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Threshold for Improvement in Insulin Sensitivity with Adolescent Weight Loss

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Abstract

Objectives—To assess the association of weight loss and insulin sensitivity, glucose tolerance, and metabolic syndrome (MS) in obese adolescents following weight loss treatment, and to determine the threshold amount of weight loss required to observe improvements in these measures.

Study design—A randomized, controlled behavioral weight loss trial was conducted with 113 obese adolescents. Changes in fasting insulin, homeostasis model assessment of insulin resistance (HOMA-IR), whole body insulin sensitivity index (WBISI), body-mass index (BMI), and MS criteria were assessed at baseline and at month 4.

Results—There was significant improvement in all measures of insulin sensitivity at month 4. Mean fasting insulin dropped to 16.6 from 22.3 μ U/mL ($p < 0.0001$). HOMA-IR decreased

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significantly from 4.9 to 3.7 ($p=0.001$) and WBISI increased significantly from 2.87 to 3.98 ($p<0.0001$). An 8% reduction in BMI led to a significant improvement in WBISI ($p=0.03$) and was the optimal threshold. Fewer individuals met criteria for MS after weight loss ($p=0.0038$), although there were no significant changes in the individual features of the syndrome.

Conclusions—In this trial, weight loss at month 4 was associated with improved insulin sensitivity in obese adolescents. An approximate decrease in BMI of 8% was the threshold level at which insulin sensitivity improved. As more weight loss programs are designed for obese adolescents, it will be important to have reasonable weight loss goals that will yield improvements in metabolic and cardiovascular disease risk factors.

Keywords

insulin sensitivity; impaired glucose tolerance; metabolic syndrome; weight loss trial

Obesity is a known risk factor for insulin resistance, and insulin resistance associated with obesity is known to play a role in the development of glucose intolerance and type 2 diabetes mellitus¹. In addition, the metabolic syndrome (MS) -- a clustering of risk factors including insulin resistance, obesity, hypertension, and dyslipidemia -- predicts higher cardiovascular morbidity and a higher risk for developing type 2 diabetes,² and is found in children as well as adults.

Insulin resistance in obese adolescents may be especially difficult to improve, even with weight loss. Adolescents experience a normal period of relative insulin resistance during mid-puberty; insulin sensitivity decreases during Tanner stages 2-4 and then returns to pre-pubertal levels by Tanner stage 5³. Obesity may aggravate the insulin resistance already present in this population. Therefore, it is all the more important in this metabolically complex population to assess changes in insulin sensitivity when examining the effectiveness of weight loss.

A weight loss intervention was conducted in 113 obese adolescents in whom weight loss and reduction in body mass index were successfully achieved, as previously reported⁴. An important goal of this study was to determine the threshold of weight loss that would significantly impact insulin sensitivity, glucose tolerance, and presence of MS in obese adolescents. The association between weight loss and change in fasting insulin was mentioned in the previous report⁴ and the present report is a full analysis of insulin sensitivity, glucose tolerance, and MS.

Methods

From 2004 to 2007, 113 subjects were recruited. Subjects had a body mass index (BMI) of 28-50 kg/m² and were 13 to 17 years of age at the initiation of the study. Subjects' baseline characteristics are shown in Table. All girls were post-menarcheal. Contraindications to study participation included cardiovascular disease, diabetes mellitus, major psychiatric disorders, pregnancy, use of a weight-loss medication or a weight loss of 5 kg or more in the prior 6 months, use of medications promoting weight gain (eg, oral steroids), and cigarette smoking. Written informed consent was obtained from the parent and assent was obtained from the adolescent. This study was approved by the institutional review boards of The Children's Hospital of Philadelphia and of the University of Pennsylvania.

The first 4 months of the study were designated as the weight loss induction phase. All adolescents received the same lifestyle modification program (described in treatment manuals⁵); however, participants were randomized either to the Conventional Diet (CD) group using regular food or to the portion-controlled Meal Replacement (MR) group (using

prepackaged meals). Those in the CD group were taught to monitor their dietary intake and then were prescribed a 1300-1500 kcal/day diet of a nutritionally balanced regular food. Those on the MR group were placed on a daily plan of SlimFast shakes and prepackaged meals with the same calorie goals as their counterparts on the CD group. Results from this trial and the differences in their short- and long-term weight loss outcomes have been published⁴. The purpose of this report is to examine the effect of weight loss on metabolic measures, collapsing across the two intervention groups (as there were no between-group differences in these measures).

Height, weight, waist circumference, blood pressure, fasting lipid panel (including triglyceride and high-density lipoprotein cholesterol [HDL] levels), fasting glucose, fasting insulin, and a 75-gram oral glucose tolerance test (OGTT) were assessed at baseline and month 4. OGTT included glucose and insulin levels drawn at 0, 30, 60, 90, and 120 minutes. Body mass index (BMI) was calculated as weight (kg) ÷ [height (m)]².

Fasting insulin, fasting glucose, and the homeostasis model assessment of insulin resistance (HOMA-IR)⁶ are variables that use fasting information to evaluate insulin sensitivity in the fasting state, but do not account for response to a glucose load. HOMA-IR, a measure based on the feedback loop between glucose and insulin, is calculated as follows: fasting insulin (μU/mL) × fasting glucose (mg/dL) ÷ 405.

The 2-hour glucose level during an OGTT evaluates insulin effectiveness in response to a standardized glucose load. A healthy person should have an appropriate compensatory insulin response and therefore maintain a glucose level <140 mg/dL at two hours.

Whole body insulin sensitivity index (WBISI) is a variable that is calculated from an OGTT and includes both fasting measures (glucose and insulin) and response to a glucose load⁷. It incorporates mean glucose and insulin levels achieved during the test in addition to the fasting levels. It has been validated in comparison with euglycemic-hyperinsulinemic clamp studies in obese children and adolescents⁸. In a previous study, WBISI was noted to better capture improvements in insulin sensitivity in adolescents than fasting measures⁹. It is calculated from the OGTT as follows: $10,000 \div [\text{fasting glucose (mg/dL)} \times \text{fasting insulin (}\mu\text{U/mL)} \times \text{mean glucose (mg/dL)} \times \text{mean insulin (}\mu\text{U/mL)}]$.

Data Analyses

Changes in measures of insulin sensitivity (fasting insulin, HOMA-IR, WBISI) after weight loss were examined by comparing means (Student t-test for normally distributed data or Sign test for non-parametric data). Changes in glucose tolerance and MS were evaluated using these methods as well.

Data were analyzed by BMI threshold groups based upon the percentage decrease in BMI observed during the weight loss induction phase of the trial (greater or lesser than 7% loss in BMI, greater or lesser than 8% loss in BMI, etc). As the WBISI data were non-parametric, the Wilcoxon Rank-Sum was used to analyze whether there was a significant difference in WBISI between the subjects above and below each threshold in order to determine what percentage decrease in BMI was needed to achieve a significant improvement in WBISI.

MS at baseline and month 4 was defined as per the consensus report of the International Diabetes Federation on MS in children and adolescents (central obesity plus any two of the following: elevated triglycerides, low HDL cholesterol, elevated blood pressure, or elevated fasting glucose)¹⁰. The Fisher Exact test was used to compare presence or absence of MS before and after the weight loss induction phase of the trial as previously stated. The population was divided into three categories by looking at which subjects started with MS

and had it resolve, which subjects had no change in their MS status (started and ended with it, or started and ended without it), and which subjects developed MS during the trial and these groups were compared using the Kruskal-Wallis one-way analysis of variance.

Statistical analysis was conducted with SAS version 9.2 software. As this study was powered for the primary outcome only, all analyses in this paper are considered exploratory with significance defined as $p < 0.05$, with no adjustment for multiple testing.

Results

Adolescents, in aggregate, lost weight during the weight loss induction phase of the trial as previously described⁴. At month 4, a mean (SD) reduction in percentage of initial BMI of 5.4% ($\pm 4.8\%$) was achieved.

Baseline mean fasting glucose was within the normal range during the study (Table). Mean fasting insulin dropped significantly at month 4 ($p < 0.0001$) to a level of 16.6 $\mu\text{U/mL}$ (± 11.6). Both HOMA-IR and WBISI were suggestive of poor insulin sensitivity at baseline when averaged across all subjects (Table). Although there are not population-based standards for these variables, one study which utilized more than 1100 healthy Caucasian subjects determined that insulin resistance was indicated by HOMA-IR > 2.29 and WBISI < 5.0 ¹¹ (We include these numbers as a general reference although they may not be as applicable to a predominantly African-American population). In our study, both variables showed improvement from baseline to month 4: HOMA-IR decreased significantly ($p = 0.001$) from 4.9 (± 3.1) to 3.7 (± 2.7) and WBISI increased significantly ($p < 0.0001$) from 2.87 (± 1.73) to 3.98 (± 2.5).

Change in WBISI at different weight loss thresholds (based on percentage change in BMI) was examined to assess the degree of weight loss that led to a statistically significant improvement in insulin sensitivity. WBISI changes were compared between those subjects who lost more or less than a specific percentage change in BMI. The improvement in WBISI was significant for those subjects who lost 8% or more of their initial BMI (30.5% of subjects) compared with those who lost less than that (Figure 1). This threshold analysis was also done for fasting insulin and HOMA, but there was no significant difference in these variables at any weight loss threshold. We also noted that not every subject who lost weight improved insulin sensitivity and vice-versa: there were 17 people who lost less than 8% of BMI but still normalized fasting insulin levels, and there were 2 people who lost more than 8% of BMI but did not normalize fasting insulin.

At baseline, 2-hour glucose levels from the OGTT were within normal limits when averaged across all subjects (Table). When evaluating subjects individually, 10 subjects had impaired glucose tolerance at baseline (defined as 2-hr glucose during OGTT ≥ 140 mg/dL), and at month 4 only 1 subject did; there was a trend toward statistically significant improvement ($p = 0.08$).

The presence of MS was compared before and after the weight loss induction phase of the trial. Significantly fewer individuals met criteria for MS after weight loss: 10.7% at month 0 and 8.6% at month 4 ($p = 0.0038$). However, even though most of the individual components of MS improved with weight loss (fewer subjects exhibited abnormal values after weight loss), these improvements did not reach statistical significance. The exception was HDL cholesterol, which paradoxically worsened after the weight loss intervention; 32.5% of subjects had HDL cholesterol > 40 mg/dL at month 0 and 41.2% did at month 4 ($p < 0.0001$).

The percentage loss in BMI between subjects whose MS resolved during the trial compared with those whose MS status remained unchanged or worsened. The average percent decrease

in BMI for those subjects whose MS resolved was 7.28% (median 8.84%; Figure 2). The two-group comparison of percent decrease in BMI between subjects whose MS resolved and those who developed it during the study was borderline-significant with a p-value of 0.05, and the three-group analysis including the subjects with unchanged MS status was not significant.

Discussion

Our goal was to evaluate the amount of weight loss that would impact insulin sensitivity, glucose tolerance, and MS following behavioral weight loss intervention in obese adolescents. There was significant improvement in all measures of insulin sensitivity at month 4 with lifestyle modification. Mean fasting insulin dropped to 16.6 from 22.3 $\mu\text{U/mL}$ ($p<0.0001$). HOMA-IR decreased significantly from 4.9 to 3.7 ($p=0.001$) and WBISI increased significantly from 2.87 to 3.98 ($p<0.0001$). We found that an 8% decrease in BMI was the threshold level at which whole body insulin sensitivity significantly improved; there was no threshold effect for fasting insulin or HOMA-IR despite improvement in these measures. WBISI does include fasting insulin in its calculations, so fasting measurements do contribute to this assessment. However, WBISI was shown in a previous study to better correlate with insulin sensitivity changes after weight loss in adolescents than fasting measures, which did not capture subtle changes and only reflect one part of overall glucose metabolism⁹. It may be that as adolescents have had less time to accrue beta cell damage, fasting measures alone are not an accurate way to gauge subtle changes in glucose metabolism in this population. Further studies powered to evaluate different measures of insulin sensitivity after weight loss are indicated.

MS was found in significantly fewer individuals after the intervention. Those with MS that resolved decreased their BMI by a similar percentage to those with improved insulin sensitivity (close to 8%). However, our results did not show statistically significant improvements in the individual components of the metabolic syndrome. There was a trend for those participants having impaired glucose tolerance, as measured by 2-hour glucose levels during an OGTT, to have this resolve after the intervention, but the results did not reach statistical significance likely due to the small number of individuals with impaired glucose tolerance in our study.

The Diabetes Prevention Program (DPP), a large multicenter clinical trial conducted in over 3,000 adults in the United States, used a weight loss goal of at least 7% in the lifestyle intervention group. DPP found an improvement in insulin sensitivity and a reduced risk of developing MS and diabetes in the lifestyle weight loss arm^{12,13}. There are fewer data available in children, however. The US Preventive Services Task Force (USPSTF) published their 2010 updated recommendations after reviewing 15 weight loss trials conducted in obese children and adolescents; but with regards to insulin sensitivity they found inconsistent reporting and insufficient information¹⁴. Several studies have reported improvements in fasting insulin or HOMA-IR with weight loss, such as the studies by Berkowitz et al¹⁵ and by the Sibutramine Adolescent Study Group report,¹⁶ as well as our previous report of the weight loss differences between our two treatment arms⁴. To our knowledge, however, no threshold weight loss level that leads to metabolic improvements in adolescents has been previously published.

A study of 10 overweight children found that after two weeks of an intensive weight management program with a 6-7% decrease in BMI, there was an improvement in insulin sensitivity as measured by the euglycemic-hyperinsulinemic clamp¹⁷. A recent small study of 8 obese adolescents who underwent infusion of a stable isotopically labeled tracer in conjunction with the clamp technique after approximately 8% weight loss also found an

improvement in insulin sensitivity¹⁸. The first study that set out to address the specific question of how much weight loss is required to improve insulin sensitivity in children used only fasting measures, and could not determine a specific weight loss cutoff point which yielded improvement¹⁹. Another study of 88 adolescents confirmed that fasting measures of insulin sensitivity are related to degree of weight loss, but also did not elucidate a specific threshold²⁰. The goal of our analysis was to find a clear weight loss threshold for obese adolescents which will yield improvements in insulin sensitivity; we did this using a measure (percent change in BMI) that a primary care physician can easily utilize. We used WBISI as our primary insulin sensitivity measure because it evaluates insulin action beyond that of fasting measures.

Children with MS have been shown to be more likely to develop cardiovascular disease as adults, with the risk increasing as BMI percentile increases²¹. Previous adolescent weight loss studies reporting metabolic syndrome outcomes have had mixed results, although that may be partially due to differing definitions of the syndrome that have been used by different groups^{22,23,24}.

In the present study the degree of weight loss relative to change in metabolic syndrome status was suggestive for the combined grouping, but not statistically significant for the individual components. Because there were few subjects with MS in this study, and we had intentionally excluded any participants with frank diabetes, a limitation of this analysis was the small number of subjects with MS, as well as with impaired glucose tolerance, at baseline.

In addition to the small number of subjects with impaired glucose tolerance at baseline, there were some other limitations of this study. Not all 113 patients had evaluable follow-up OGTT data, so the overall sample size for WBISI at both time points was 72. This study was conducted primarily in a low-income urban population, which may not be generalizable to other populations. Although the subjects were followed for 12 months in the original study, weight loss peaked at 4 months so we could not evaluate changes in insulin sensitivity with long-term weight loss. It is possible that part of the improvement in insulin sensitivity could be attributed to the advancement into late puberty by our subjects during the four-month period. Although physical activity counseling was part of the lifestyle intervention, we did not perform assessments of physical activity during the study – it is possible that different levels of exercise may have affected insulin sensitivity outcomes independently of weight loss. Several studies have shown that exercise alone can improve insulin resistance in adolescents, independent of changes in body composition^{25,26}. Although the OGTT is a much more convenient test than the euglycemic-hyperinsulinemic clamp, studies have demonstrated within-subject variability that may be a confounding factor²⁷. Finally, these are secondary, exploratory outcomes, and further studies designed to power a threshold analysis of insulin sensitivity in adolescent weight loss are needed.

Successful weight loss in adolescents is associated with improvements in risk factors for metabolic and cardiovascular disease. Almost a third (30.5%) of subjects in our insulin sensitivity analysis were able to decrease their BMI by 8% or more. Further studies with larger sample sizes will be needed to confirm the degree of weight loss necessary for improvements in insulin sensitivity and other metabolic variables. Having evidence to guide the goal setting with regard to the amount of weight loss necessary to yield improvements in metabolic and cardiovascular risk and increase the health of obese and overweight children will be of benefit in the creation of these programs.

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Figure 1.

Each BMI threshold represents the entire population with evaluable WBISI at both timepoints (N=72), divided between those who lost less than that percent of their BMI and those who lost more than that percent of their BMI.

* represents a significant difference in change in WBISI between the two groups ($p < 0.05$)

Figure 2.

We categorized MS Status as Resolved (N=5), Developed (N=4), or Unchanged (N=82; those who either started and finished the trial with MS, or those who started and finished the trial without MS). 91 subjects had complete MS data at both timepoints. Kruskal-Wallis analysis between all three groups $p=0.29$. Kruskal-Wallis analysis between those whose MS resolved and those who developed MS $p=0.05$.

Table 1
Patient Characteristics at Initiation of Study, N=113

Characteristics	Mean (SD)
Age, years	15.0 (1.3)
Sex, female number (%)	91 (81%)
Race, number (%)	
White	28 (26%)
African-American	69 (62%)
Other	13 (12%)
Weight, kg	101.1 (17.7)
Body-mass index, kg/m ²	37.1 (5.1)
Waist circumference, cm	109.2 (12.0)
Fasting glucose, mg/dL	87.8 (7.8)
2-hr glucose (OGTT), mg/dL *	107.9 (24.0)
Fasting insulin, uU/mL *	22.4 (12.9)
HOMA-IR *	4.9 (3.0)
Whole body insulin sensitivity index (WBISI) *	2.87 (1.73)
Hemoglobin A1c, %	4.96 (0.41)

* The number of subjects differs: 2-hr glucose (N=111), fasting insulin (N=110), HOMA-IR (N=103), and WBISI (N=80).