muscle and ultimately with insulin resistance and the metabolic syndrome.

RESEARCH DESIGN AND METHODS

This cross-sectional study reports on the abdominal fat patterning and cardiometabolic profile of 118 obese adolescents recruited from the Yale Pediatric Obesity Clinic. Some participants are part of an ongoing study on the pathophysiology of pre-diabetes in youth and were previously reported (5,8). Subjects were eligible if they were healthy, had a BMI >95th percentile, and were taking no medications known to affect glucose metabolism and/or abdominal fat distribution. There were 46 Caucasian, 36 African-American, and 36 Hispanic children and adolescents. The Yale Human Investigation Committee approved the study, and written informed consent and assent were obtained.

Subjects were invited to the Yale Clinical Research Center at 8:00 A.M. following an overnight fast, and fasting measures of plasma glucose, insulin, C-peptide, proinsulin, total and high-molecular-weight adiponectin, leptin, C-reactive protein (CRP), interleukin (IL)-6, free fatty acids (FFAs), lipid profile, and liver enzymes were obtained. Subsequently, a standard 3-h oral glucose tolerance test was performed (8). Impaired glucose tolerance was defined in accordance with the American Diabetes Association guidelines (9). Insulin sensitivity was estimated using the Matsuda index (10,11). To make the diagnosis of metabolic syndrome in children, we modified the criteria from the National Cholesterol Education Adult Treatment Program and the World Health Organization (8). This set of criteria was recently compared with three others used in pediatric studies (J. D. and S. C., unpublished observations). Although somewhat lower prevalence rates were found using the Weiss compared with the Ford criteria, the overall differences were small.

TABLE 1
Demographic, anthropometric, and clinical characteristics of the study cohort across visceral tertiles

	Tertile 1: 0.027–0.089	Tertile 2: 0.089–0.121	Tertile 3: 0.122–0.224	<i>P</i> for trend	
				Unadjusted	Adjusted*
<i>n</i>	39	40	39		
Sex					
Female (<i>n</i> = 79)	30 (76.9%)	27 (67.5%)	22 (56.4%)	0.16	
Male (<i>n</i> = 39)	9 (23.1%)	13 (32.5%)	17 (43.6%)		
Race/ethnicity					
White (<i>n</i> = 46)	11 (28.2%)	15 (37.5%)	20 (51.3%)	<0.001	
African American (<i>n</i> = 36)	21 (53.9%)	13 (32.5%)	2 (5.1%)		
Hispanic (<i>n</i> = 36)	7 (17.9%)	12 (30.0%)	17 (43.6%)		
Age (years)	14.9 (14.0–15.8)	14.5 (13.6–15.4)	14.5 (13.6–15.4)	0.35	
BMI (kg/m ²)	39.1 (37.2–40.9)†	38.1 (36.3–39.9)‡	35.5 (33.6–37.3)	0.008	0.07
BMI <i>Z</i> score	2.45 (2.36–2.55)	2.45 (2.36–2.55)	2.33 (2.24–2.43)	0.19	0.15
Percentage fat (%)	42.8 (41.0–44.6)†	42.3 (40.5–44.0)‡	39.1 (37.3–40.9)	0.002	0.002
Fat-free mass (kg)	56.3 (52.5–60.2)	56.9 (53.0–60.7)	54.4 (50.6–58.3)	0.78	0.51
Fat mass (kg)	44.3 (40.6–48.0)†	43.9 (40.2–47.7)§	36.4 (32.6–40.1)	0.004	0.02
Waist circumference (cm)	110.5 (106.3–114.7)	111.6 (107.2–116.0)	107.0 (102.5–111.4)	0.28	0.15
Systolic blood pressure (mmHg)	117.4 (113.5–121.3)	120.3 (116.5–124.1)	118.3 (114.4–122.1)	0.37	0.23
Diastolic blood pressure	71.0 (68.1–73.9)	73.8 (70.9–76.6)	72.2 (69.3–75.0)	0.69	0.32
Liver enzymes (U/l)					
ALT	14.9 (11.5–19.4)†	18.4 (14.4–23.5)	25.2 (19.5–32.6)	<0.001	0.04
AST	19.3 (16.6–22.4)†	20.3 (17.7–23.4)‡	26.3 (22.7–30.5)	<0.001	0.04
GGT	18.8 (15.7–22.6)	20.3 (16.7–24.7)	23.4 (19.4–28.1)	0.02	0.03

Data are *n* (%) and means (95% CI) and for liver enzymes geometric mean (95% CI). *Adjusted for age, sex, and race/ethnicity. †*P* < 0.01 for difference between tertile 1 and tertile 3. ‡*P* < 0.05 for difference between tertile 2 and tertile 3. §*P* < 0.01 for difference between tertile 2 and tertile 3. Data in bold indicate significance.

Abdominal magnetic resonance imaging. Abdominal magnetic resonance imaging (MRI) studies were performed on a GE or Siemens Sonata 1.5 Tesla system, as previously described (12). A single slice, obtained at the level of the L4/L5 disc space, was analyzed for each subject. The fascia superficialis was used as the division between the deep and superficial subcutaneous fat. Because the fascia superficialis is rarely visible in the anterior portion of the abdomen, a horizontal line was drawn along the anterior edge of the vertebra, as described by Ross et al. (13). Deep and superficial subcutaneous fat were measured posterior to the horizontal line.

Intrahepatic fat: fast MRI. Hepatic fat accumulation (hepatic fat fraction [HFF]), an estimate of the percentage of fat in the liver, was measured as previously described (12). HFF was measured in a single slice of the liver in 77 of the 118 subjects. We validated this method against hepatic fat measured by proton magnetic resonance spectroscopy (¹H-MRS) and found a strong correlation (*r* = 0.93, *P* < 0.001) (14).

IMCL: ¹H-MRS. IMCL was measured in the soleus muscle using a 4.0 Tesla Biospec system, as previously described (15). IMCL was measured in 89 of the 118 subjects.

Total body composition. Total body composition was measured by dual-energy X-ray absorptiometry with a Hologic scanner.

Biochemical analysis. Plasma glucose levels were measured using the YSI 2700 STAT Analyzer (Yellow Springs Instruments), and lipid levels were measured using an Autoanalyzer (model 747–200; Roche-Hitachi). Plasma insulin, proinsulin, leptin, and total adiponectin were measured using double antibody radioimmunoassays (Millipore). High-molecular-weight adiponectin was measured using ELISA kits (Millipore), and C-peptide was measured using double antibody radioimmunoassay (Diagnostic Products). CRP was measured using ultrasensitive assays (Kamiya Biomedica), and IL-6 was measured using ELISA high-sensitivity kits (R&D Systems). FFAs were measured using Wako Diagnostics assays, and liver enzymes were measured using automated kinetic enzymatic assays (Yale Clinical Chemistry Laboratory).

Statistical analysis. We stratified our cohort into tertiles based on the proportion of visceral fat in the abdomen [visceral fat (cm²)/visceral fat + subcutaneous fat (cm²)], with subjects in tertile 1 having the lowest proportion of visceral fat and highest proportion of subcutaneous fat and those in tertile 3 having the opposite phenotype. The rationale for not using absolute visceral fat is that subjects with smaller body frames may have a lower amount of visceral fat than subjects with larger body frames; however, the relatively low amount of visceral fat may still be associated with negative metabolic effects for these individuals. Moreover, the use of this proportion is justified by the fact that there was a very modest relationship between visceral

and subcutaneous fat in this cohort (*r* = 0.37, *P* = 0.001), indicating poor if any collinearity. We also analyzed the data using residuals from the regression between visceral and subcutaneous fat and found a similar pattern of reduced superficial subcutaneous fat as visceral fat increased across tertiles, which was also associated with an alteration in glucose and insulin metabolism. Furthermore, intrahepatic lipid and IMCL increased while insulin sensitivity decreased across tertiles. Given the similarity in the anatomic and metabolic profiles using either the proportion or the residuals between visceral and subcutaneous fat, we here present data only by the proportion. Statistical analyses were performed with SAS version 9.1 (SAS Institute, Cary, NC). Multiple linear and logistic regression with adjustment for age, sex, and race/ethnicity were used to compare means and proportions, respectively, across tertiles. Tests for trend were performed using proportion of visceral fat as a continuous variable. Where appropriate, log transformations were used to normalize and stabilize outcomes with positively skewed distributions and heterogeneous variance. Unless otherwise stated, data are expressed as frequencies or means/geometric means with 95% CIs.

RESULTS

Demographic, anthropometric, and clinical characteristics. The percentage of female subjects was lower in tertile 3 than in tertile 1, while the percentage of male subjects was higher; however, this trend was not significant (*P* = 0.16) (Table 1). There was, however, a clear shift in the racial/ethnic distribution, with African Americans more likely to have a lower proportion of visceral fat than Caucasians or Hispanics (*P* < 0.001). While there was no significant difference in age, BMI *Z* score, waist circumference, or fat-free mass across tertiles, subjects in tertile 3 had a lower BMI (*P* = 0.007), percentage of fat (*P* = 0.004), and fat mass (*P* = 0.003) than those in tertile 1. There were no differences in blood pressure across tertiles. Notably, there was a trend for higher liver enzymes across tertiles. **Abdominal, muscle, and hepatic fat.** As expected, the amount of total visceral fat increased across tertiles; in contrast, subcutaneous fat decreased (Fig. 1). When the posterior subcutaneous fat was divided into deep and superficial, we found a decrease in both fat layers across

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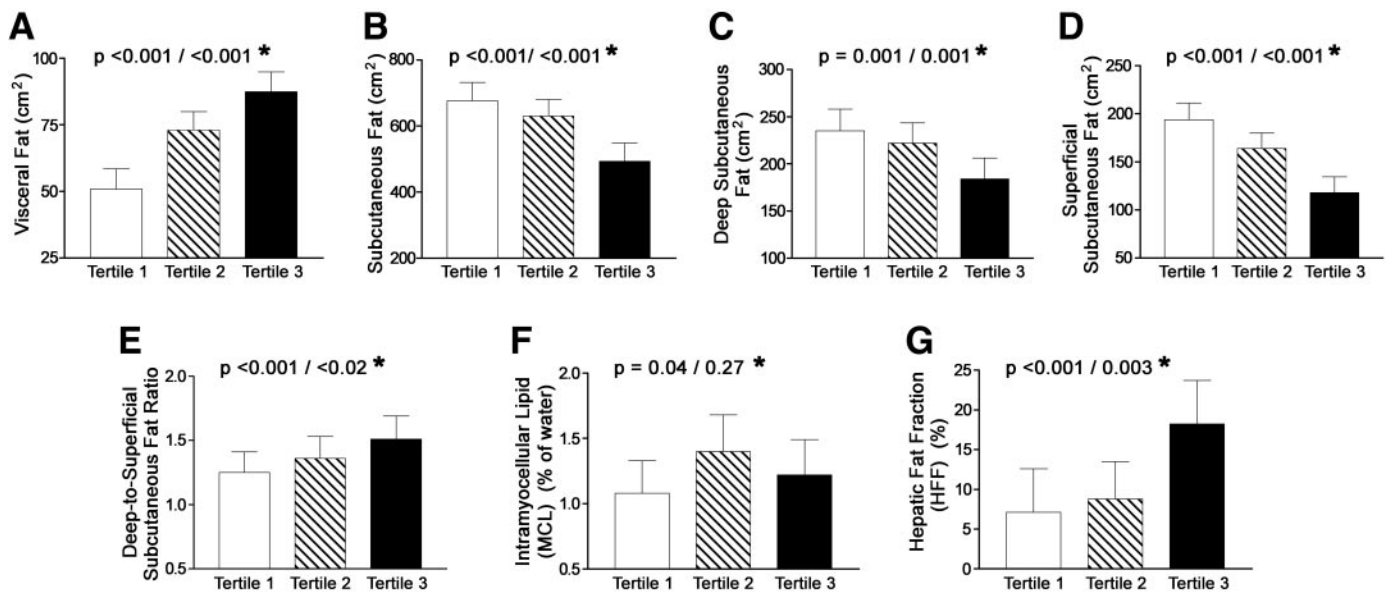


FIG. 1. Lipid deposition: abdominal fat depots, muscle lipid, and liver fat according to visceral tertile, adjusted for age, sex, and race/ethnicity. *P* values are for trend across visceral tertiles, both unadjusted and *adjusted for age, sex, and race/ethnicity.

tertiles. IMCL rose from tertile 1 to 2, then slightly decreased in tertile 3. Intrahepatic fat (HFF) increased across tertiles, which was paralleled by a significant increase in liver enzymes (Table 1). With the exception of IMCL, all trends were significant before and after adjusting for age, sex, and race/ethnicity.

Metabolic characteristics and adipokines. While there were no differences in fasting glucose, 2-h glucose increased significantly across tertiles, as did fasting insulin, proinsulin, and C-peptide (Table 2). We also observed significantly lower insulin sensitivity (Matsuda index) and higher insulin resistance (homeostasis model assessment) across tertiles. Plasma triglycerides were higher while HDL was lower across tertiles. The increase in fasting FFAs across tertiles did not reach statistical significance. Total and high-molecular-weight adiponectin were lower across visceral tertiles; however, the trends did not reach statistical significance (adjusted *P* = 0.08 and 0.11, respec-

tively). Nonetheless, those in tertile 3 had a lower mean adiponectin than those in tertile 1 (adjusted *P* = 0.03). There was a significant trend for lower leptin levels across tertiles. In contrast, no significant differences emerged for IL-6 or CRP.

Subjects in tertile 3 were 5.2 times more likely to have the metabolic syndrome than those in tertile 1 (adjusted *P* = 0.003). Furthermore, those in tertile 3 were 3.7 times more likely to have the metabolic syndrome than those in tertile 2 (adjusted *P* = 0.003). In addition, for each 0.05 increase in the proportion of visceral fat, the odds of having the metabolic syndrome was three times higher (*P* = 0.003).

To further illustrate the metabolic phenotype associated with this altered partitioning in abdominal fat, we selected representative male and female subjects from each tertile. Figure 2 shows the MRIs for three obese white male subjects (Fig. 2A) and female subjects (Fig. 2B), along

TABLE 2

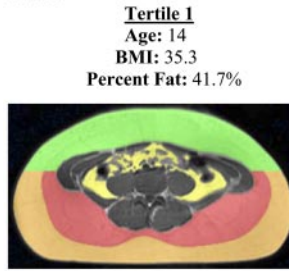
Metabolic characteristics of the study cohort across visceral tertiles, adjusted for age, sex, and race/ethnicity

	Tertile 1: 0.027–0.089	Tertile 2: 0.089–0.12	Tertile 3: 0.122–0.224	<i>P</i> for trend	
				Unadjusted	Adjusted
<i>n</i>	39	40	39		
Fasting glucose (mg/dl)*	93.0 (90.0–95.9)	92.5 (89.7–95.3)	92.8 (89.9–95.8)	0.69	0.33
2-h glucose (mg/dl)*	115.7 (108.4–123.0)	123.1 (116.3–129.9)	129.7 (122.5–137.0)	0.006	0.003
Fasting insulin (μU/ml)†	29.4 (25.1–34.4)	34.2 (29.5–40.0)	41.3 (35.3–48.2)	0.02	<0.001
Proinsulin (pmol/l)†	19.1 (15.2–24.2)	24.1 (19.4–29.8)	27.5 (21.8–34.7)	0.01	0.01
Fasting C-peptide (pmol/l)†	1,034 (905–1,181)	1,227 (1,085–1,388)	1,401 (1,229–1,598)	0.001	0.002
Insulin sensitivity (Matsuda index)†	1.87 (1.53–2.28)	1.35 (1.13–1.61)	1.04 (0.87–1.26)	<0.001	<0.001
Homeostasis model assessment	6.7 (5.7–8.0)	7.8 (6.6–9.1)	9.4 (8.0–11.1)	0.02	<0.001
Fasting FFA (μmol/l)*	463.8 (413.3–514.2)	508.2 (460.4–555.9)	545.7 (493.3–598.1)	0.14	0.22
Triglycerides (mg/dl)†	71.6 (60.4–84.8)	88.4 (75.6–103.4)	103.9 (87.9–122.8)	<0.001	<0.001
HDL (mg/dl)†	45.4 (42.5–48.4)	44.1 (41.4–46.9)	41.8 (38.8–44.7)	<0.001	0.03
Adiponectin (μg/ml)†	8.1 (6.9–9.5)	6.9 (5.9–8.0)	6.2 (5.3–7.3)	0.12	0.08
High-molecular-weight adiponectin (μg/ml)†	1.67 (1.25–2.24)	1.20 (0.92–1.57)	1.21 (0.91–1.61)	0.28	0.11
Leptin (ng/ml)†	40.6 (35.6–45.6)	33.8 (29.3–38.3)	27.9 (23.1–32.7)	<0.001	0.003
CRP (mg/dl)†	1.2 (0.8–1.8)	1.8 (1.3–2.6)	1.5 (1.0–2.2)	0.79	0.40
IL-6 (pg/ml)†	1.4 (1.1–1.8)	1.9 (1.6–2.4)	1.7 (1.4–2.1)	0.62	0.16

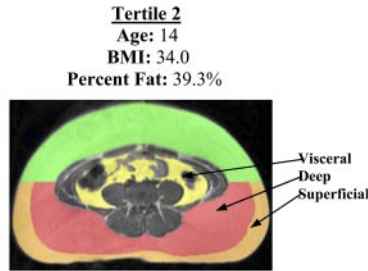
Data are *n* (%), *means (95% CI), and †geometric means (95% CI). Data in bold indicate significance.

A

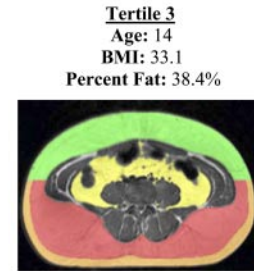
Males



Proportion of Visceral Fat: 0.08
Visceral Fat: 56 cm²
Subcutaneous Fat: 628 cm²
Deep-to-Superficial Ratio: 0.84
Matsuda Index: 2.60
Fasting Insulin: 23 μU/ml
2-hr Glucose: 80 mg/dl
TG: 100 mg/dl
HDL: 39 mg/dl



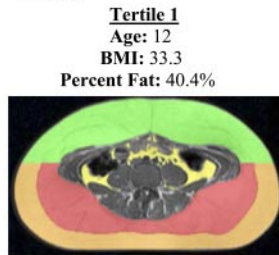
Proportion of Visceral Fat: 0.10
Visceral Fat: 68 cm²
Subcutaneous Fat: 616 cm²
Deep-to-Superficial Ratio: 2.08
Matsuda Index: 1.17
Fasting Insulin: 33 μU/ml
2-hr Glucose: 118 mg/dl
TG: 109 mg/dl
HDL: 34 mg/dl



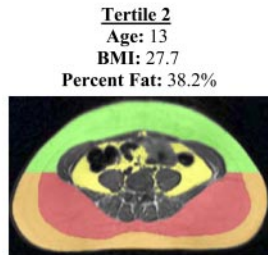
Proportion of Visceral Fat: 0.15
Visceral Fat: 89 cm²
Subcutaneous Fat: 519 cm²
Deep-to-Superficial Ratio: 2.84
Matsuda Index: 0.82
Fasting Insulin: 43 μU/ml
2-hr Glucose: 124 mg/dl
TG: 140 mg/dl
HDL: 40 mg/dl

B

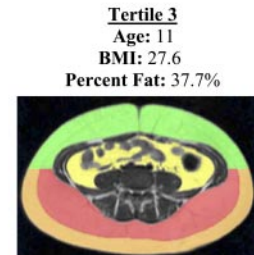
Females



Proportion of Visceral Fat: 0.05
Visceral Fat: 28 cm²
Subcutaneous Fat: 518 cm²
Deep-to-Superficial Ratio: 1.15
Matsuda Index: 1.90
Fasting Insulin: 33 μU/ml
2-hr Glucose: 95 mg/dl
TG: 15 mg/dl
HDL: 44 mg/dl



Proportion of Visceral Fat: 0.11
Visceral Fat: 50 cm²
Subcutaneous Fat: 409 cm²
Deep-to-Superficial Ratio: 1.26
Matsuda Index: 1.15
Fasting Insulin: 32 μU/ml
2-hr Glucose: 165 mg/dl
TG: 82 mg/dl
HDL: 61 mg/dl



Proportion of Visceral Fat: 0.15
Visceral Fat: 58 cm²
Subcutaneous Fat: 338 cm²
Deep-to-Superficial Ratio: 1.39
Matsuda Index: 0.27
Fasting Insulin: 77 μU/ml
2-hr Glucose: 185 mg/dl
TG: 143 mg/dl
HDL: 33 mg/dl

FIG. 2. Representative MRI images of Caucasian male (A) and female (B) subjects from each of the three visceral tertiles. Note the increase in visceral fat, decrease in subcutaneous fat, and increase in deep-to-superficial subcutaneous fat ratio across tertiles. In addition, there is a decrease in insulin sensitivity (Matsuda index) and an increase in fasting insulin, 2-h glucose, and triglycerides.

with their metabolic profiles. When comparing subjects from tertiles 1 and 3, one can appreciate the increased visceral fat and decreased superficial subcutaneous fat in tertile 3, along with the pronounced differences in the metabolic phenotype.

DISCUSSION

In this study, we found that a high proportion of visceral fat was associated with muscle and hepatic steatosis, high triglycerides, and low HDL, leptin, and adiponectin levels in obese adolescents. Notably, the risk for the metabolic syndrome was five times greater in the adolescents with this fat partitioning profile. This phenotype of altered abdominal fat partitioning and its associated metabolic abnormalities has interesting parallels with partial lipodystrophy. Lipodystrophy, which is the total or partial loss of subcutaneous fat, is often accompanied by hepatic steatosis and increased IMCL, followed by insulin resistance and type 2 diabetes (16). In lipotrophic animals, transplantation of adipose tissue back into the animals reverses the phenotype (17,18). These studies demonstrate that an

inadequate subcutaneous depot leads to ectopic fat storage with its associated metabolic sequelae. Thus, in obesity, type 2 diabetes, and lipodystrophy, insulin resistance may develop because of alterations in the partitioning of fat between the adipocyte and muscle or liver (6).

Our study supports the hypothesis that the ability to retain fat in the subcutaneous depot, especially the superficial layer, is beneficial in obese adolescents, since it is associated with reduced visceral and hepatic fat and a more favorable metabolic profile. The subcutaneous depot has been proposed to act as a “sink,” with the capability to accommodate excess triglycerides and thus prevent the flow of lipid to other areas. This hypothesis has been elegantly explored by Ravussin and Smith (19,20). Here, we present the first evidence that this phenotype may be present in obese adolescents.

It remains unclear why the subcutaneous depot in some individuals has a limited capacity to expand and accommodate excess triglycerides. It may be due to an inability of the existing adipocytes to signal preadipocytes to proliferate and differentiate, instead increasing in size in

response to the influx of triglycerides. In addition to being more insulin resistant, large adipocytes have been shown to release less adiponectin than small adipocytes (21). Therefore, the lower adiponectin levels in the subjects with a high proportion of visceral fat may be due in part to the presence of large adipocytes in the subcutaneous fat. In addition, consistent with the reduced subcutaneous fat in these subjects, we found decreased levels of leptin. Both leptin and adiponectin have antisteatotic effects (22,23). This supports the contention that adipocyte secretory products are required to protect nonadipose tissue from lipid-induced damage. Total and high-molecular-weight adiponectin not only have anti-inflammatory actions but also activate AMP-activated protein kinase, leading to increased fat oxidation (23,24). Thus, reduced leptin and adiponectin levels are certainly not ideal with respect to protection from the cluster of cardiometabolic risk factors. A schematic view of our hypothetical model is shown in Fig. 3 of the online appendix (available at <http://dx.doi.org/10.2337/db07-0932>). Interestingly, we did not find an increase in CRP or IL-6, the two prototypic markers of inflammation.

In summary, our findings demonstrate a lipid partitioning profile reminiscent of partial lipodystrophy—a high proportion of visceral fat and a relatively low amount of subcutaneous fat. The adolescents who fit this profile are not necessarily the most severely obese, yet they suffer from severe metabolic complications of obesity and are at a high risk of having the metabolic syndrome.

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