Prevalence of the Metabolic Syndrome Among Obese Adolescents Enrolled in a Multidisciplinary Weight Management Program: Clinical Correlates and Response to Treatment

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Abstract

Objective: The aim of this study was to determine the prevalence of the metabolic syndrome at baseline and after 6 months of lifestyle modification among obese adolescents referred to a multidisciplinary weight management program.

Methods: A total of 165 obese adolescents were evaluated at baseline, and measurements were repeated in 57 subjects who completed 6 months of the program. Metabolic syndrome was defined as having three or more of the following: a body mass index (BMI) >97th percentile, hypertension, low high-density lipoprotein cholesterol (HDL-C), hypertriglyceridemia, and impaired fasting glucose (IFG).

Results: The prevalence of a BMI >97th percentile, hypertension, hypertriglyceridemia, low HDL-C, and IFG was 92.7, 54.5, 29.1, 26.7, and 2.4%, respectively. The prevalence of the metabolic syndrome at baseline was 30.3%. After 6 months of lifestyle modification, BMI z scores, percent body fat, total cholesterol, and low-density lipoprotein cholesterol (LDL-C) decreased significantly from baseline; however, there was no significant change in the number of subjects demonstrating $\geq$ three criteria of the metabolic syndrome.

Conclusions: Approximately one third of the study subjects met the criteria of the metabolic syndrome, emphasizing the growing concern for the future development of premature cardiovascular disease in this high-risk population. Our data suggest that new strategies for lifestyle modification may be needed to improve cardiovascular risk factors significantly among adolescents with obesity.

Introduction

THE PREVALENCE OF OBESITY is increasing worldwide.¹ In children, obesity is defined by a body mass index (BMI) $\geq$ 95th percentile for age and sex.² As reported in the 2003–2004 National Health and Nutrition Examination Survey (NHANES), 17.4% of 12- to 19-year-old adolescents are obese.³ The metabolic syndrome, a constellation of cardiovascular risk factors associated with insulin resistance, is already present in many obese adolescents.⁴ Alarming, a recent prospective study demonstrated an approximately 15-fold increased risk of premature cardiovascular disease among adults who demonstrated metabolic syndrome in childhood compared with those without the syndrome.⁵

Consequently, the identification of children at highest risk is of paramount importance.

Currently, the mainstay of treatment for pediatric obesity is lifestyle modification with increased physical activity and dietary modification.^{1,2} However, counseling from individual health-care providers is frequently inadequate, and a comprehensive multidisciplinary approach is often required. As part of an initiative to develop such an approach, we report the prevalence of components of the metabolic syndrome at baseline among 165 obese adolescents enrolled in a multidisciplinary weight management program at an academic medical center. Additionally, alterations in selected variables were evaluated in 57 subjects who completed 6 months of program participation.

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Subjects and Methods

Subjects

A total of 165 obese adolescents (ages 11–18 years) were enrolled in a comprehensive weight management program at Virginia Commonwealth University (VCU) from November, 2003, to February, 2006. Adolescents with a BMI $\geq 95^{\text{th}}$ percentile for age and sex^{2,6} were eligible for participation. Informed consent was obtained from parents and assent was given by each subject. The study protocol was approved by our institutional review board.

Anthropometric and biochemical measurements

Baseline anthropometric and metabolic testing was performed at the General Clinical Research Center. BMI was calculated from height and weight, measured to the nearest 0.1 cm or 0.1 kg, respectively. BMI z-scores were determined using Epi Info software program (Centers for Disease Control, Version 3.3). Percent body fat was determined by bioelectric impedance analysis (Quantum II, RJL Systems). After subjects were seated quietly for 5 minutes, a single blood pressure measurement was obtained using an automated device (Dynamap Pro 100, General Electric).

Fasting venous blood samples were collected for measurement of plasma glucose, insulin, lipids, hepatic transaminases, leptin, and adiponectin. Plasma glucose and insulin levels were determined using glucose oxidase methodology (YSI 2300 Stat Plus Glucose Analyzer Yellow Springs Instruments [YSI]), and an enzyme-linked immunoassay (ELISA; ALPCO Diagnostics), respectively. Insulin resistance was estimated by the homeostasis model of insulin resistance (HOMA-IR = [fasting glucose (mmol/L) $\times$ fasting insulin (mU/L)]/22.5).⁷ Plasma leptin and adiponectin levels were measured using sandwich ELISAs (Linco Research). Total cholesterol (TC), triglycerides, and high-density lipoproteins (HDL) were measured using a Roche automated clinical chemistry analyzer. Low-density lipoprotein cholesterol (LDL-C) was calculated by the Friedewald equation (LDL = TC – HDL – [Triglycerides/5]).⁸

At baseline, 122 participants also completed a 2-hour oral glucose tolerance test (OGTT). Plasma glucose and insulin were measured at baseline and 30, 60, 90, and 120 minutes following administration of 75 grams of oral glucose solution.⁹ Impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) were defined as a fasting glucose 100–125 mg/dL and a 2-hour glucose 140–199 mg/dL, respectively.¹⁰ Diabetes mellitus (DM) was defined by a fasting glucose ≥ 126 mg/dL or 2-hour glucose ≥ 200 mg/dL.¹⁰ In subjects undergoing an OGTT, insulin sensitivity was also estimated using the Whole-Body Insulin Sensitivity Index (WBISI),¹¹ where FPG and FPI represent fasting plasma glucose and insulin, respectively: $WBISI = 10,000/\sqrt{([FPG \times FPI] \times [\text{mean glucose} \times \text{mean insulin}])}$. Using this formula, insulin sensitivity was estimated by a number (0–12), with higher numbers corresponding to greater insulin sensitivity.

Definition of metabolic syndrome

Subjects meeting three or more of the following five criteria were classified as having metabolic syndrome: BMI $>97^{\text{th}}$ percentile for age and sex⁶; triglycerides ≥ 110 mg/dL;

HDL-C ≤ 40 mg/dL; systolic or diastolic blood pressure $>90^{\text{th}}$ percentile for age, sex, and height¹²; and fasting glucose ≥ 100 mg/dL.

Multidisciplinary weight management program

The intervention program consisted of three components: nutrition education, physical activity, and behavioral support/modification. Whereas the current report presents data obtained after 6 months of program participation, the complete program spans 2 years.

During the study period, subjects and parents attended a biweekly nutritional education session with a registered dietician. These interactive sessions consisted of a standardized series of lessons addressing topics including the U.S. Department of Agriculture (USDA) Food Guide Pyramid, portion sizes, food labels, healthy snacking, and meal planning. High-risk eating habits were identified, and healthy alternatives were provided. Enrolled adolescents also attended biweekly, same-sex, peer support groups that addressed compliance with the program goals, barriers to lifestyle changes, and motivation.

Subjects were expected to exercise for a minimum of 1 hour, 3 days a week. Sessions included 10 minutes of warm up, 20–30 minutes of aerobic activity, 20–30 minutes of resistance training, and a 10-minute cool-down period. At least one exercise session a week was performed at a dedicated facility where faculty assessed and modified each adolescent's exercise intensity using heart rate monitors (E600, Polar Electro Inc.). Memberships to local YMCAs were also provided to each family (unsupervised activity).

Statistical analysis

Baseline metabolic characteristics were compared between African American and non-Hispanic white participants using two-tailed *t*-tests. Differences in the proportion of male/female adolescents according to race/ethnicity and the proportion of subjects meeting zero, one, two, three, four, and five components of the metabolic syndrome according to race/ethnicity were compared using chi-squared tests. Continuous variables were compared at baseline and 6 months using paired *t*-tests. Univariate linear regression analyses were used to correlate measurements of WBISI, BMI, and leptin at baseline, and changes in BMI and percent body fat with changes in leptin and adiponectin after 6 months of lifestyle modification. To examine potential predictors of BMI change at 6 months, multiple linear regression analysis was performed with age, sex, ethnicity, and baseline BMI as independent variables. Data are presented as means $\pm$ standard deviation (SD). Results were considered statistically significant at $P < 0.05$. Statistical analyses were performed using JMP 6.02 (SAS Institute, Inc., Cary, NC).

Results

Baseline characteristics

Baseline characteristics of the 165 adolescents enrolled in the intervention are outlined in Table 1. Of the 165 participants, 70.3% were African American, 26.1% were non-Hispanic white, and 1.8% were Hispanic. At baseline, 4 (2.4%) of the adolescents demonstrated IFG. During the OGTT,

TABLE 1. BASELINE DEMOGRAPHIC, PHYSICAL, AND BIOCHEMICAL CHARACTERISTICS OF FIRST 165 OBESE ADOLESCENTS ENROLLED IN MULTIDISCIPLINARY WEIGHT MANAGEMENT PROGRAM AT AN ACADEMIC MEDICAL CENTER

Characteristics	Subjects (n = 165)
Demographic information	
Age (years)	13.9 ± 1.9
Gender (% males/females)	38/62
Obese parent(s) (%)	64
Family history of HTN (%)	79
Family history of type 2 DM (%)	64
Physical characteristics	
Weight (kg)	104.4 ± 26.4
Body mass index (kg/m ²)	38.1 ± 8.0
Body mass index z score (SD)	2.44 ± 0.31
Percent body fat (%)	43.6 ± 12.2
Systolic blood pressure (mmHg)	125 ± 14.8
Diastolic blood pressure (mmHg)	68 ± 9.0
Acanthosis nigricans present (%)	35%
Biochemical characteristics	
Alanine aminotransferase (ALT;U/L)	31.9 ± 13.1
Aspartate aminotransferase (AST;U/L)	25.2 ± 10.0
Alkaline phosphatase (ALP;U/L)	211.2 ± 107.7
Total cholesterol (mg/dL)	170.2 ± 33.7
LDL-C (mg/dL)	104.5 ± 26.5
HDL-C (mg/dL)	47.2 ± 10.2
Triglycerides (mg/dL)	97.4 ± 56.8
Fasting glucose (mg/dL)	84.6 ± 9.4
Fasting insulin level (μU/L)	18.9 ± 13.5
Leptin level (ng/mL)	66.3 ± 36.5

Values are expressed as means ± SD except where noted. Fasting insulin and leptin levels were obtained in 159 and 158 subjects, respectively.

Abbreviations: HTN, hypertension; DM, diabetes mellitus; SD, standard deviation; HDL-C, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol.

1 (0.8%) and 12 (9.8%) subjects met criteria for diabetes mellitus (DM) and IGT, respectively. WBISI values ranged from 0.85 to 9.56 and correlated inversely with BMI (Fig. 1; $r = -0.21$, $P = 0.02$).

The mean number of metabolic syndrome criteria per participant was 2.05 ± 0.91 at baseline, with over 95% of subjects meeting one or more criteria. Table 2 outlines the prevalence of the individual metabolic syndrome components at baseline. Defining metabolic syndrome as three or more criteria, 30.3% of subjects had the metabolic syndrome at baseline (Fig. 2).

Racial/ethnic differences at baseline

Given the high percentage of African American subjects, baseline characteristics between African American ($n = 116$) and non-Hispanic white ($n = 43$) subjects were compared. A higher proportion of white subjects were male compared with African American subjects ($\chi^2_{df=1} = 4.08$, $P = 0.04$). As a result, differences in baseline characteristics between racial/ethnic groups were considered separately for male and female subjects (Table 3). Among males, white subjects demonstrated

lower mean body weight ($P = 0.04$), BMI ($P = 0.02$), BMI z score ($P < 0.01$), and percent body fat ($P = 0.04$) compared with African American subjects. Despite the differences in weight/BMI among these groups, there were no significant differences in age or other metabolic parameters observed in male subjects according to race/ethnicity. Considering females, mean weight and BMI did not differ between ethnic/racial groups; however, fasting triglyceride levels were higher in white compared with African American female subjects ($P < 0.01$). The mean number of metabolic syndrome criteria ($P = 0.32$) and the proportions of individuals meeting zero, one, two, three, or four components of the metabolic syndrome ($\chi^2_{df=4} = 1.52$, $P = 0.82$) did not differ significantly between racial/ethnic groups.

Intervention results

Of the initial 165 adolescents, 57 subjects returned for re-evaluation after 6 months of participation. Table 4 demonstrates mean changes in BMI, BMI z-scores, percent body fat, and insulin resistance over this time period. The mean decrease in BMI was 0.53 kg/m^2 (not significant [NS]).

FIG. 1. Correlation between whole-body insulin sensitivity index (WBISI) and body mass index (BMI) in kg/m² in 122 obese adolescents undergoing a baseline 2-hour oral glucose tolerance test.

However, mean BMI z scores, leptin, and percent body fat decreased significantly after 6 months (Table 4; $P < 0.001$). Furthermore, changes in leptin positively correlated with changes in BMI (Fig. 3; $r = 0.39$, $P = 0.004$). Insulin resistance (determined by HOMA-IR) and adiponectin did not improve after 6 months of participation. However, although mean adiponectin levels did not change significantly, individual changes in adiponectin did negatively correlate with changes in BMI (Fig. 4, $r = -0.34$, $P = 0.01$). A significant relationship between changes in adiponectin and HOMA-IR was not observed ($P = 0.48$).

In the 57 subjects completing 6 months, the mean number of metabolic syndrome criteria present in each subject was 2.11 ± 0.96 and did not differ significantly ($P = 0.34$) from baseline (1.98 ± 0.95). There was no significant change in the number of subjects demonstrating three or more metabolic syndrome criteria (14 subjects at baseline and 17 subjects at 6 months, $P = 0.47$). Mean blood pressure, triglyceride, HDL, and fasting glucose values did not change significantly after 6 months. However, both total cholesterol (163.3 versus 175.8 mg/dL, $P < 0.0001$) and LDL-C levels (98.1 versus 107.2 mg/dL, $P < 0.001$) decreased significantly compared with baseline. When subject age, sex, ethnicity, and baseline BMI values were evaluated as potential predictors of BMI change at 6 months, none of the outlined variables were significant predictors (data not shown).

TABLE 2. PERCENT OF OVERWEIGHT ADOLESCENTS MEETING INDIVIDUAL METABOLIC SYNDROME CRITERIA AT BASELINE ($n = 165$)

BMI $\geq 97^{\text{th}}$ percentile for age and gender	92.7%
Triglycerides ≥ 110 mg/dL	29.1%
HDL-C ≤ 40 mg/dL	26.7%
BP $> 90^{\text{th}}$ percentile for age, height, and gender	54.5%
Fasting glucose ≥ 100 mg/dL	2.4%

Abbreviations: BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; BP, blood pressure.

Discussion

As the number of obese children increases worldwide, greater attention is being placed on the presence of cardiovascular risk factors in this population. The metabolic syndrome is a constellation of cardiovascular risk factors, including central adiposity, elevated blood pressure, dyslipidemia characterized by low HDL-C and elevated triglyceride levels, and insulin resistance characterized by impaired fasting glucose. In adults, the presence of the metabolic syndrome predicts the future development of type 2 DM,¹³ and atherosclerotic disease and is associated with increased cardiovascular and all-cause mortality.^{14,15} In the present study, one third of adolescents met modified criteria for the metabolic syndrome. Furthermore, at least one metabolic syndrome component was identified in 95% of subjects. These findings support an increased risk for future cardiovascular disease among obese adolescents.

There is no consensus definition for the metabolic syndrome in children and adolescents; however, most researchers use definitions based on modified World Health Organization (WHO) or Adult Treatment Panel III (ATP III) criteria.^{16–21} For this study, the proposed metabolic syndrome definition was based on modified National Cholesterol Education Program (NCEP)-ATP III criteria similar to those proposed by Cook et al.²² Although the original definition included waist circumference as a criterion, waist circumference data was unavailable for all subjects in this study. Consequently, our proposed metabolic syndrome definition includes BMI $> 97^{\text{th}}$ percentile⁶ as one criterion. This cut off corresponds to BMI z-score greater than 2 SD, correlates strongly with visceral adiposity,⁴ and may represent a reasonable surrogate for waist circumference. For dyslipidemia, cut-off values of ≤ 40 mg/dL for HDL-C and ≥ 110 mg/dL for triglycerides were used in both males and females. These criteria, first proposed by Cook et al.,²² have been used by subsequent researchers^{23,24} and are based on the midpoint values for borderline-low HDL-C levels for all sexes and ages and borderline-high triglyceride levels in children 10–19 years of age.²⁵ Consistent with a revised adult NCEP-

FIG. 2. Percentage of obese adolescents ($n = 165$) meeting no, one, two, three, and four criteria of the metabolic syndrome at baseline. No subject met all five of the proposed criteria.

TABLE 3. COMPARISON OF BASELINE ANTHROPOMETRIC AND BIOCHEMICAL CHARACTERISTICS OF OBESE MALE ($n = 61$) AND FEMALE ($n = 98$) SUBJECTS ACCORDING TO RACE/ETHNICITY

Characteristics	Male subjects ($n = 61$)		Female subjects ($n = 98$)	
	African American ($n = 39$)	Non-Hispanic white ($n = 22$)	African American ($n = 77$)	Non-Hispanic white ($n = 21$)
Age (years)	14.0 $\pm$ 2.1	13.8 $\pm$ 1.7	13.7 $\pm$ 1.8	14.0 $\pm$ 1.7
Weight (kg)	113.7 $\pm$ 27.2	98.4 $\pm$ 27.2 ^a	102.3 $\pm$ 27.2	99.6 $\pm$ 29.6
Body mass index (kg/m ²)	40.1 $\pm$ 8.8	34.8 $\pm$ 6.6 ^a	38.3 $\pm$ 0.9	36.8 $\pm$ 6.7
Body mass index z score (SD)	2.61 $\pm$ 0.26	2.35 $\pm$ 0.41 ^b	2.42 $\pm$ 0.28	2.32 $\pm$ 0.29
Percent body fat (%)	31.9 $\pm$ 6.9	28.4 $\pm$ 4.8 ^a	52.1 $\pm$ 6.4	51.2 $\pm$ 5.4
Systolic blood pressure (mmHg)	128 $\pm$ 14.2	128 $\pm$ 16.5	123 $\pm$ 15.7	125 $\pm$ 11.4
Diastolic blood pressure (mmHg)	71 $\pm$ 10.0	67 $\pm$ 9.9	68 $\pm$ 8.0	67 $\pm$ 9.2
Alanine aminotransferase (ALT;U/L)	37.5 $\pm$ 16.5	35.1 $\pm$ 8.6	28.6 $\pm$ 11.4	31.4 $\pm$ 14.1
Aspartate aminotransferase (AST;U/L)	29.5 $\pm$ 11.0	27.8 $\pm$ 6.8	23.4 $\pm$ 9.7	23.6 $\pm$ 10.3
Alkaline phosphatase (ALP;U/L)	287.8 $\pm$ 131.3	232.3 $\pm$ 89.1	183.0 $\pm$ 86.5	164.3 $\pm$ 61.0
Total cholesterol (mg/dL)	177.4 $\pm$ 31.4	173.2 $\pm$ 36.8	167.2 $\pm$ 35.5	166.3 $\pm$ 29.5
LDL-C (mg/dL)	112.7 $\pm$ 27.2	106.7 $\pm$ 26.8	102.2 $\pm$ 26.2	94.7 $\pm$ 25.1
HDL-C(mg/dL)	45.4 $\pm$ 9.1	45.1 $\pm$ 8.6	49.5 $\pm$ 10.9	46.9 $\pm$ 10.7
Triglycerides (mg/dL)	98.2 $\pm$ 65.9	107.1 $\pm$ 61.2	86.9 $\pm$ 53.6	122.7 $\pm$ 44.5 ^b
Fasting glucose (mg/dL)	88.1 $\pm$ 9.3	84.5 $\pm$ 5.1	83.3 $\pm$ 10.7	83.6 $\pm$ 7.4
Fasting insulin level (μ U/L)	21.4 $\pm$ 20.6	16.1 $\pm$ 10.2	19.0 $\pm$ 10.9	18.4 $\pm$ 10.4
HOMA-IR	4.6 $\pm$ 4.5	3.3 $\pm$ 2.0	4.0 $\pm$ 2.5	3.9 $\pm$ 2.2
Leptin level (ng/mL)	54.4 $\pm$ 23.8	46.9 $\pm$ 19.8	77.3 $\pm$ 42.1	66.7 $\pm$ 35.0
Number of metabolic syndrome criteria	2.3 $\pm$ 0.9	2.0 $\pm$ 0.9	1.9 $\pm$ 0.9	2.3 $\pm$ 1.0

Values are expressed as means $\pm$ SD.

^a $P < 0.05$ between African American and non-Hispanic white subjects of the same sex.

^b $P < 0.01$ between African American and non-Hispanic white subjects of the same sex.

Abbreviations: SD, standard deviation; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance.

ATP III metabolic syndrome definition,²⁶ our definition uses fasting glucose ≥ 100 mg/dL as a cut-off for hyperglycemia.

Our findings are similar to those of other groups that estimate the prevalence of metabolic syndrome among obese adolescents to be between 12.4 and 44.2%,^{4,17,18,22,23,27–31} reaching approximately 50% in some populations.^{4,32} Most studies analyzed data from large population studies; however, at least two groups^{27,30} have examined the prevalence of metabolic syndrome among obese adolescents referred to specialized intervention programs. Invitti et al. reported a metabolic syndrome prevalence of 23% among obese children referred to a specialized center; however, their population was of Caucasian origin.³⁰ Our study population is similar to the one examined by Quintos et al.,²⁷ who reported the prevalence of metabolic syndrome in a predominantly African American population referred to a specialized pediatric obesity center.

Despite a similar overall prevalence of metabolic syndrome, the prevalence of individual components of the syndrome reported in our population are different than those described by other researchers.^{22,23,28,29,32} In our study, 54% of subjects met the criteria for hypertension or prehypertension (systolic or diastolic blood pressure $>90^{\text{th}}$ percentile). Using the same definition of elevated blood pressure, Monzavi et al.³² reported a prevalence rate 33.3% among obese African American youths. However, the African American subjects

included in the Monzavi study were younger (11.5 $\pm$ 1.9 years) than in our population (13.9 $\pm$ 1.9 years). Cook et al.²² reported that 11.2% of obese adolescents demonstrated elevated blood pressure based on NHANES data. Cook et al. also found that the prevalence of elevated blood pressure was slightly higher in African American (6.2%) as compared to white (5.2%) adolescents; however, these values were determined using a population of both normal weight and obese adolescents. The higher prevalence of elevated blood pressure in our population could be explained by the inclusion of subjects at particular risk for the development of hypertension (i.e., African American adolescents with significant obesity). However, mean blood pressure values were not significantly different between the African American and white subjects at baseline.

In our study, blood pressure was determined using a single measurement, and the prevalence of elevated blood pressure may have been lower if values from serial measurements were averaged. Alternatively, the higher prevalence of hypertension may represent a referral bias because our subjects were referred by primary-care providers.

Although the applied metabolic syndrome definition did not include a criterion directly assessing insulin resistance, multiple indices support the presence of significant insulin resistance in our population. Acanthosis nigricans, a cutaneous manifestation of insulin resistance, was present in

TABLE 4. CHANGES IN MEAN VALUES FOR BODY MASS INDEX, BODY MASS INDEX Z-SCORES, PERCENT BODY FAT, LEPTIN, ADIPONECTIN, AND INSULIN RESISTANCE FROM BASELINE AND 6 MONTHS AMONG 57 OBESE ADOLESCENTS ENROLLED IN A MULTIDISCIPLINARY WEIGHT MANAGEMENT PROGRAM

Variable	Baseline (Mean $\pm$ SD)	6 Months (Mean $\pm$ SD)	P value
BMI (kg/m ²)	38.2 $\pm$ 8.5	37.7 $\pm$ 8.9	0.058
BMI z-score (SD)	2.47 $\pm$ 0.34	2.40 $\pm$ 0.39	<0.001
Percent body fat (%)	43.1 $\pm$ 12.9	41.8 $\pm$ 13.0	<0.001
Leptin (ng/mL)	66.3 $\pm$ 40.0	53.4 $\pm$ 45.5	<0.001
Adiponectin (μ g/mL)	6.8 $\pm$ 3.3	6.9 $\pm$ 3.5	0.536
HOMA-IR	4.20 $\pm$ 3.57	3.58 $\pm$ 3.29	0.249

HOMA-IR, leptin, and adiponectin values were available at baseline and six months in 52, 54, and 53 subjects, respectively. P values were performed using a two-tailed t-test.

Abbreviations: SD, standard deviation; BMI, body mass index; HOMA-IR, homeostasis model of insulin resistance.

35% of subjects. At baseline, 2.4% of subjects demonstrated IFG. However, IFG develops as a late manifestation of severe insulin resistance. Therefore, the presence of IGT is a more sensitive marker of insulin resistance, and 9.8% of adolescents completing an OGTT met this criterion. A fasting insulin ≥ 15 μ U/L is considered abnormal in children,³³ and approximately 50% of enrolled adolescents had insulin levels greater than this cut-off.

In this study, obese adolescents participating in 6 months of lifestyle modification demonstrated a statistically significant, although modest, reduction in percent body fat and BMI z-scores. Consistent with the observed decrease in body fat, leptin levels also decreased significantly after 6 months of participation. Furthermore, total and LDL-C levels decreased significantly with lifestyle modification. However, despite these changes, significant changes in adiponectin, an adipocyte-derived hormone with antidiabetic,³⁴ antiinflammatory, and antiatherogenic properties,^{35,36} estimates of insulin resistance, and other metabolic syndrome criteria were not observed.

Results from other studies investigating the response of metabolic syndrome in obese adolescents to lifestyle modification have varied. Among 26 obese adolescents treated with lifestyle modification for at least 6 months, Harden and colleagues³⁷ demonstrated a decrease in BMI but failed to show significant changes in other metabolic syndrome parameters. Monzavi and colleagues³² reported improvements in BMI, systolic blood pressure, total cholesterol, LDL-C, and triglycerides in 43 overweight adolescents enrolled in a 12-week outpatient program. However, similar to our findings, Monzavi et al. failed to show a significant change in insulin resistance after the intervention; and, despite reporting a baseline prevalence of metabolic syndrome of 49.5%, the group did not report the prevalence of metabolic syndrome at follow up. In contrast, Caranti et al.³⁸ demonstrated a decrease in metabolic syndrome prevalence among 83 obese adolescents participating in 6 months of a multidisciplinary lifestyle intervention (27.16% at baseline; 14.5% at 6 months), with even greater decreases after 1 year (8.3%). It should be noted that the Caranti study used a modified

FIG. 3. Correlation between change in body mass index (BMI) and change in leptin from baseline in obese adolescents ($n = 54$) completing 6 months of a multidisciplinary weight management program.

FIG. 4. Correlation between change in body mass index (BMI) and change in adiponectin values from baseline in obese adolescents ($n = 53$) completing 6 months of a multidisciplinary weight management program.

WHO metabolic syndrome definition, demonstrated greater decreases in BMI, and included a different ethnic population (Brazilian adolescents) from other studies. Last, Chen and colleagues³⁹ demonstrated complete resolution of metabolic syndrome among 16 obese adolescents; however, their intervention consisted of an intensive 2-week residential program.

Several factors may explain the observed varied results. First, each study used different metabolic syndrome definitions, and the prevalence of metabolic syndrome in a given pediatric population varies widely depending on the definition applied.^{17–19} Consequently, it is not unreasonable to assume that documented changes in metabolic syndrome with lifestyle modification may also depend on the specific definition used. Second, there are substantial differences in the populations studied. Our population is predominantly African American and reported a low socioeconomic status, characteristics previously found to predict a high rate of attrition from a pediatric weight management program.⁴⁰ Additionally, there are significant variations in the components of outpatient lifestyle modification programs. In our intervention, large decreases in BMI and percent body fat may not have been observed due to the minimal physical activity requirements (i.e., 1 day per week of supervised activity and 2 nonsupervised days at a local fitness facility). Although the intensity of nonsupervised exercise sessions was not documented, participants were encouraged to perform each session at a level comparable to their supervised sessions. Consequently, as supported by the Caranti data⁴¹ more intense exercise programs or longer intervention periods may be required in this particular patient population to see more significant changes.

The results of this study and others underscore several important findings. First, there is a high prevalence of known cardiovascular risk factors among obese adolescents enrolling in a weight management program; and, among a predominantly African American population, over one third of subjects demonstrated three or more metabolic syndrome criteria. These results support the growing concern for the future development of premature cardiovascular disease in this high-risk population. Although 6 months of lifestyle modification with behavioral reinforcement resulted in statistical decreases in BMI z-scores, percent body fat, total cholesterol, and LDL-C among obese adolescents in our program, there were no significant changes in insulin resistance or other components of the metabolic syndrome. Consequently, the long-term cardiovascular impact of such changes remains unclear. Last, there are significant variations in the documented changes in metabolic syndrome and other cardiovascular risk factors among ethnically diverse pediatric populations participating in different lifestyle intervention programs. These discrepancies support the development of larger controlled trials to establish the optimal treatment regimen for addressing the looming epidemic of premature cardiovascular disease among today's obese youth.

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Author Disclosure Statement

No competing financial interests exist.

References

1. Rudolf MC, Anhalt H, Camacho-Hubner C, Chiarelli F, Eliakim A, Freemark M, Gruters A, Hershkovitz E, Iughetti L, Krude H, Latzer Y, Lustig RH, Pescovitz OH, Pinhas-Hamiel O, Rogol AD, Shalitin S, Sultan C, Stein D, Vardi P, Werther GA, Zadik Z, Zuckerman-Levin N, Hochberg Z. Childhood obesity. *J Clin Endocrinol Metab* 2005;90:1871–1887.
2. Barlow SE. Expert committee recommendations regarding the prevention, assessment, and treatment of child and adolescent overweight and obesity: summary report. *Pediatrics* 2007;120(Suppl 4):S164–192.
3. Ogden CL, Carroll MD, Curtin LR, McDowell MA, Tabak CJ, Flegal KM. Prevalence of overweight and obesity in the United States, 1999–2004. *JAMA* 2006;295:1549–1555.
4. Weiss R, Dziura J, Burgert TS, Tamborlane WV, Taksali SE, Yeckel CW, Allen K, Lopes M, Savoye M, Morrison J, Sherwin RS, Caprio S. Obesity and the metabolic syndrome in children and adolescents. *N Engl J Med* 2004;350:2362–2374.
5. Morrison JA, Friedman LA, Gray-McGuire C. Metabolic syndrome in childhood predicts adult cardiovascular disease 25 years later: the Princeton Lipid Research Clinics Follow-up Study. *Pediatrics* 2007;120:340–345.
6. Kuczamarski RJ, Ogden CL, Guo SS, Grummer-Strawn LM, Flegal KM. 2000 CDC Growth Charts for the United States: Methods and Development 246, 1–190 Hyattsville, MD: National Center for Health Statistics Vital Series and Health Statistics Series 11, 2002.
7. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* 1985;28:412–419.
8. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin Chem* 1972;18:499–502.
9. Keskin M, Kurtoglu S, Kendirci M, Atabek ME, Yazici C. Homeostasis model assessment is more reliable than the fasting glucose/insulin ratio and quantitative insulin sensitivity check index for assessing insulin resistance among obese children and adolescents. *Pediatrics* 2005;115:e500–e503.
10. Standards of medical care in diabetes—2008. *Diabetes Care* 2008;31(Suppl 1):S12–S54.
11. Matsuda M, DeFronzo RA. Insulin sensitivity indices obtained from oral glucose tolerance testing: comparison with the euglycemic insulin clamp. *Diabetes Care* 1999;22:1462–1470.
12. The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. *Pediatrics* 2004;114(2 Suppl 4th Report):555–576.
13. Lorenzo C, Okoloise M, Williams K, Stern MP, Haffner SM. The metabolic syndrome as predictor of type 2 diabetes: the San Antonio heart study. *Diabetes Care* 2003;26:3153–3159.
14. Isomaa B, Almgren P, Tuomi T, Forsen B, Lahti K, Nissen M, Taskinen MR, Groop L. Cardiovascular morbidity and mortality associated with the metabolic syndrome. *Diabetes Care* 2001;24:683–689.
15. Lakka HM, Laaksonen DE, Lakka TA, Niskanen LK, Kumpusalo E, Tuomilehto J, Salonen JT. The metabolic syndrome and total and cardiovascular disease mortality in middle-aged men. *JAMA* 2002;288:2709–2716.

16. Bitsori M, Kafatos A. Dysmetabolic syndrome in childhood and adolescence. *Acta Paediatr* 2005;94:995–1005.
17. Lee S, Bacha F, Gungor N, Arslanian S. Comparison of different definitions of pediatric metabolic syndrome: relation to abdominal adiposity, insulin resistance, adiponectin, and inflammatory biomarkers. *J Pediatr* 2008;152:177–184.
18. Cook S, Auinger P, Li C, Ford ES. Metabolic syndrome rates in United States adolescents, from the National Health and Nutrition Examination Survey, 1999–2002. *J Pediatr* 2008;152:165–170.
19. Golley RK, Magarey AM, Steinbeck KS, Baur LA, Daniels LA. Comparison of metabolic syndrome prevalence using six different definitions in overweight pre-pubertal children enrolled in a weight management study. *Int J Obes (Lond)* 2006;30:853–860.
20. Jessup A, Harrell JS. The metabolic syndrome: look for it in children and adolescents, too! *Clin Diabetes* 2005;23:26–32.
21. Goodman E. Pediatric metabolic syndrome: smoke and mirrors or true magic? *J Pediatr* 2006;148:149–151.
22. Cook S, Weitzman M, Auinger P, Nguyen M, Dietz WH. Prevalence of a metabolic syndrome phenotype in adolescents: findings from the third National Health and Nutrition Examination Survey, 1988–1994. *Arch Pediatr Adolesc Med* 2003;157:821–827.
23. de Ferranti SD, Gauvreau K, Ludwig DS, Neufeld EJ, Newburger JW, Rifai N. Prevalence of the metabolic syndrome in American adolescents: findings from the Third National Health and Nutrition Examination Survey. *Circulation* 2004;110:2494–2497.
24. Ford ES, Ajani UA, Mokdad AH. The metabolic syndrome and concentrations of C-reactive protein among US youth. *Diabetes Care* 2005;28:878–881.
25. American Academy of Pediatrics National Cholesterol Education Program: Report of the Expert Panel on Blood Cholesterol Levels in Children and Adolescents. *Pediatrics* 1992;89(3 Pt 2):525–584.
26. Grundy SM, Brewer HB Jr, Cleeman JI, Smith SC Jr, Lenfant C. Definition of metabolic syndrome: Report of the National Heart, Lung, and Blood Institute/American Heart Association conference on scientific issues related to definition. *Circulation* 2004;109:433–438.
27. Quintos JB, Muzumdar H, George M, Mercado AB, Lu H, Sternberg A, Rao M, Castells S. The prevalence of metabolic syndrome in inner city obese African-American youth. *Pediatr Endocrinol Rev* 2006;3(Suppl 4):571–575.
28. Kranz S, Mahood LJ, Wagstaff DA. Diagnostic criteria patterns of US children with Metabolic Syndrome: NHANES 1999–2002. *Nutr J* 2007;6:38.
29. Cruz ML, Weigensberg MJ, Huang TT, Ball G, Shaibi GQ, Goran MI. The metabolic syndrome in overweight Hispanic youth and the role of insulin sensitivity. *J Clin Endocrinol Metab* 2004;89:108–113.
30. Invitti C, Maffei C, Gilardini L, Pontiggia B, Mazzilli G, Girola A, Sartorio A, Morabito F, Viberti GC. Metabolic syndrome in obese Caucasian children: prevalence using WHO-derived criteria and association with nontraditional cardiovascular risk factors. *Int J Obes (Lond)* 2006;30:627–633.
31. Rodriguez-Moran M, Salazar-Vazquez B, Violante R, Guerrero-Romero F. Metabolic syndrome among children and adolescents aged 10–18 years. *Diabetes Care* 2004;27:2516–2517.
32. Monzavi R, Dreimane D, Geffner ME, Braun S, Conrad B, Klier M, Kaufman FR. Improvement in risk factors for metabolic syndrome and insulin resistance in overweight youth who are treated with lifestyle intervention. *Pediatrics* 2006;117:e1111–e1118.
33. Williams CL, Hayman LL, Daniels SR, Robinson TN, Steinberger J, Paridon S, Bazzarre T. Cardiovascular health in childhood: A statement for health professionals from the Committee on Atherosclerosis, Hypertension, and Obesity in the Young (AHOY) of the Council on Cardiovascular Disease in the Young, American Heart Association. *Circulation* 2002;106:143–160.
34. Spranger J, Kroke A, Mohlig M, Bergmann MM, Ristow M, Boeing H, Pfeiffer AF. Adiponectin and protection against type 2 diabetes mellitus. *Lancet* 2003;361:226–228.
35. Ouchi N, Kihara S, Arita Y, Nishida M, Matsuyama A, Okamoto Y, Ishigami M, Kuriyama H, Kishida K, Nishizawa H, Hotta K, Muraguchi M, Ohmoto Y, Yamashita S, Funahashi T, Matsuzawa Y. Adipocyte-derived plasma protein, adiponectin, suppresses lipid accumulation and class A scavenger receptor expression in human monocyte-derived macrophages. *Circulation* 2001;103:1057–1063.
36. Yokota T, Oritani K, Takahashi I, Ishikawa J, Matsuyama A, Ouchi N, Kihara S, Funahashi T, Tenner AJ, Tomiyama Y, Matsuzawa Y. Adiponectin, a new member of the family of soluble defense collagens, negatively regulates the growth of myelomonocytic progenitors and the functions of macrophages. *Blood* 2000;96:1723–1732.
37. Harden KA, Cowan PA, Velasquez-Mieyer P, Patton SB. Effects of lifestyle intervention and metformin on weight management and markers of metabolic syndrome in obese adolescents. *J Am Acad Nurse Pract* 2007;19:368–377.
38. Caranti DA, de Mello MT, Prado WL, Tock L, Siqueira KO, de Piano A, Lofrano MC, Cristofalo DM, Lederman H, Tufik S, Damaso AR. Short- and long-term beneficial effects of a multidisciplinary therapy for the control of metabolic syndrome in obese adolescents. *Metabolism* 2007;56:1293–1300.
39. Chen AK, Roberts CK, Barnard RJ. Effect of a short-term diet and exercise intervention on metabolic syndrome in overweight children. *Metabolism* 2006;55:871–878.
40. Zeller M, Kirk S, Claytor R, Khoury P, Grieme J, Santangelo M, Daniels S. Predictors of attrition from a pediatric weight management program. *J Pediatr* 2004;144:466–470.
41. Caranti DA, de Mello MT, Prado WL, Tock L, Siqueira KO, de Piano A, Lofrano MC, Cristofalo DM, Lederman H, Tufik S, Damaso AR. Short- and long-term beneficial effects of a multidisciplinary therapy for the control of metabolic syndrome in obese adolescents. *Metabolism* 2007;56:1293–1300.

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