# Threshold for Improvement in Insulin Sensitivity with Adolescent Weight Loss

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**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, 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 from 22.3 to 16.6 $\mu$U/mL ($P < .0001$). Homeostasis model assessment of insulin resistance decreased significantly from 4.9 to 3.7 ($P = .001$) and WBISI increased significantly from 2.87 to 3.98 ($P < .0001$). An 8% reduction in BMI led to a significant improvement in WBISI ($P = .03$) and was the optimal threshold. Fewer individuals met criteria for MS after weight loss ($P = .0038$), 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. *(J Pediatr 2013;163:785-90)*.

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 mellitus.[1] 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 5.[3] 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 (BMI) were successfully achieved, as previously reported.[4] 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 report,[4] and the present report is a full analysis of insulin sensitivity, glucose tolerance, and MS.

## Methods

From 2004-2007, 113 subjects were recruited. Subjects had a BMI of 28-50 kg/m$^2$ and were 13-17 years of age at the initiation of the study. Subjects' baseline characteristics are shown in the Table. All girls were postmenarcheal. Contraindications to study participation included cardiovascular disease, diabetes mellitus, major psychiatric disorders, pregnancy, use of a weight-

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| BMI | Body mass index |
| CD | Conventional diet |
| HDL | High-density lipoprotein |
| HOMA-IR | Homeostasis model assessment of insulin resistance |
| MS | Metabolic syndrome |
| OGTT | Oral glucose tolerance test |
| WBISI | Whole body insulin sensitivity index |

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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 manuals[5]); however, participants were randomized either to the conventional diet (CD) group using regular food or to the portion-controlled meal replacement 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 meal replacement group were placed on a daily plan of SlimFast shakes (Unilever, Englewood Cliffs, New Jersey) 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 published.[4] The purpose of this report is to examine the effect of weight loss on metabolic measures, collapsing across the 2 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 [HDL] cholesterol levels), fasting glucose, fasting insulin, and a 75-g 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. 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 ($\mu$U/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 2 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 load.[7] 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 adolescents.[8] In a previous study, WBISI was noted to better capture improvements in insulin sensitivity in adolescents than fasting measures.[9] It is calculated from the OGTT as follows: 10 000 ÷ √[fasting glucose (mg/dL) × fasting insulin ($\mu$U/mL) × mean glucose (mg/dL) × mean insulin ($\mu$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 nonparametric 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 (eg, greater or lesser than 7% loss in BMI, greater or lesser than 8% loss in BMI). As the WBISI data were nonparametric, the Wilcoxon rank-sum was used to analyze whether there was a significant difference in WBISI between the subjects above and below each threshold 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 2 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 3 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 ANOVA.

Statistical analysis was conducted with SAS v. 9.2 software (SAS Institute, Cary, North Carolina). As this study was powered for the primary outcome only, all analyses in this article are considered exploratory with significance defined as $P < .05$, with no adjustment for multiple testing.

## Results

Adolescents, in aggregate, lost weight during the weight loss induction phase of the trial as previously described.[4] At month 4, a mean (SD) reduction in percentage of initial BMI of 5.4% (±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 ($P < .0001$) to a level of 16.6 $\mu$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, 1 study, which used 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