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Weight Gain and Metabolic Consequences of Risperidone in Young Children With Autism Spectrum Disorder

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Abstract

Objective—We examine weight gain and metabolic consequences of risperidone monotherapy in children with autism spectrum disorder (ASD).

Method—This was a 24-week, multisite, randomized trial of risperidone only versus risperidone plus parent training in 124 children (mean age 6.9 ± 2.35 years; 105 boys, 19 girls) with ASD and serious behavioral problems. We monitored height, weight, waist circumference, and adverse effects during the trial. Fasting blood samples were obtained pretreatment and at Week 16.

Results—In 97 patients with a mean of 22.9 ± 2.8 weeks risperidone exposure, there was a 5.4 ± 3.4 kg weight gain over 24 weeks ($p < .0001$); waist circumference increased from 60.7 ± 10.4 cm to 66.8 ± 11.3 cm ($p < .0001$). At baseline 60.8% (59 of 97) patients were classified as having normal weight; by Week 24, only 29.4% (25 of 85) remained in that group. Growth curve analysis showed a significant change in body mass index (BMI) z-scores from pretreatment to Week 24 ($p < .0001$). This effect was significantly greater for patients with reported increased appetite in the first 8 weeks. From pretreatment to Week 16, there were significant increases in glucose ($p = .02$), hemoglobin A1c ($p = .01$), insulin ($p < .0001$), homeostatic model assessment–insulin resistance (HOMA-IR; $p < .001$), alanine aminotransferase ($p = .01$), and leptin ($p < .0001$). Adiponectin declined ($p = .003$). At baseline, 7 patients met conventional criteria for metabolic syndrome; by Week 16, 12 additional patients were so classified.

Conclusion—Rapid weight gain with risperidone treatment may promote the cascade of biochemical indices associated with insulin resistance and metabolic syndrome. Appetite, weight, waist circumference, liver function tests, blood lipids, and glucose warrant monitoring.

Clinical trial registration information—Drug and Behavioral Therapy for Children With Pervasive Developmental Disorders; <http://clinicaltrials.gov/>; NCT00080145

Keywords

autism spectrum disorder; risperidone; weight gain; metabolic syndrome; insulin resistance

INTRODUCTION

Risperidone is approved for treating irritability in children with *DSM-IV*-defined autistic disorder.^{1,2,3} In addition, risperidone has also demonstrated stable reductions in serious behavioral problems for up to six months with rapid return of symptoms with gradual discontinuation of treatment.^{4,5} Although there is variability across pediatric patients,

exposure to risperidone may cause weight gain and adverse metabolic consequences.⁶⁻⁹ Weight gain and increased visceral adipose tissue may herald the emergence of insulin resistance and the metabolic syndrome.^{10,11} The metabolic syndrome is a cluster of clinical indices including increased waist circumference, elevated glucose and triglyceride, reduced high-density cholesterol, and hypertension.¹² These alterations increase the risk of non-alcoholic fatty liver disease, type 2 diabetes, and cardiovascular disease.^{13,14} Weight gain with accumulation of visceral adipose tissue also affects the release of adiponectin and leptin. These cytokines are two of several secreted by adipocytes that play a role in glucose regulation, lipid metabolism, inflammation, and insulin sensitivity.^{11,15} Adiponectin declines in obesity, which may contribute to insulin resistance and metabolic syndrome.^{15,16} Lower levels of adiponectin are also associated with elevations in the inflammatory biomarker C-reactive protein.¹⁵ Leptin, which plays a role in appetite regulation and energy expenditure, tends to increase with weight gain.¹⁷

Several studies have documented weight gain with olanzapine, risperidone, and aripiprazole in children, but few have examined the range of metabolic changes in risperidone-treated children with ASD.¹⁸ In this study, we monitored weight, waist circumference, and body mass index (BMI), as well as lipids, hepatic transaminases, insulin, adiponectin, leptin, glucose, the homeostatic model assessment of insulin resistance (HOMA-IR), and glycosylated hemoglobin (HgA1c) in children with ASD treated with risperidone for up to six months. The patients were participants in the Research Units on Pediatric Psychopharmacology (RUPP) Autism Network trial of risperidone alone versus risperidone plus parent training.^{19,20}

METHOD

Design

The study design and primary results have been reported elsewhere.^{19,20} Briefly, 124 medication-free children were randomly assigned to medication plus parent training (n=75) or medication only (n=49) for 24 weeks. The unbalanced randomization was based on the assumption that parents would prefer combined treatment. Patients were seen weekly for the first 8 weeks, then monthly until Week 24. Blood pressure, pulse, height, and weight were measured at each visit. Adverse events were also systematically reviewed and documented at each visit. A fasting blood sample was collected at the pretreatment screening visit and Week 16. We repeated the blood sample at Week 16 to reduce subject assessment burden at the detailed endpoint visit.

During the acute phase (first 8 weeks), two treatment-blinded clinicians followed each patient: an independent evaluator who monitored therapeutic response and a treating clinician who adjusted the risperidone dose and monitored adverse effects. After Week 8, the treating clinician could consult with the behavior therapist for urgent clinical matters. The independent evaluator remained blinded for the entire study. The weight-based, twice-daily risperidone dose was gradually increased over the first four weeks. For children weighing 14 to 20 kg, the maximum dose was 1.75 mg/day. Children weighing between > 20 and 45 kg had a maximum dose of 2.5 mg/day. For children weighing > 45 kg, the maximum dose was 3.5 mg/day. At each visit, the treating clinician reviewed health complaints and changes in

activity level, sleep, and appetite. The treating clinician could delay a dose increase or reduce the dose to manage suspected adverse effects. The protocol allowed patients who did not meet positive response criteria (see below) at Week 8 to switch to aripiprazole. These patients were no longer informative for evaluating the weight and metabolic effects of risperidone and were excluded from analyses.

Setting and Sample

The institutional review board at each site (Indiana University, Ohio State University, and Yale University) approved the study. After obtaining informed consent from parents, patients received the same comprehensive assessment at each site. Eligible patients were between 4 and 14 years of age, healthy, and medication-free (two weeks for most psychotropic medications, four weeks for fluoxetine or antipsychotic medications; anticonvulsants for seizures were allowed if the dose was stable and the patient was seizure-free for 6 months). Children with > 2 weeks exposure to risperidone at 1.5 mg/day were excluded. Entry requirements also included IQ ≥ 35 , *DSM-IV* diagnosis of autism spectrum disorder (ASD; autistic disorder, Asperger's disorder or pervasive developmental disorder – not otherwise specified [PDD-NOS]), serious behavioral problems (≥ 18 on the parent-rated Aberrant Behavior Checklist-Irritability subscale) and at least moderate on the Clinical Global Impression - Severity scale (see below).

Measures in This Report

Aberrant Behavior Checklist (ABC).^{21,22}—The ABC is a 58-item parent rating, scored from 0 to 3 with five factors: Irritability, Social Withdrawal, Stereotypy, Hyperactivity, and Inappropriate Speech. The 15-item Irritability subscale includes items on tantrums, aggression, and self-injury.

Vineland Adaptive Behavior Scales (Vineland).²³—The Vineland is a parent interview that provides standard scores (100 ± 15 adjusted for age and gender) for Communication, Socialization, and Daily Living.

Autism Diagnostic Interview-Revised (ADI-R).²⁴—The ADI-R is a semi-structured parent interview used to support the diagnosis of ASD.

Tanner Stage of Sexual Maturation.²⁵—Tanner staging was assigned at the pretreatment physical examination. The randomization was stratified by Tanner stage < 3 versus ≥ 3 .

Height and Weight Collection—Height and weight were collected at baseline and monthly during the study. BMI was calculated as [weight (kg) / height (m²)]. We used BMI norms from the Centers for Disease Control to define normal weight (< 85th percentile), overweight ($\geq 85^{\text{th}}$ to < 95th percentile), and obese ($\geq 95^{\text{th}}$ percentile).²⁶ BMI z-scores were used to track change in weight over time. Site clinical teams conferred with parents regarding continued risperidone treatment for any child who gained 20% of body weight over baseline and exceeded 95th percentile for weight for age and gender.

Blood Pressure—Sitting blood pressure was obtained manually at baseline and each follow up visit. Blood pressure percentiles were based on age, gender, and height.²⁷

Waist Circumference—Waist circumference (WC) was used to estimate visceral adipose tissue. Increased visceral adipose tissue is strongly associated with the adverse metabolic and cardiovascular effects of obesity. WC was measured monthly with a tape measure placed directly over the umbilicus. The values, inches rounded to the nearest quarter inch, were converted to centimeters to permit comparison to normative data for age and gender.²⁸

Biochemical Measurements—Fasting laboratory tests: glucose, glycosylated hemoglobin (HbA1c), liver enzymes, and lipids were analyzed in a certified laboratory at each center. Archived fasting samples for adiponectin, insulin, and leptin levels collected at baseline and Week 16 were analyzed in duplicate at the General Clinical Research Center at Yale University using Linco radioimmunoassays.

Derived Measures—The triglyceride/ high-density lipoprotein (HDL) ratio was used as a marker of cardiometabolic risk.²⁹ A triglyceride/HDL ratio ≥ 2.0 in children is associated with insulin resistance and cardiometabolic abnormalities.³⁰ Insulin resistance was estimated using homeostatic model assessment of insulin resistance (HOMA-IR): $HOMA-IR = \frac{G^b \times I^b}{405}$ (G^b is the fasting glucose concentration, I^b is the fasting insulin concentration, and k (405) is a constant).³¹

Analytic Plan

Patients who dropped out before Week 14 ($n=15$) and patients who switched to aripiprazole at Week 8 ($n=12$) were censored. Baseline characteristics of the available sample were evaluated using frequency counts, means, and medians. We evaluated changes in weight, BMI, and waist circumference from baseline to Week 24 by paired t-test. Second, using generalized mixed effect model with autoregressive covariance structure within-subject correlation, we conducted growth curve analysis with BMI z-scores to examine the trend of weight gain from baseline to Week 24 for the entire sample. Using growth curve analysis, we also explored the impact of age (median split at age 7) and the effect of increased appetite on BMI z-scores. Third, we tracked change in weight classification (normal weight, overweight, or obese) from baseline to Week 24.²⁶ Fourth, change in pretreatment and Week 16 values for glucose, liver enzymes (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]), cholesterol, triglyceride, adiponectin, leptin, insulin, triglyceride/HDL ratio, HOMA-IR, and Hgb A1c were compared by paired t-test.

To evaluate metabolic status by BMI category (normal, overweight, obese), we compared the number of patients in each group that exceeded thresholds for metabolic syndrome (adjusted for age, gender, and height as needed) at baseline and Week 16. The specific thresholds included: systolic or diastolic blood pressure $\geq 90^{\text{th}}$ percentile, waist circumference $\geq 90^{\text{th}}$ percentile, triglyceride level $\geq 90^{\text{th}}$ percentile, HDL cholesterol $\leq 10^{\text{th}}$ percentile, and glucose ≥ 100 mg/dL.^{27,28,32,33} The proportion of patients exceeding the threshold for metabolic syndrome between baseline and Week 16 was examined with McNemar's test for paired samples.

To explore the consequences of the metabolic syndrome (pre-existing and new cases) at Week 16, we compared insulin, HOMA-IR, liver enzymes, HbA1c, triglyceride/HDL ratio, adiponectin, leptin, and waist circumference for cases of metabolic syndrome and non-cases using a nonparametric (Wilcoxon Rank Sum) test. All analyses were done using SAS 9.1. Given that this report is focused on safety, p values $<.05$ without correction for multiple tests were considered statistically significant.

RESULTS

The full study sample at baseline ($n=124$) included 105 boys and 19 girls (mean age 6.9 ± 2.35 years). Twenty seven participants dropped out before Week 14 ($n=15$) or switched to aripiprazole ($n=12$) at Week 8 per protocol. As shown in Table 1, there were no differences in the proportion of males, participants with IQ below 70, or participants below Tanner 3 in these 27 individuals compared to the 97 in this report. Similarly, there were no significant group differences in the mean age, mean scores on the Aberrant Behavior Checklist-Irritability subscale, or Vineland domains.

In the 97 participants followed for at least 14 weeks (mean exposure 22.9 ± 2.8 weeks), there were no differences by randomized treatment group ($n=41$ risperidone alone; $n=56$ risperidone plus parent training) in baseline weight, waist circumference, or BMI percentile. Moreover, there were no group differences in weight gain, change in waist circumference, or BMI percentile. At Week 4 (end of the dose adjustment phase), there was a small, but statistically significant, difference in the mean dose for combined treatment (1.80 ± 0.55 mg/day) compared to risperidone only (1.92 ± 0.70 mg/day [$p=.04$]). Of the 97 participants, 43 were medication naïve; another 6 had less than one month treatment with any psychotropic medication. The remaining 48 were taking medications from various classes (e.g., antidepressants, antipsychotics, or stimulants) deemed ineffective by parents. Subsequent analyses proceeded without adjustment for treatment group or prior exposure.

Change in Weight, Waist Circumference and BMI Category From Baseline to Week 24

The average weight gain was 2.5 ± 1.6 kg at Week 8; 4.2 ± 2.8 kg at Week 16; and 5.4 ± 3.4 kg at Week 24. Waist circumference increased from 60.7 ± 10.4 centimeters at baseline to 66.8 ± 11.3 centimeters at Week 24 ($p < .0001$), suggesting increase in visceral adipose tissue (see Table 2).

At baseline, 60.8% (59 of 97) had a BMI-for-age $< 85^{\text{th}}$ percentile; 20.6% ($n=20$) were overweight (BMI-for-age 85^{th} percentile and 95^{th} percentile); 18.6% ($n=18$) were obese (BMI-for-age $> 95^{\text{th}}$ percentile). Figure 1 shows the change in status for each BMI group at baseline (normal, overweight, or obese) across time. Of the 85 participants with complete height and weight data at Week 24, 29.4% were in the BMI normal weight group (24 from the normal weight group at baseline and one from the overweight group at baseline). By Week 24, the number of children in the obese category increased from 18 to 35. During the trial, 20 children gained 20% of weight over baseline and exceeded the 95^{th} percentile for weight. Following discussion with parents, one of these 20 children and one other child exited the study due to weight gain.

Growth curve analysis of BMI z-scores showed a rapid rise in the first 12 weeks with leveling off after Week 16. Figure 2a shows the significant change in BMI z-scores from 0.69 to 1.43 (0.74 ± 0.064 , $p < .0001$) over time. Figure 2b displays the change in BMI z-scores for 75 participants with reported increase in appetite in the first 8 weeks of treatment compared to 22 participants without such reports. Increased appetite early in treatment predicted weight gain and higher BMI z-scores over time ($p = .01$). Dividing the sample at the median (≥ 7 , $n = 49$), younger children (< 7 , $n = 48$) showed a more rapid rise in BMI z-score ($p = .009$; Figure 2c). Compared to children with IQ ≥ 70 ($n = 54$), there was no difference in BMI z-scores over time for those with IQ < 70 ($n = 43$) ($p = .13$).

Change in Biochemical Indices

As noted, 15 participants exited before Week 14, and 12 participants switched to aripiprazole at Week 8. Biochemical data were also missing due to non-fasting, insufficient, or hemolyzed samples. Thus, the sample size varied slightly across biochemical tests. Table 3 presents results on several biochemical indices collected pretreatment and at Week 16.

Although significant, the increases in mean glucose and HbA1c were modest. The number of children with a baseline glucose ≥ 100 mg/dL almost tripled from 4.8% ($n = 4$) at baseline to 12.5% ($n = 11$) at Week 16. There were significant increases in insulin, HOMA-IR, and leptin and a significant decrease in adiponectin. There were no significant mean changes for any blood lipids. ALT level increased from $17.8 \text{ mg/dL} \pm 6.8$ to 20.7 ± 11.3 ($p = .01$), but there was no change in AST level ($p = .42$).

We used HOMA-IR (≥ 1.58), HbA_{1c} (≥ 5.5), and ALT ($> 35 \text{ mg/dL}$) as thresholds. At baseline, 40.6% of participants exceeded HOMA-IR, 25.5% HbA_{1c}, and 3.5% ALT. At Week 16, 55.1%, 38.1%, and 6.8% of participants exceeded these thresholds, respectively. McNemar's test for matched pairs showed no difference for ALT. However, significantly more participants exceeded threshold for HOMA-IR ($\chi^2 = 4.76$, $p = .03$) and HbA_{1c} ($\chi^2 = 6.54$, $p = .01$) at Week 16 than at baseline.

Table 4 provides counts of participants who met or exceeded biomarkers of metabolic syndrome at pretreatment and Week 16. At baseline 7 (8.4%) children met conventional criteria for metabolic syndrome (positive on 3 of 5 indices) compared to 19 (22.6%) at Week 16 (McNemar's test $\chi^2 = 8.00$, $p = .005$). At Week 16, pre-existing or new cases of metabolic syndrome had higher triglyceride/HDL ratio than those not so classified (2.89 ± 1.18 versus 1.02 ± 0.57 ; $p < .0001$) and greater waist circumference (68.6 ± 10.6 versus 61.9 ± 9.8 ; $p = .01$).

DISCUSSION

This study examined the effects of risperidone on appetite, weight, BMI, waist circumference, and indices associated with the metabolic syndrome and insulin resistance. Overall, participants with a mean risperidone exposure of 22.9 weeks gained an average of $5.4 \pm 3.4 \text{ kg}$, which is consistent with our previous study of 63 children with ASD, but greater than the $3 \pm 2.6 \text{ kg}$ reported by Demb et al.^{6,34} This difference may be related to the lower doses used in this sample: 0.65 mg/day compared to 1.8–1.9 mg/day in the RUPP

This study provides new information on the metabolic effects of risperidone in children with ASD and serious behavioral problems. These results indicate that appetite, body weight, waist circumference, liver function tests, blood lipids, and glucose should be measured before starting treatment with risperidone and periodically thereafter.⁴² We observed group effects on insulin, leptin, and adiponectin. These results provide insight into the potential metabolic effects of risperidone, but results of these tests in individual children may be difficult to interpret.

The study did not include placebo control. We did not use newer magnetic resonance imaging techniques or ultrasonography to examine fat deposition in the abdomen, liver, or carotid arteries.^{13,30,43} Glucose tolerance tests before and after treatment could have provided more accurate measurement of glucose dysregulation and insulin sensitivity.^{31,44} We did not differentiate the low, middle, and high-molecular weight isoforms of adiponectin and did not track pro-inflammatory cytokines, TNF – alpha, IL6, or C-reactive protein.^{15,45} Our sample did not include a sufficient number of girls or minority participants to examine the metabolic effects of risperidone in these subgroups.^{43, 46} The study did not include the systematic collection of obesity in the family history. Our data are limited to 6 months of exposure.⁴⁷

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Clinical Guidance

- Over 24 weeks there was a rise in BMI z-score from 0.65 to 1.4; the rise in BMI z-scores was significantly greater in children < 7 years compared to those ≥ 7 years.
- Children with reported increase in appetite during the first 8 weeks showed more rapid rise in BMI z-scores than did those without reported appetite increase. These results suggest that increased appetite mediates weight gain.
- Appetite, body weight, waist circumference, liver function tests, blood lipids, and glucose should be measured before starting children treated with atypical antipsychotic medications. Appetite, body weight, and waist circumference should be monitored early and regularly during treatment; liver function tests, blood lipids, and glucose should be monitored periodically. In this study, changes were detected 4 months after baseline.
- The observed alterations in insulin, leptin, and adiponectin provide insight into the potential metabolic effects of risperidone, but results of these tests in individual children may be difficult to interpret.
- Parents should be educated about the risk of rapid weight gain at the start of treatment, with guidance on food and beverage choices.

Figure 1.

Change in age and gender-adjusted weight categories across time. Note: Centers for Disease Control and prevention body mass index (BMI) reference ranges: Normal 85th percentile; Overweight 85th percentile to < 95th percentile; Obese 95th percentile.²⁶ n=97 at baseline; 94 at Week 8; 95 at Week 16; 85 at Week 24. Of 59 participants with normal weight at baseline, 24 remained in normal weight at endpoint, 21 became overweight, 7 became obese; 7 were missing at Week 24. Of the 20 participants overweight at baseline, 1 was in normal weight; 3 remained overweight, 14 became obese; 2 were missing at Week 24. Of the 18 participants obese at baseline, 1 was overweight and 14 remained obese, 3 were missing.

Figure 2.

A. Predictive growth curve of body mass index (BMI) z-score with 95% CI from mixed effect model with autoregressive correlation matrix on age–gender-adjusted BMI z-scores from 2000 Centers for Disease Control and Prevention (CDC) growth charts and CDC SAS code (<http://www.cdc.gov/nccdphp/dnpao/growthcharts/resources/gc-calculate-BIV.sas>).

Note: The differences in BMI z-score from baseline are 0.71 (95% CI=[0.605, 0.808], $p < .0001$) and 0.74 (95% CI=[0.613, 0.866], $p < .0001$) at Weeks 16 and 24, respectively.

B. Predicted growth curves of BMI z-score for participants with reported increase in appetite in the first 8 weeks ($n=75$) compared to those with no reported change in appetite ($n=22$).

C. Predictive growth curves in children ≥ 7 years ($n=49$) and < 7 years ($n=48$).

Table 1

Baseline Demographic and Clinical Characteristics of Children With Autism Spectrum Disorder (ASD) in a Randomized Trial of Risperidone Only Versus Risperidone Plus Parent Training

	Full sample (N=124) n (%)	Participants included in analysis (n=97) n (%)	Participants not included (n=27) ^d n (%)
Age (years)			
4–6	63 (50.8)	48 (49.5)	15 (55.6)
7–10	50 (40.3)	39 (40.2)	11 (40.7)
11–13	11 (8.9)	10 (10.3)	1 (3.7)
Tanner stage < 3	119 (96.0)	92 (94.8)	27 (100)
Tanner stage ≥ 3	5 (4.0)	5 (6.2)	0
Diagnosis			
Autistic disorder	81 (65.3)	64 (66.0)	17 (63.0)
Asperger's disorder	8 (6.4)	7 (7.2)	1 (3.7)
PDD-NOS	35 (28.2)	26 (26.8)	9 (33.3)
Race			
White/non-Hispanic	93 (75.0)	75 (77.3)	18 (66.7)
Hispanic	9 (7.3)	7 (7.2)	2 (7.4)
African-American	18 (14.5)	13 (13.4)	5 (18.5)
Asian	2 (2.4)	2 (2.1)	1 (3.7)
Native American	1 (0.8)	0 (0)	1 (3.7)
IQ < 70 ^b	53 (42.7)	43 (44.3)	10 (40.0)
IQ ≥ 70	69 (55.6)	54 (55.7)	15 (60.0)
Clinical Global Impression-Severity			
Moderate	39 (31.5)	26 (26.8)	13 (48.2)
Marked	52 (41.9)	46 (47.4)	6 (22.2)
Severe	32 (25.8)	24 (24.7)	8 (29.6)
Extreme	1 (0.8)	1 (1.0)	0 (0)
	Mean [95% CI]	Mean [95% CI]	Mean [95% CI]
Vineland Adaptive Scales			
Communication	59.2 [54.5, 64.0]	59.0 [54.0, 63.9]	61.1 [42.6, 79.6]
Daily living	45.3 [41.4, 49.2]	44.9 [40.6, 49.3]	46.6 [37.1, 56.0]
Socialization	62.3 [58.4, 66.3]	62.5 [58.3, 66.8]	60.8 [48.2, 73.4]
Aberrant Behavior Checklist			
Irritability	29.5 [28.3, 30.7]	29.5 [28.2, 30.8]	29.5 [26.6, 32.3]
Social withdrawal	15.9 [14.4, 17.5]	15.7 [13.9, 17.5]	16.8 [13.5, 20.0]
Hyperactivity	35.6 [34.1, 37.1]	35.3 [33.6, 37.1]	36.7 [33.6, 39.8]

	Full sample (N=124) n (%)	Participants included in analysis (n=97) n (%)	Participants not included (n=27) ^a n (%)
Stereotypy	8.8 [7.8, 9.7]	9.2 [8.1, 10.3]	7.2 [5.1, 9.2]
Inappropriate speech	6.0 [5.3, 6.6]	6.2 [5.5, 7.0]	5.1 [3.7, 6.6]

Note: PDD-NOS = pervasive developmental disorder not otherwise specified.

^a 15 participants dropped out before week 14; 12 participants switched to aripiprazole at week 8.

^b IQ missing for two participants.

Table 2

Weight, Waist Circumference, and Body Mass Index (BMI) at Baseline and Week 24

	Baseline Mean (SD) [95% CI]	Week 24 Mean (SD) [95% CI]		
Measure	Baseline n = 97	Week 24 n = 87	Mean Change [95% CI]	p Value ^a
Weight (kg)	29.3 (11.5) [27.0, 31.7]	34.0 (12.6) [31.3, 36.8]	5.3 (3.4) [4.6, 6.1]	<.0001
Waist circumference (cm)	60.7 (10.4) [58.7, 63.0]	66.8 (11.3) [64.5, 69.3]	6.1 (5.18) [5.1, 7.4]	<.0001
BMI Z-score ^b	0.69 (1.13) [0.46, 0.91]	1.43 (0.94) [1.23, 1.63]	0.76 ^c [0.62, 0.89]	<.0001
Systolic BP	103.5 (11.5) [101.1, 105.9]	105.4 (9.9) [103.2, 107.6]	2.58 (12.49) [-0.25, 5.42]	.07
Diastolic BP	66.9 (7.9) [65.3, 68.6]	66.1 (8.4) [64.3, 67.9]	-0.61 (8.88) [-2.63, 1.40]	.55
Pulse	95.4 (15.1) [92.3, 98.6]	99.5 (13.8) [96.5, 102.5]	4.19 (14.5) [0.93, 7.45]	.01

Note: BP = blood pressure.

^a p value from two-sided paired-t test.^b n = 85, two participants had missing height at week 24.^c Difference baseline to end point; difference presented in Figure 2 is from the mixed model.

Table 3

Glucose, HbA1c, Insulin, Homeostatic Model Assessment–Insulin Resistance (HOMA-IR), Adiponectin, Leptin Levels, Lipid Levels at Pretreatment and Week 16^a

	Baseline n ^b , Mean (SD) [95% CI]	Week 16 n ^b , Mean (SD) [95% CI]	Difference n ^b , Mean (SD) [95% CI]	p Value ^c
Glucose mg/dL	84, 83.14 (11.68) [80.61, 85.68]	88, 85.92 (10.94) [83.60, 88.24]	77, 3.52 (12.87) [0.60, 6.44]	.0189
Hemoglobin A1c	94, 5.24 (0.34) [5.18, 5.31]	84, 5.31 (0.33) [5.24, 5.38]	83, 0.07 (0.27) [0.02, 0.13]	.0146
Insulin μU/ml	64, 7.19 (4.35) [6.10, 8.27]	73, 10.14 (6.22) [8.69, 11.59]	62, 2.98 (5.61) [1.55, 4.40]	<.0001
HOMA-R	64, 1.52 (0.97) [1.28, 1.76]	69, 2.13 (1.38) [1.80, 2.46]	59, 0.63 (1.32) [0.29, 0.98]	.0005
Leptin ng/ml	68, 3.41 (3.73) [2.51, 4.32]	75, 5.45 (5.12) [4.28, 6.63]	66, 2.15 (4.14) [1.13, 3.17]	<.0001
Adiponectin ug/ml	68, 17.47 (7.87) [15.56, 19.37]	75, 15.54 (6.87) [13.96, 17.12]	66, -1.85 (4.80) [-3.03, -0.67]	.0027
Total cholesterol mg/dL	84, 154.6 (24.0) [149.4, 159.8]	83, 155.6 (24.1) [148.2, 163.1]	73, -2.36 (26.60) [-8.56, 3.85]	.4516
LDL cholesterol mg/dL	84, 89.0 (22.4) [84.1, 93.9]	83, 92.4 (26.5) [86.6, 98.2]	73, 0.56 (15.80) [-3.12, 4.25]	.7622
HDL cholesterol mg/dL	95, 52.6 (15.0) [49.6, 55.7]	83, 52.2 (15.0) [48.9, 55.5]	81, -0.84 (8.46) [-2.71, 1.03]	.3743
Triglycerides mg/dL	84, 61.7 (29.7) [55.3, 68.2]	83, 65.3 (39.2) [56.8, 73.9]	73, 4.73 (31.37) [-2.59, 12.04]	.2021
Triglyceride/HDL ratio	84, 1.29 (0.76) [1.12, 1.45]	83, 1.42 (1.07) [1.19, 1.66]	73, 0.17 (0.81) [-0.02, 0.36]	.08
Alanine Aminotransferase mg/dL (ALT)	86, 17.8 (6.8) [16.3, 19.3]	88, 20.7 (11.2) [18.3, 23.1]	79, 2.77 (9.64) [0.61, 4.93]	.01

Note: HDL = high-density lipoprotein; LDL = low-density lipoprotein.

^aFasting samples.

^bChanges in sample sizes due to missing data.

^cDifferences and p-value from two-sided paired-t test

Table 4

Count of Participants Exceeding Threshold on Indicators of Metabolic Syndrome

	Normal Weight		Overweight		Obese	
	Baseline (n= 59)	Wk 16 (n=33)	Baseline (n= 20)	Wk 16 (n= 26)	Baseline (n= 18)	Wk 16 (n= 36)
Waist circumference (90 th percentile) ²⁸	1 (1.7%)	0 (0%)	6 (30%)	6 (23.1%)	14 (77.8%)	25 (69.4%)
Triglyceride (90 th percentile) ³²	7 (11.9%)	6 (18.2%)	6 (30%)	2 (7.7)	6 (33.3%)	12 (33.3%)
HDL cholesterol (10 th percentile) ^b	11 (18.6%)	7 (21.2%)	7 (35%)	8 (30.8%)	4 (22.2%)	13 (36.1%)
Glucose (100 mg/dL) ³³	3 (5.1%)	5 (15.1%)	1 (5%)	3 (11.5%)	0 (0%)	3 (8.3%)
Hypertension (SBP and/or DBP > 90 th percentile) ²⁷	28 (47.4%)	18 (54.5%)	11 (55%)	12 (46.1%)	10 (55.5%)	19 (52.8%)

Note: DBP = diastolic blood pressure; HDL = high-density lipoprotein; SBP = systolic blood pressure.