Published in final edited form as:

Obesity (Silver Spring). 2012 February ; 20(2): 371–375. doi:10.1038/oby.2011.264.

Impaired Insulin Sensitivity and Elevated Ectopic Fat in Healthy Obese vs. Nonobese Prepubertal Children

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Abstract

Insulin sensitivity is impaired and ectopic fat (accretion of lipids outside of typical adipose tissue depots) increased in obese adults and adolescents. It is unknown how early in life this occurs; thus, it is important to evaluate young children to identify potential factors leading to the development of metabolic syndrome. We examined an ethnically diverse cohort of healthy, exclusively prepubertal children (N = 123; F = 57, M = 66; age 8.04 ± 0.77 years) to examine differences in insulin sensitivity and ectopic and visceral fat deposition between obese and nonobese youth. Obesity was categorized by age- and sex-adjusted BMI z-scores (nonobese = z-score <2 (N = 94) and obese = z-score ≥2 (N = 29)). Insulin sensitivity was assessed by both a frequently sampled intravenous glucose tolerance test (S_i) and the homeostatic model assessment of insulin resistance ($HOMA_{IR}$). Intramyocellular lipids (IMCLs) from soleus and intrahepatic lipids (IHLs) were assessed by magnetic resonance spectroscopy, visceral adipose tissue (VAT) by magnetic resonance imaging, and total body fat by dual-energy X-ray absorptiometry. We also examined serum lipids (total cholesterol, triglycerides, high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol) and blood pressure (diastolic and systolic). Obese children exhibited significantly lower S_i (5.9 ± 5.98 vs. 13.43 ± 8.18 $(m\mu/l)^{-1}\cdot min^{-1}$, P = 0.01) and HDL-C and higher $HOMA_{IR}$ (1.68 ± 1.49 vs. 0.63 ± 0.47, P < 0.0001), IMCL (0.74 ± 0.39 vs. 0.44 ±

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DISCLOSURE

The authors declared no conflict of interest.

0.21% water peak, $P < 0.0001$), IHL (1.49 ± 1.13 vs. 0.54 ± 0.42% water peak, $P < 0.0001$), VAT (20.16 ± 8.01 vs. 10.62 ± 5.44 cm^2, $P < 0.0001$), total cholesterol, triglycerides, low-density lipoprotein cholesterol, and systolic blood pressure relative to nonobese children. These results confirm significantly increased ectopic fat and insulin resistance in healthy obese vs. nonobese children prior to puberty. Excessive adiposity during early development appears concomitant with precursors of type 2 diabetes and the metabolic syndrome.

INTRODUCTION

Over the past 30 years, the prevalence of obesity has increased considerably among children and adolescents (1). Although a recent national report indicates a leveling off of this trend, a significant portion of the pediatric population remains obese and thus at risk for developing future metabolic disease, particularly those related to carbohydrate metabolism (1,2). Furthermore, regional secular trends, especially in areas with traditionally higher obesity prevalence rates, may not mirror national estimates. This was evidenced in a recent report of rural Louisiana communities which indicated a sustained increase in the prevalence of childhood obesity across race and sex (3).

Obese children and adolescents, especially with severe conditions, are more likely than their nonobese counterparts to exhibit components of the metabolic syndrome and, thus, are at higher risks for chronic disease development (4–6). Three recent examinations of children and adolescents reported no cases of metabolic syndrome among nonobese youth (4–6). However, among obese participants, metabolic syndrome was observed in 12–39% of moderately obese (BMI *z*-score 2–2.5) and 31–50% of severely obese (BMI *z*-score >2.5) children. Greater adiposity was also associated with carbohydrate dysregulation, dyslipidemia, and increased hepatic and visceral fat stores.

It is widely accepted that obesity during childhood is linked to impaired glucose metabolism, insulin resistance, and type 2 diabetes mellitus (T2DM) (7). The amount of body fat as well as its location, particularly within the liver, appears to play a critical role in disease development (8). Among adults, steatosis because of excessive intrahepatic lipid (IHL) accumulation occurs more frequently as obesity increases. Its presence elevates the risk for the development of the metabolic syndrome, T2DM, and several other cardiovascular and metabolic diseases (9). Recent reports of obese, prepubertal children indicated that hepatic lipid stores were already present and in quantities sufficient enough to predispose to disease (10,11).

The aim of this study was to examine differences in insulin sensitivity, ectopic and visceral fat deposition, and other biomarkers that often precede the development of the metabolic syndrome in a sample of exclusively prepubertal, healthy nonobese vs. obese children, 7–9 years of age.

METHODS AND PROCEDURES

The MET study (Mechanisms for the Metabolic Syndrome in Prepubertal Youth) is a cross-sectional study exploring mechanisms for the metabolic syndrome in healthy, prepubertal

children. The study population is comprised of a multiethnic sample (white = 77 and nonwhite = 46 (African American = 41, Hispanic = 4, and Asian/Pacific Islander = 1)) of children 7–9 years of age recruited from southeast Louisiana. Details of the MET study's data collection, inclusion and exclusion criteria, and recruitment methods have been previously described (12). Prior to enrollment, medical and family histories were obtained through a detailed phone interview of the parents/guardians of interested volunteers. If eligible, a physical examination that included a complete medical history and screening blood test (with comprehensive metabolic panel and complete blood count with differential) was performed to ensure the child's eligibility to participate in the study. Prepubertal status was confirmed during a physical examination administered by a pediatrician and defined as pubertal stage <2 according to criteria established by Tanner (13). The study was approved by the Institutional Review Boards of Louisiana State University Health Sciences Center, Children's Hospital of New Orleans, and the Pennington Biomedical Research Center. Participants' legal guardians read and signed an approved consent form, and children provided their written assent prior to participation in any study procedures.

A pediatric registered nurse measured anthropometrics and vital signs including height, weight, waist circumference, and blood pressure during the initial screening visit. BMI scores were calculated using the following formula: weight (kg)/height $(m)^2$. Children participated in a frequently sampled intravenous glucose tolerance test (FSIVGTT) following a 12-h overnight fast. Upon infusion of dextrose (minute 0) and insulin (minute 20), serum glucose and insulin were sampled and analyzed at three baseline measurements and 11 timed collections over a 180-min period. A detailed description of the FSIVGTT procedure in this study population has been previously described (12). Insulin sensitivity was calculated using the MINMOD Millennium software (version 6.02, Richard N. Bergman, Los Angeles, CA) based on Bergman's Minimal Model (14).

A baseline sample of blood was drawn prior to the FSIVGTT to analyze serum lipid profiles (including total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol, and triglycerides). Glucose was assayed using an Ortho Clinical Diagnostics VITROS 5,1 FS (Rochester, NY) and serum insulin using an EIA kit from ALPCO (Salem, NH). Homeostatic model assessment of insulin resistance ($HOMA_{IR}$) was determined using the homeostatic model assessment methodology and calculated using the following formula: fasting glucose (mmol/l) × fasting insulin (FI) (mIU/l)/22.5 (15).

Body composition including total body fat was measured by dualenergy X-ray absorptiometry using a Hologic QDR 4500A (Bedford, MA) and accompanying QDR software for Windows version 11.1.2. IHL and intramyocellular lipid (IMCL) depots of the soleus muscle were assessed noninvasively using proton magnetic resonance spectroscopy (^{1}H-MRS (water suppressed)) on a General Electric (GE) Sigma Excite (3.0 Tesla). Details of this protocol's testing methodology and analysis in our study population have been previously described (16,17). Visceral adipose tissue (VAT) was assessed by magnetic resonance imaging on the same system (GE Medical Systems, Milwaukee, WI). VAT was assessed in the fourth through fifth lumbar (L4–L5) vertebrae area (18).

Statistical analyses were performed with SAS version 9.2 (SAS Institute, Cary, NC). Children were stratified into two dichotomous groups based upon adiposity level. Age- and sex-adjusted BMI *z*-scores were used to define children as either nonobese (*z*-score <2) or obese (*z*-score ≥2). Thresholds were determined using the Centers for Disease Control and Prevention's (CDC) SAS program for calculating BMI percentiles and *z*-scores. The SAS program's datasets were generated using the 2000 CDC growth charts (19). Tests to detect differences in means were employed to determine whether obese children exhibited significantly different metabolic profiles and larger ectopic and visceral fat stores than nonobese children. Least square means difference analysis (adjusted for race, sex, and with and without total body fat) was used to determine whether mean values differed significantly across adiposity groups. Partial correlation coefficients (adjusted for race and sex) were calculated to examine relationships between insulin sensitivity, ectopic and visceral fat, and other potential markers for the metabolic syndrome. A *P* value of <0.05 was considered statistically significant. The sample of 123 children represents the total number for which data were collected; however, study data are not available for all children in the MET study because of occasional technical problems and/or the election of the child not to participate in a portion of the study, which required travelling 1 h each way to another clinical study site.

RESULTS

Characteristics of the study sample are presented in Table 1. According to BMI *z*-score thresholds, 23.6% of children in the study sample were obese (94 nonobese and 29 obese children) (19). Raw, unadjusted mean values for selected biomarkers and corresponding *P* values to detect differences in mean values among adjusted data are presented in Table 2 for nonobese vs. obese children. When adjusted for race and sex, obese children were less insulin sensitive ($P = 0.01$) and exhibited higher FI concentrations ($P < 0.0001$) and $HOMA_{IR}$ ($P < 0.0001$) than their nonobese counterparts. Obese children also exhibited significantly larger ectopic (IHL ($P < 0.0001$) and IMCL ($P < 0.0001$)) and visceral ($P < 0.0001$) fat stores and a more impaired lipid profile (total cholesterol ($P < 0.05$), HDL-C ($p < 0.01$), low-density lipoprotein cholesterol ($p = 0.03$), triglycerides ($p < 0.01$)) when compared to nonobese. With the addition of total body fat as a covariate, significant differences between nonobese and obese groups remained in IHL ($P < 0.01$), $HOMA_{IR}$ ($P = 0.01$), FI ($P = 0.02$), and HDL-C ($P = 0.04$).

Correlations of anthropometric variables (waist circumference and total body fat) and indicators of ectopic fat stores (IMCL, IHL, and VAT) to markers of the metabolic syndrome (intravenous glucose tolerance test (S_i), IR, and FI) appear in Table 3. When adjusted for race and sex, insulin sensitivity was inversely associated with IHL ($P = 0.04$), VAT ($P = 0.03$), waist circumference ($P < 0.01$), and total body fat ($P = 0.001$) but not IMCL ($P = 0.14$). Furthermore, both $HOMA_{IR}$ and FI were significantly correlated with waist circumference ($P < 0.05$ and $P < 0.05$, respectively) and total body fat ($P < 0.001$ and $P < 0.001$, respectively); however, we did not observe significant associations between $HOMA_{IR}$ and FI and ectopic or visceral fat.

Obese children in this sample exhibit multiple conditions that indicate elevated risk for future metabolic disease development relative to their nonobese counterparts. Although a

clear definition for the metabolic syndrome in children and adolescents has not yet been established (20), definitions of the metabolic syndrome specific to prepubertal populations as reviewed by Golley (21) indicate that 16% of our study population met criteria for the metabolic syndrome proposed by Lambert and colleagues (22). However, when a modified version of Lambert's definition (21) and the European Group for the Study of Insulin Resistance (23) were applied, only 8% met criteria for metabolic syndrome.

DISCUSSION

Data from this cohort indicate significant differences in several key markers for metabolic syndrome among obese and nonobese children. Our study population was predominately nonobese with slightly less than one quarter of the children classified as obese (by BMI *z*-score). The proportion of obese children in our sample was higher than a national sample of 6- to 11-year-old children reported from 2007–2008 (23.6 vs. 19.6%) (1), but less than a recent reporting of children from rural Louisiana communities (23.6 vs. 27.4%) (24). We observed significant differences in several components of the metabolic syndrome using state-of-the-art methodologies assessing insulin resistance and tissue lipid stores. Our data confirm that healthy obese prepubertal children may already be predisposed to the development of metabolic disease as has been demonstrated in adult populations.

Several investigations have linked increasing whole-body adiposity, as defined by BMI, to poorer metabolic profiles in both children and adolescents (4–6). Findings from our examination are in agreement with those previously reporting a positive association between components of the metabolic syndrome and BMI in youth (4–6) and adults (25). Prepubertal children identified with the metabolic syndrome in our sample (16%), as defined by prepubertal-specific criteria published by Lambert (22), had a mean BMI *z*-score of 2.26 and total body fat percentage of 37.8%, whereas those children not meeting this criteria had a mean BMI *z*-score of only 0.9 and a much lower average body fat of 24.6%. Thus, our findings confirm the detrimental impact of excess adiposity on metabolic health even in young children who have not yet entered puberty and suggest that efforts to prevent and manage childhood obesity should begin very early in life.

In this sample of 75 prepubertal youth, we found five children (6.7%) were insulin resistant according to a prepubertal-specific cutoff designated by Masuccio (26) when using $HOMA_{IR}$ data. Of the children exceeding the cutoff ($HOMA_{IR}$ >2.03), four of the five were obese according to BMI *z*-score classification. The nonobese child with IR as documented with $HOMA_{IR}$, although not obese by our criteria, approached the obesity threshold (BMI *z*-score of 1.83) and had a body fat percentage almost equal to the mean value of the obese group (37.7 vs. 37.8%). Furthermore, when examining only the obese children in our cohort, we found that 13.8% were insulin resistant compared to only 1.1% of nonobese children. These findings are in agreement with several prior investigations. Cali and Caprio reported that the prevalence of impaired glucose tolerance more than quadrupled between the overweight (≥85th BMI <97th percentile) and severely obese (BMI *z*-score >2.5) groups (6). Moreover, Calcaterra *et al*. reported an increasing trend in both FI and $HOMA_{IR}$ with increasing BMI among prepubertal and pubertal obese children and adolescents (5).

Along with impaired glucose metabolism, increased visceral and ectopic fat, especially within the liver, are commonly two key precursors linked to the metabolic syndrome and T2DM (27). Our analysis of this prepubertal sample indicated that obese children not only exhibited markers (e.g., elevated ectopic and visceral fat) but also developed significant insulin resistance (assessed by S_i and $HOMA_{IR}$), a major and known contributor for the development of T2DM. Of particular significance is that obese children, as a group, had nearly three times the IHL content (1.49% vs. 0.54%) and almost double the amount of visceral fat (20.2 vs. 10.6 cm^2) than that of nonobese children. Furthermore, we noted that insulin resistance (by $HOMA_{IR}$ and/or FI) was more than double and insulin sensitivity (assessed by FSIVGTT) less than half in obese vs. nonobese children. Our findings agree with a previous report of a mixed cohort of older predominately pubertal children and adolescents, 10–13 years of age, that found similar differences in IHL and visceral fat when stratified into tertiles according to the proportion of visceral fat in the abdomen (6). Data presented by Cali and Caprio indicated significant differences across tertiles in hepatic ($P = 0.003$) and visceral ($P < 0.0001$) fat, but not IMCL (6). The substantial variations in biomarkers we observed in our sample of healthy, exclusively prepubertal (7–9 years) obese and nonobese children suggest that excess adiposity prior to puberty may disrupt normal metabolism thus impairing glucose tolerance and increasing the risk for T2DM later in life.

Studies in adults indicate that hepatic and visceral fat content are both better correlates and predictors of insulin sensitivity than IMCL (8,28). Kirchhoff and colleagues reported that insulin sensitivity exhibited a stronger relationship with liver and visceral fat ($r = -0.53$, $P < 0.0001$ and $r = -0.43$, $P < 0.0001$, respectively) than with IMCL ($r = -0.26$, $P < 0.0001$). Both were also stronger predictors of S_i using multivariate regression models. Data from our sample of prepubertal children are in agreement with findings reported by Kirchhoff as both IHL and VAT ($r = -0.49$, $P = 0.04$ and $r = -0.58$, $P = 0.01$, respectively) were stronger correlates of insulin sensitivity than IMCL ($r = -0.33$, NS). Our results also agree with a previous study which evaluated S_i by FSIVGTT in a similar sample of African American and white prepubertal children (29). In this study, Gower and colleagues reported significant associations between S_i and total body fat (African American: $r = -0.7$, $P < 0.001$; white: $r = -0.78$, $p < 0.001$) and visceral fat (African American: $r = -0.5$, $P < 0.01$ and white: $r = -0.75$, $P < 0.001$). However, ectopic fat was not measured in this investigation. A more recent study by Maffeis and colleagues (30), however, found significant associations between S_i and hepatic fat content ($r = -0.436$, $P < 0.05$), but not IMCL in a small cohort ($n = 30$) of overweight and obese children. While similar to our findings, in primarily nonobese youth, Maffeis did not find a significant association of S_i with VAT (30). We speculate that lipid accumulation in skeletal muscle (IMCL) can be dependent upon several additional factors (e.g., race, family history, aerobic fitness, obesity status, and maturation level), which may in part explain the lack of association with markers of insulin sensitivity. Collectively, findings from previous studies in obese children and adolescents and our current findings in younger nonobese and obese youth provide support for a link between excess adiposity and, in particular, ectopic fat and established precursors to metabolic disease in children prior to puberty.

Several factors including sample size and missing data for some of the testing may be seen as a weakness of this investigation. However, the benefits of including accurate, state-of-the-art methodologies (e.g., FSIVGTT, ectopic fat by ^{1}H-MRS, etc.) to assess differences among obese and nonobese may compensate for the loss of some data. Such studies in young children are notoriously difficult to perform, thus limiting our completion of FSIVGTT in only 40 children as opposed to simpler, more routine measurements (e.g., FI, *n* = 76) (12). Notwithstanding, we believe that our inclusion of such advanced measurements and methods is warranted as currently there are no studies that have simultaneously examined S_i by FSIVGTT and ectopic and visceral fat by ^{1}H-MRS/MRS in exclusively prepubertal obese and nonobese children.

Our data confirm that obesity in children increases the risk for developing components of the metabolic syndrome, which leads to several chronic diseases including T2DM. In addition, we found that localized fat deposition, especially around certain tissues and organs, may play an even more critical role in the pathology of metabolic disease (27). Greater lipid deposition, especially within the liver, is an important signal of glucose metabolism dysfunction and oftentimes precedes disease onset. The amount of ectopic and visceral fat was significantly different between obese and nonobese children in our cohort. However, while we observed an inverse relationship of S_i to both IHL and VAT, we failed to find any significant associations between IMCL and S_i, IR, or FI. Regardless, the results of this investigation reveal an apparent difference in several key predictors for the development of T2DM in obese vs. nonobese healthy, prepubertal children. Our findings highlight the importance of interventions to prevent and manage obesity during the prepubertal years and suggest this as a possible means of reducing metabolic disease risk and combating the increasing prevalence of T2DM.

Acknowledgments

This work is supported by NICHD R01HD41071 and R01HD49046, NIDDK (NORC) 1P30 DK072476, and the LSU Health Sciences Center and Tulane University Clinical and Translational Research Center.

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Table 1

Subject characteristics and anthropometric data

	Total (*n* = 123)	**Nonobese (*n* = 94)**	**Obese (*n* = 29)**
Sex (M/F)	66/58	46/48	20/9
Age (years)			
Mean ± s.d.	8.04 ± 0.77	8.04 ± 0.76	8.07 ± 0.8
Range	7–9	7–9	7–9
Race (white/nonwhite)	77/46	61/33	16/13
BMI (kg/m^2)			
Mean ± s.d.	20.12 ± 4.96	17.98 ± 2.28	27.06 ± 4.96
Range	13.9–46.7	13.91–23.16	20.97–46.7
BMI *z*-score			
Mean ± s.d.	1.08 ± 1.01	0.69 ± 0.81	2.35 ± 0.25
Range	−1.56–2.88	−1.56–1.99	2.03–2.88
Body fat (%)			
Mean ± s.d.	27.17 ± 8.6	23.87 ± 6.58	37.84 ± 4.88
Range	12.12–49.73	12.12–37.81	30.32–49.73
Total body fat (kg)			
Mean ± s.d.	10.49 ± 7.25	7.63 ± 3.19	19.77 ± 8.87
Range	3.05–53.38	3.05–17.41	10.3–55.38
Waist circumference (cm)			
Mean ± s.d.	67.64 ± 13.95	62.22 ± 6.99	86.62 ± 15.69
Range	48.01–141.5	48.01–80.01	67.06–141.5
Weight (kg)			
Mean ± s.d.	35.75 ± 12.12	31.15 ± 5.77	50.65 ± 15.12
Range	18.8–107.9	18.8–47.3	28.8–107.9

Table 2

Values of selected biomarkers in nonobese and obese children

	n	Nonobese (*n* = 94)	Obese (*n* = 29)	*P* value[a]	*P* value[b]
IMCL (% water peak)	99	0.44 ± 0.21	0.74 ± 0.39	<0.0001	0.47
IHL (% water peak)	92	0.54 ± 0.42	1.49 ± 1.13	<0.0001	<0.01
VAT (cm^2)	83	10.62 ± 5.44	20.16 ± 8.01	<0.0001	0.18
Insulin sensitivity $(m\mu/l)^{-1} \bullet min^{-1}$	40	13.43 ± 8.18	5.9 ± 5.98	0.01	0.19
Insulin resistance (HOMA)	75	0.63 ± 0.47	1.68 ± 1.49	<0.0001	0.01
Glucose (mmol/l)	82	4.12 ± 0.55	4.33 ± 0.47	0.28	0.94
Insulin (μU/ml)	76	3.31 ± 2.39	8.23 ± 6.37	<0.0001	0.02
Total cholesterol (mg/dl)	79	155.29 ± 26.77	168.81 ± 24.29	<0.05	0.76
HDL-cholesterol (mg/dl)	80	50.76 ± 10.41	45.35 ± 9.01	<0.01	0.04
LDL-cholesterol (mg/dl)	80	90.14 ± 24.14	102.47 ± 18.55	0.03	0.46
Triglycerides (mg/dl)	79	71.89 ± 42.67	98.69 ± 55.18	<0.01	0.41
Systolic BP (mm Hg)	123	107.96 ± 9.95	114.17 ± 9.89	<0.01	0.63
Diastolic BP (mm Hg)	123	64.37 ± 5.59	65.41 ± 5.82	0.44	0.68

Data presented as mean value ± s.d.

BP, blood pressure; HDL, high-density lipoprotein; HOMA, homeostatic model assessment; IHL, intrahepatic lipid; IMCL, intramyocellular lipid; LDL, low-density lipoprotein; VAT, visceral adipose tissue.

[a] Adjusted for race and sex.

[b] Adjusted for race, sex, and total body fat.

Table 3

Correlation coefficients for measures of adiposity and fat deposition to markers of glucose metabolism

	Insulin sensitivity	Insulin resistance	Fasting insulin
IMCL	−0.36	0.03	0.02
IHL	−0.49[a]	0.07	0.13
VAT	−0.58[a]	0.19	0.21
Waist circumference	−0.64[b]	0.47[a]	0.48[a]
Total body fat	−0.72[c]	0.71[c]	0.71[c]

Correlations adjusted for race and sex.

IHL, intrahepatic lipid; IMCL, intramyocellular lipid; VAT, visceral adipose tissue.

[a] $P < 0.05$,

[b] $P < 0.01$,

[c] $P < 0.001$.