Reversal of Early Abnormalities in Glucose Metabolism in Obese Youth: Results of an Intensive Lifestyle Randomized Controlled Trial

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OBJECTIVE

The childhood obesity epidemic has been accompanied by an increasing prevalence of type 2 diabetes (T2D), particularly in minority children. Twenty to thirty percent of obese youth have "prediabetes," a precursor to diabetes marked by insulin resistance, β-cell dysfunction, and impaired glucose tolerance. The Diabetes Prevention Program demonstrated that T2D could be prevented/delayed by intensive lifestyle modification in adults with prediabetes, but efficacy of similar interventions in youth has not been established. Therefore, we evaluated the effects of the Bright Bodies (BB) Healthy Lifestyle Program on 2-h oral glucose tolerance test (OGTT) glucose in comparison with adolescents receiving standard of care.

RESEARCH DESIGN AND METHODS

A parallel-group randomized controlled trial comparing BB with standard clinical care (CC) in obese adolescents (10–16 years old, Tanner stage >2) with elevated OGTT 2-h blood glucose (130–199 mg/dL) from a racially/ethnically diverse population. OGTTs, including cardiovascular and anthropometric assessments, were conducted at baseline and 6 months. Children attended BB twice per week for exercise and nutrition/behavior modification, and the CC group received CC from their pediatrician. Primary outcome was change in 2-h OGTT glucose and percentage conversion from elevated 2-h blood glucose to nonelevated (<130 mg/dL) 2-h blood glucose. Changes in outcomes were compared between groups using an ANCOVA, with adjustment for baseline outcome and multiple imputation for missing data.

RESULTS

Reductions in 2-h glucose were more favorable in BB compared with CC (−27.2 vs. −10.1 mg/dL; difference = −17.1, 95% CI; *P* = 0.005). Moreover, greater conversion to <130 mg/dL 2-h glucose occurred in BB than CC (*P* = 0.003), and other insulin sensitivity indices were significantly improved.

CONCLUSIONS

Compared with standard of care, the Yale BB Program is a more effective means of reducing the risk of T2D in obese adolescents with elevated 2-h glucose levels.

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The epidemic of childhood obesity has been accompanied by an increasing prevalence of type 2 diabetes (T2D), particularly among African American and Hispanic children (1). Prior to the development of T2D, obese children pass through a period of impaired glucose tolerance (IGT) due to severe insulin resistance and early β-cell dysfunction (2). Previous studies indicate that 20–30% of obese youth have IGT (3–5) and that progression from IGT to T2D may be more rapid in children than adults, due to continued excessive weight gain (6). Although IGT has been defined as a 2-h glucose of 140–199 mg/dL during an oral glucose tolerance test (OGTT), obese adolescents with 2-h plasma glucose 120–139 mg/dL already manifest defects in insulin secretion and action that are indistinguishable from those seen in adolescents with a 2-h glucose ≥140 mg/dL (7,8). Follow-up of these adolescents indicates that impaired β-cell function relative to insulin sensitivity is a strong predictor of progression from normal glucose tolerance to IGT (9). The Diabetes Prevention Program demonstrated that T2D could be prevented or delayed by an intensive lifestyle program in adults with prediabetes, but the efficacy of similar interventions in reversing early abnormalities in glucose tolerance in youth with prediabetes has not been established (10).

Yale's Bright Bodies (BB) Program is a family-based, lifestyle intervention tailored for inner-city minority children and their families. In a randomized trial involving a large, ethnically diverse population of obese children, the BB Program was remarkably successful in limiting weight gain and improving body composition, insulin sensitivity, and lipids compared with a control group who received conventional dietary counseling (11). In a 2-year follow-up with no intervention after 12 months, treatment effects were sustained (12). Moreover, results of OGTTs in a small subset of subjects in the trial suggested that the program also improved oral glucose tolerance (13). These studies prompted us to develop a new randomized trial whose primary aim was to compare the effects of the BB Program and standard clinical care (CC) on glucose tolerance in obese adolescents with elevated 2-h plasma glucose levels.

RESEARCH DESIGN AND METHODS

Participants

Participants were recruited for the study from the Yale Pediatric Obesity Clinic as part of a community-wide program to increase screening for IGT in obese children and adolescents being cared for in community general pediatric practices in the New Haven, CT, area. Youth who were found to have prediabetes on OGTT were referred to the Yale Pediatric Obesity Clinic for further evaluation and then to the Yale Center for Clinical Investigation's research unit for possible enrollment in this study. Eligibility criteria were an age of 10–16 years, 2-h OGTT plasma glucose between 130 and 199 mg/dL, BMI >95th percentile, and Tanner stage ≥2. Exclusion criteria were diabetes or other serious medical condition that would preclude participation in the program. Individuals taking medications that affect weight, insulin sensitivity, or glucose metabolism were also excluded. Individuals involved in another lifestyle program or plans of moving within 6 months were not eligible. Participants' race and ethnicity were based on parents' self-report. The Yale Human Investigation Committee approved the study, and written informed assent and consent were obtained from participants and parents.

Study Design

This was a parallel-group, randomized trial comparing effects of the BB Program with standard CC. Eligible participants were randomly assigned (1:1) to the two treatment groups using an electronic randomization program with permuted blocks. Randomization sequence was maintained by the study statistician to assure concealment.

Treatment Groups

BB Program

Participants in this group attended the program twice per week for 6 months, offered in the evening at two separate locations (one Spanish-speaking with bilingual instructors). As previously described (11,12), the program consisted of two 50-min exercise sessions per week, one weekly weigh-in, and a 40-min nutrition/behavior modification class. Participants were encouraged to exercise 3 additional days per week and record the duration and type of exercise. The primary motivational tool was a BB "buck" (i.e., raffle ticket) with a monthly drawing for a gift card. A participant earned a weekly raffle ticket if their weight stayed the same or they lost weight and, in some cases, for returning their weekly exercise log.

The nutrition component used a nondiet, healthy food-choice approach that emphasized low-fat foods of moderate portions. As in our previous studies, the dietitian who directed the classes used the *Smart Moves Workbook*, offered in English and Spanish, for a consistent curriculum (11–14). Topics included "Determining Portion Sizes," "Better Food Choices: A Non-Diet Approach," "Making Sense of a Food Label," and "Bag It!—The Pros to Bringing Lunch to School."

The behavior modification component, primarily facilitated by the dietitian, used techniques such as self-awareness, goal setting, stimulus control, coping skills training, cognitive behavior strategies, and contingency management. Sample behavior modification topics of the *Smart Moves Workbook* included "Risky Business: Identifying High-Risk Situations," "Mirror, Mirror on the Wall," "Bullies, Teasers, and Other Annoying People," and "Oops, I Slipped—Understanding a Relapse." While children received behavior modification instruction, parents/caregivers attended their own support class in which elements of solution-focused brief therapy were used by a psychologist or dietitian. Solution-focused brief therapy tools included strength cards (picture cards that indicate positive personal characteristics) to help the parent identify their own and their child's constructive characteristics.

The exercise component was facilitated by an exercise physiologist or physical therapist. Each 50-min session consisted of a warm-up, high-intensity, and cool-down period. High-intensity exercises consisted of typical children's games

that were modified to increase heart rate. Once per month there were special exercise activities such as martial arts, dance-off contests, Zumba, and the use of Just Dance (Ubisoft Entertainment, Brittany, France).

Standard CC

Participants randomized to CC were given diet and exercise instruction by the Obesity Clinic's bilingual dietitian, including standardized topics such as discontinuing juice/soda intake, bringing low-fat lunches to school, and decreasing portion sizes. Sedentary activities were discouraged, and activities the child enjoyed were encouraged. Each subject was given an instructional handout and a goal sheet in English or Spanish, which was mailed to the participant's clinician.

CC group participants were followed by their usual clinician for standard care every 2–3 months during the study. To provide consistent education across sites, the study dietitian trained all clinicians and supplied the clinic with educational materials.

Outcome Measures

Outcome measures for both groups were obtained at baseline and 6 months at the Yale Center for Clinical Investigation research unit.

OGTT

Subjects were instructed to consume a ≥250-g carbohydrate diet and refrain from strenuous activity the day before the OGTT. The OGTT was performed in the morning following an overnight 10-h fast. An intravenous catheter was inserted into an arm vein for blood sampling, and participants rested for 15 min before two baseline, prechallenge samples were obtained for measurement of plasma glucose, insulin, lipids, alanine aminotransferase (ALT), and hemoglobin A1c (HbA_{1c}). Flavored glucose (Orangedex; Custom Laboratories, Baltimore, MD) in a dose of 1.75 g/kg body weight (maximum 75 g) was then given orally, and blood samples were obtained for the measurement of glucose and insulin every 30 min for 2 h. Plasma glucose levels were measured with a chemistry analyzer (YSI 2700 STAT Analyzer, Yellow Springs Instruments, Yellow Springs, OH), and plasma insulin levels were measured by radioimmunoassay (Linco Laboratories, St Charles, MO). Coefficients of variation for fasting and 2-h glucose have been demonstrated to be 6.9 and 12.7%, respectively (15,16).

Anthropometrics and Blood Pressure

Weight was measured (participant in socks, no shoes, light gown) to the nearest 0.1 kg using a medical weight scale (CN20, Detecto, Division of Cardinal Scale Manufacturing Co, Webb City, MO). Harpenden stadiometer (Cambridge, MD), calibrated in 0.2-cm intervals, determined height. BMI was calculated as weight in kilograms divided by height in meters squared. BMI *z* scores were based on the Centers for Disease Control and Prevention growth charts (17). Percentage of body fat was determined by a body fat analyzer (TBF 300, Tanita, Arlington Heights, IL), which has a high correlation with dual-energy X-ray absorptiometry in children (18). Blood pressure was measured automatically with a sphygmomanometer (Model 01–752, American Diagnostics, Hauppauge, NY) twice after participants sat for 10 min and then averaged for analysis.

The study nurse who obtained the anthropometric and blood pressure data was blinded to the participant's treatment group.

Indices of Insulin Sensitivity and Secretion

Homeostasis model assessment of insulin resistance (HOMA-IR) was calculated from fasting glucose, and insulin described by Matthews et al. (19). The whole-body insulin sensitivity index (WBISI) (20) was derived from glucose and insulin levels from the OGTT. The index is calculated as follows:

$$\text{WBISI} = \frac{10,000}{\sqrt{(\text{fasting glucose} \times \text{fasting insulin})\ (\text{mean glucose} \times \text{mean insulin})}}$$

This index correlates with M values derived from the hyperinsulinemic–euglycemic clamp in obese children (21). Insulinogenic index (IGI) was calculated as the ratio of the increment in plasma insulin level to that in plasma glucose level during the first 30 min after ingestion of glucose. Oral disposition index (DI_O) was calculated as the product of WBISI and IGI obtained during the OGTT (22,23). HbA_{1c} was measured by the DCA Vantage Analyzer (Siemens Healthcare Diagnostics, Tarrytown, NY).

Other Outcomes

Plasma total cholesterol, HDL, LDL, and triglyceride levels were measured with an autoanalyzer (Model 747–200, Roche-Hitachi, Indianapolis, IN). ALT was measured with an ACE Autoanalyzer (Alfa Wassarmann Incorporated).

Statistical Analysis

Sample size estimates were based on detecting a difference in the primary outcome, 6-month change in 2-h plasma glucose. In our previous trial, we observed 12-month reductions in 2-h glucose of −5.5 (SD = 6.0) mg/dL in the BB group and increases of 9.1 (5.8) mg/dL in the control group, a difference of 14.6 mg/dL (13). Group sizes of 36 would provide 80% power to detect differences of 30% of this observed effect size (i.e., 4.4 mg/dL) at a two-sided 0.05 significance level, allowing for a 15% loss to follow-up. Baseline characteristics were compared with independent samples *t* tests and χ^2 analysis for continuous and categorical variables, respectively. The primary analysis was conducted based on the intent-to-treat principle, with participants analyzed in their original randomized group. Changes in outcomes were compared between groups using ANCOVA with adjustment for the baseline outcome and body weight. Analyses were also adjusted for baseline factors associated with dropout (HbA_{1c}, HOMA-IR, AST, and disposition index [DI]). For positively skewed variables, log transformations were used prior to analysis. Least squares means and 95% CIs were estimated for changes in outcomes. The sex by treatment group interaction was

also estimated to determine whether the magnitude of the treatment difference was modified by sex. Path analysis using MPLUS (24) was used to determine the amount of the treatment effect on selected outcomes that could be explained by changes in body weight.

Given that 6-month follow-up assessments were missing in 17 (23%; 7 BB, 10 CC) individuals, multiple imputation with data augmentation under the multivariate normal model by PROC MI (SAS Institute, Cary, NC) was performed. Details of this process are described by Allison (25). Briefly, imputation was conducted on continuous missing data with log transformations applied for normality where necessary. Baseline and 6-month outcomes, age, sex, race, treatment, and BMI *z* score were included in the imputation model. Five imputations using a sequential chain of iterations followed by 100 iterations between successive imputations were performed. Following imputation, each "filled-in" data set was analyzed separately using ANCOVA described above, and parameter estimates were averaged across the data sets. Variance estimates included both a within-imputation and an across-imputation component. The assumption of this multiple imputation process is that data are missing at random, i.e., missing observations may depend on values of observed data but are conditionally independent of unobserved values. An additional analysis was performed on only those completing the 6-month follow-up but had little effect on treatment estimates and is therefore not presented.

RESULTS

Participants

Of 577 children screened (Supplementary Fig. 1), 432 did not meet the primary inclusion criteria of a 2-h OGTT plasma glucose between 130 and 199 mg/dL. Of 145 who met this primary inclusion criteria, 53 were excluded, 44 were treated with a medication known to result in weight gain/loss or to change insulin sensitivity, 6 lived too far, and 3 were already involved in a weight-management program. Seventeen subjects declined participation, and the remaining 75 were randomized. Eighty percent of children lived in homes with incomes less than $30,000.

Two BB participants dropped out (never attended) and were lost to follow-up, and 5 did not finish the study, but postrandomization anthropometric data were available to carry forward: two had transportation issues, one had a broken ankle, one had psychiatric hospitalization, and one started prednisone. Two CC subjects were lost to follow-up, and 5 were withdrawn from the study because their clinicians started them on metformin.

Randomization produced similar distributions of baseline characteristics in both groups (Table 1). There were no significant differences in these variables in the participants who completed the 6 months of the study. However, dropout was associated with higher HbA_{1c} and HOMA-IR and lower DI (data not shown).

Effects of the BB Intervention

Glucose and Insulin Outcomes

Significant reductions from baseline in 2-h glucose were observed in both BB (−27.2 mg/dL) and CC (−10.1 mg/dL) groups (Fig. 1 and Table 2). Improvements were significantly greater in BB compared with CC

Table 1—Baseline characteristics of children randomized to intervention and control groups

	All randomized participants		Completers	
Characteristics	BB group (*n* = 38)	CC group (*n* = 37)	BB group (*n* = 31)	CC group (*n* = 27)
Demographic				
Race, *n* (%)				
Non-Hispanic white	12 (31.6)	13 (35.1)	11 (35.5)	8 (29.6)
Hispanic white	15 (39.5)	12 (32.4)	13 (41.9)	10 (37.0)
Black	11 (29.0)	10 (27.0)	7 (22.6)	7 (25.9)
Other	0	2 (5.4)	0	2 (7.4)
Sex, *n* (%)				
Male	12 (31.6)	14 (37.8)	10 (32.3)	9 (33.3)
Female	26 (68.4)	23 (62.2)	21 (67.7)	18 (66.7)
Age (years)	12.7 (1.9)	13.2 (1.8)	12.9 (2.0)	12.9 (1.5)
Glucose and insulin metabolism				
2-h glucose (mg/dL)	153.6 (18.2)	148.6 (14.8)	153.9 (16.1)	147.0 (14.5)
2-h insulin (μIU/mL)‡	269.2 (1.3)	302.0 (1.9)	251.2 (1.9)	288.4 (1.7)
Fasting glucose (mg/dL)	92.9 (7.0)	92.4 (8.0)	93.0 (7.3)	92.1 (8.0)
Fasting insulin (μIU/mL)‡	38.0 (1.6)	40.7 (1.6)	36.3 (1.6)	39.0 (1.5)
HOMA-IR‡	8.7 (1.7)	9.3 (1.6)	8.3 (1.7)	8.9 (1.5)
WBISI	1.2 (0.8)	1.1 (0.5)	1.2 (0.8)	1.1 (0.5)
HbA_{1c} (%)	5.7 (0.4)	5.6 (0.4)	5.6 (0.3)	5.6 (0.3)
IGI	4.4 (3.3)	4.3 (2.4)	4.5 (3.4)	4.5 (2.6)
DI_o	4.3 (2.8)	4.2 (2.6)	4.5 (2.9)	4.6 (2.8)
Anthropometric				
Weight (kg)	83.7 (19.0)	92.0 (24.0)	85.0 (19.7)	87.8 (24.3)
Height (cm)	160.9 (10.3)	162.0 (10.5)	161.6 (10.8)	160.6 (10.3)
BMI	32.1 (5.2)	34.6 (6.8)	32.2 (5.6)	33.6 (7.0)
BMI *z* score	2.2 (0.4)	2.3 (0.4)	2.2 (0.4)	2.2 (0.4)
% Body fat	43.1 (6.3)	43.1 (7.4)	43.5 (6.9)	41.9 (7.2)
Fat mass (kg)	36.3 (11.6)	40.9 (16.2)	37.2 (12.5)	37.7 (15.5)
Cardiovascular				
Blood pressure, systolic (mmHg)	118.5 (10.3)	123.3 (11.7)	117.9 (11.2)	123.1 (11.8)
Blood pressure, diastolic (mmHg)	67.3 (8.3)	67.8 (7.4)	67.4 (9.0)	68.4 (7.5)
Cholesterol, total (mg/dL)	151.1 (34.0)	159.2 (35.9)	148.6 (33.2)	158.1 (38.5)
HDL (mg/dL)	40.1 (9.6)	39.8 (8.1)	39.2 (9.2)	39.6 (8.2)
LDL (mg/dL)	88.3 (27.1)	92.5 (31.0)	87.6 (27.4)	91.7 (32.8)
Triglycerides (mg/dL)‡	102.3 (1.6)	116.9 (1.8)	100.0 (1.5)	120.2 (1.8)
ALT	23.7 (15.4)	21.4 (10.4)	21.5 (11.0)	21.0 (10.8)

Mean (SD) are presented for baseline characteristics. ‡Data are presented as geometric means and geometric SDs.

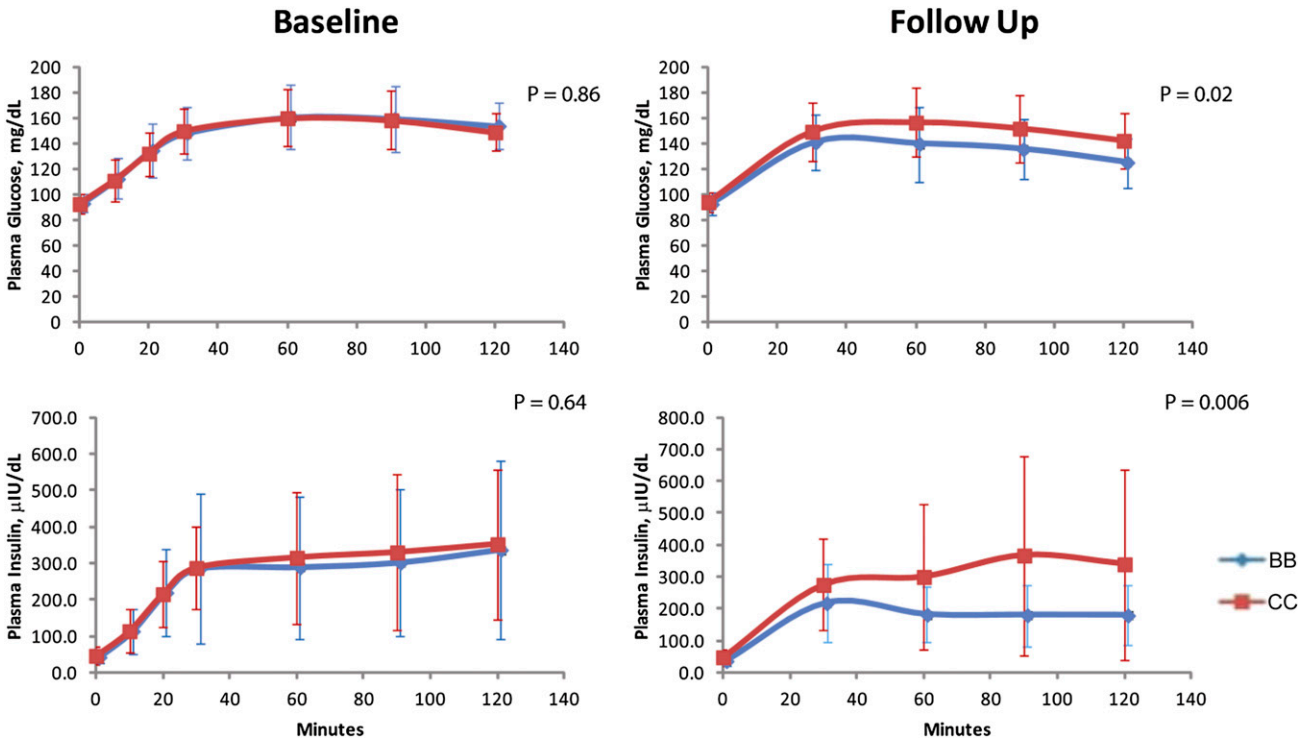

Figure 1—OGTT data at baseline and follow-up between the BB and CC groups. *P* value is from comparing area under curve (AUC 120) using *t* test.

(difference = −17 mg/dL; 95% CI −29 to −5; *P* = 0.005). As shown in Fig. 1 and Table 2, significantly greater improvements were observed in the BB group for changes in fasting plasma insulin (*P* = 0.026), 2-h plasma insulin (*P* < 0.001), HOMA-IR (*P* = 0.03), and WBISI (*P* = 0.02). HbA_{1c}, IGI, and DI showed nonsignificant changes

Table 2—Comparison of 6-month changes in outcomes between BB and CC groups, adjusting for baseline outcome, weight, HbA_{1c}, HOMA-IR, and DI

Outcomes	BB group	CC group	Treatment effect (BB–CC)	*P* value
Glucose and insulin metabolism				
2-h glucose (mg/dL)	−27.2 (−35.2 to −19.1)	−10.1 (−18.4 to −1.8)	−17.1 (−29.0 to −5.1)	0.005
2-h insulin (μIU/mL)‡	−108.6 (−137.9 to −73.4)	−15.7 (−66.2 to 46.6)	−92.9 (−131.2 to −43.9)	<0.001
Fasting glucose (mg/dL)	−0.5 (−3.1 to 2.0)	2.5 (−0.7 to 5.7)	−3.0 (−7.3 to 1.2)	0.16
Fasting insulin (μIU/mL)‡	−4.9 (−10.0 to 1.1)	5.2 (−1.3 to 12.9)	−10.1 (−17.1 to −1.4)	0.03
HOMA-IR‡	−1.2 (−2.4 to 0.3)	1.4 (−0.3 to 3.4)	−2.6 (−4.3 to −0.4)	0.03
WBISI	0.41 (0.17–0.64)	−0.01 (−0.24 to 0.22)	0.42 (0.08–0.76)	0.02
HbA_{1c}	−0.16 (−0.27 to −0.05)	−0.05 (−0.17 to 0.07)	−0.11 (−0.27 to 0.05)	0.19
IGI	2.1 (−0.3 to 4.5)	−0.1 (−2.6 to 2.4)	2.2 (−1.2 to 5.6)	0.20
DI_o	4.7 (0.5–8.8)	0.4 (−3.2 to 4.1)	4.2 (−0.8 to 9.3)	0.10
Anthropometric				
Weight (kg)	0.6 (−0.9 to 2.1)	3.7 (2.1–5.2)	−3.1 (−5.3 to −0.9)	0.006
Height (cm)	1.9 (1.2–2.5)	1.7 (1.0–2.3)	0.1 (−0.7 to 1.0)	0.73
BMI (kg/m^2)	−0.37 (−0.86 to −0.11)	0.67 (0.13–1.21)	−1.05 (−1.78 to −0.32)	0.005
BMI *z* score	−0.05 (−0.09 to −0.01)	0.04 (0.00–0.08)	−0.09 (−0.14 to −0.04)	<0.001
Body fat (%)	−3.3 (−4.8 to −1.8)	0.4 (−1.5 to 2.4)	−3.8 (−6.3 to −1.3)	0.003
Fat mass (kg)	−2.7 (−4.5 to −0.9)	2.3 (−0.2 to 4.8)	−5.0 (−8.2 to −1.8)	0.002
Cardiovascular				
Blood pressure, systolic (mmHg)	−6.2 (−9.1 to −3.2)	−0.7 (−3.4 to 2.1)	−5.5 (−9.3 to −1.7)	0.005
Blood pressure, diastolic (mmHg)	−0.9 (−8.4 to 6.6)	8.3 (−0.1 to 16.8)	−9.2 (−19.9 to 1.5)	0.09
Cholesterol, total (mg/dL)	−10.8 (−21.9 to 0.5)	−2.1 (−11.4 to 7.3)	−8.7 (−23.1 to 5.7)	0.24
HDL (mg/dL)	−2.8 (−5.8 to 0.3)	−3.9 (−6.9 to −0.9)	1.1 (−3.1 to 5.3)	0.60
LDL (mg/dL)	−1.3 (−9.5 to 6.9)	3.5 (−3.8 to 10.8)	−4.8 (−15.2 to 5.6)	0.37
Triglycerides (mg/dL)‡	−28.4 (−38.9 to −16.4)	−4.6 (−17.3 to 9.9)	−23.9 (−37.2 to −7.9)	0.005
ALT	−3.9 (−6.8 to −0.9)	−6.7 (−9.1 to −4.2)	2.8 (−0.9 to 6.6)	0.14

Data are mean (95% CI) unless otherwise stated. ‡Data are presented as geometric mean.

between groups. Mediation analysis revealed that 12.6, 11, 38, and 27% of the treatment-related changes in 2-h glucose, 2-h insulin, WBISI, and triglycerides, respectively, were explained by changes in body weight.

No participants developed diabetes during the study. However, 19 of the 31 (61%) of BB subjects with 2-h blood glucose ≥130 mg/dL converted to <130 at 6 months, while only 6 of 21 (22%) converted in the CC group ($P = 0.003$). Moreover, 42% of BB subjects versus only 7% of the CC group had 2-h glucose levels <120 mg/dL at the end of the study ($P = 0.003$).

Anthropometric Outcomes

Changes in anthropometric outcomes are shown in Table 2. Significantly greater improvements were observed in BB compared with CC with respect to changes in weight (difference = −3.1 kg; $P = 0.006$), BMI (−1.1 kg/m^2; $P = 0.005$), BMI *z* score (−0.10; $P = <0.001$), percentage body fat (−3.8%; $P = 0.003$), and fat mass (−5.0 kg; $P = 0.002$).

Other Outcomes

Significantly greater improvements for BB were also observed in systolic blood pressure (difference = −5.5 mmHg; $P = 0.005$) and fasting triglycerides (−24 mg/dL; $P = 0.005$), but there were no significant differences in diastolic blood pressure, cholesterol measures (total, HDL, and LDL), and ALT levels (Table 2).

Of note, no modifications of treatment effects by sex were detected (i.e., interactions of sex with treatment group for all outcomes were not significant; $P > 0.05$; Supplementary Table 1).

CONCLUSIONS

The BB Program significantly decreased 2-h glucose in children at high risk for diabetes after 6 months in comparison with standard of care. We included subjects with 2-h glucose levels between 130 and 139 mg/dL as high-risk because of the compelling evidence that children who fall in this range (and as low as 120–129 mg/dL) have similar defects in both insulin action and β-cell function as youngsters with 2-h glucose levels between 140 and 199 mg/dL (6–8).

As previously observed in obese adolescents with normal glucose tolerance (11,12), the BB program lowered BMI *z* scores by helping subjects maintain their body weight close to baseline values as compared with continued weight gain in the CC group. The effect of BB on body composition was even more impressive, as the BB group reduced total body fat by >2 vs. >2 kg gain in body fat in CC group. We acknowledge the lack of differentiation in central and visceral adiposity as a limitation to this study. Moreover, while we were unable to detect differences in the treatment effect between sexes, the potential for modification of the treatment effect by sex remains, as this study was not powered to determine subgroup differences. None the less, the favorable changes in indices of adiposity observed in this multiethnic group of inner-city adolescents are consistent with those described by the HEALTHY study, the largest school-based multicomponent intervention project ever reported in children at risk for obesity and T2D (26).

Changes in body composition, as well as enhanced physical fitness demonstrated previously (27), undoubtedly contributed to the marked improvements in insulin sensitivity in the BB versus CC group. Moreover, although β-cell function may have also contributed to metabolic improvement, insulin sensitivity is likely to have played a role in the lowering of 2-h glucose concentrations in the BB subjects. The improvement in glucose tolerance in BB versus CC group was both statistically significant and clinically important. Clinical relevance is reflected in the fact that 42% of children in the BB group were able to lower 2 h blood glucose levels to <120 mg/dL compared with only 7% in the CC group. These findings confirmed and extended the findings of our previous study that suggested that the BB intervention could improve or even normalize glucose tolerance in obese youth with prediabetes (13). The BB program also had a favorable effect on other cardiometabolic risk factors.

The recent results of the TODAY and other studies have served to illustrate the challenges in managing T2D during adolescence (28,29). The success of our intensive lifestyle intervention program aimed at improving and even normalizing glucose metabolism in obese youth with prediabetes suggests that this approach may be a more effective treatment strategy than being content on waiting until these youngsters develop T2D. Further studies are needed to determine whether lifestyle interventions can be translated into sustainable improvements in clinical practice that reduce the risk of developing T2D in overweight youth.

While the relatively short 6-month duration of the study could be interpreted as a limitation, it could equally be viewed as a strength since the improvements in glucose metabolism were seen relatively quickly. Moreover, our previous study demonstrated that the treatment effect of BMI and body composition that were observed with the BB program in comparison with standard of care were sustained for up to 2 years (12), making the family commitment to an intensive lifestyle program worthwhile.

In fact, one limitation faced in widespread dissemination of lifestyle interventions is the major commitment required from families, communities, and care providers. Thus another successful factor in this study is the support that it received from the local community, as practices initiated enhancement programs aimed at identifying prediabetes by more active OGTT screening. Although the OGTT is more labor-intensive and commitment-intensive for families, the use of the HbA_{1c} as a more practical alternative (30) lacks sensitivity in the pediatric population, particularly in a short-term study such as this (31). Therefore, we chose to use the gold standard method of the OGTT to measure changes in glucose metabolism.

It is worth noting that our curriculum has served as a basis for pediatric obesity programs throughout the U.S. and other countries such as Chile, Scotland, and Finland. A standardized curriculum saves training time and salary cost and cultivates smoother dissemination. Although a cost–benefit analysis is beyond the scope of this article, we have completed such an analysis after an initial 1-year efficacy

trial and demonstrated that the program is cost-effective in spite of its intensity (32).

In summary, obese youth with altered glucose tolerance should be followed closely because of vulnerable β-cell function, which can easily deteriorate with continued weight gain. Early use of lifestyle interventions to limit future weight gain and improve glucose tolerance is a nonpharmacological treatment approach that is free from serious side effects. Moreover, behavior modification strategies can have long-lasting positive effects (12).

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References

1. Dabelea D, Bell RA, D'Agostino RB Jr, et al.; Writing Group for the SEARCH for Diabetes in Youth Study Group. Incidence of diabetes in youth in the United States. JAMA 2007; 297:2716–2724
2. Weiss R. Impaired glucose tolerance and risk factors for progression to type 2 diabetes in youth. Pediatr Diabetes 2007;8 (Suppl. 9):70–75
3. Sinha R, Fisch G, Teague B, et al. Prevalence of impaired glucose tolerance among children and adolescents with marked obesity. N Engl J Med 2002;346: 802–810
4. 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
5. Kleber M, de Sousa G, Papcke S, Reinehr T. Risk factors for impaired glucose tolerance in obese children and adolescents. World J Diabetes 2010;1:129–134
6. Weiss R, Taksali SE, Tamborlane WV, Burgert TS, Savoye M, Caprio S. Predictors of changes in glucose tolerance status in obese youth. Diabetes Care 2005;28:902–909
7. Burns SF, Bacha F, Lee SJ, Tfayli H, Gungor N, Arslanian SA. Declining β-cell function relative to insulin sensitivity with escalating OGTT 2-h glucose concentrations in the nondiabetic through the diabetic range in overweight youth. Diabetes Care 2011;34: 2033–2040
8. Yeckel CW, Taksali SE, Dziura J, et al. The normal glucose tolerance continuum in obese youth: evidence for impairment in beta-cell function independent of insulin resistance. J Clin Endocrinol Metab 2005; 90:747–754
9. Giannini C, Weiss R, Cali A, et al. Evidence for early defects in insulin sensitivity and secretion before the onset of glucose dysregulation in obese youths: a longitudinal study. Diabetes 2012;61: 606–614
10. Knowler WC, Barrett-Connor E, Fowler SE, et al.; Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med 2002;346:393–403
11. Savoye M, Shaw M, Dziura J, et al. Effects of a weight management program on body composition and metabolic parameters in overweight children: a randomized controlled trial. JAMA 2007;297:2697–2704
12. Savoye M, Nowicka P, Shaw M, et al. Long-term results of an obesity program in an ethnically diverse pediatric population. Pediatrics 2011;127:402–410
13. Shaw M, Savoye M, Cali A, Dziura J, Tamborlane WV, Caprio S. Effect of a successful intensive lifestyle program on insulin sensitivity and glucose tolerance in obese youth. Diabetes Care 2009;32: 45–47
14. Savoye M, Berry D, Dziura J, et al. Anthropometric and psychosocial changes in obese adolescents enrolled in a Weight Management Program. J Am Diet Assoc 2005;105:364–370
15. Ollerton RL, Playle R, Ahmed K, Dunstan FD, Luzio SD, Owens DR. Day-to-day variability of fasting plasma glucose in newly diagnosed type 2 diabetic subjects. Diabetes Care 1999;22:394–398
16. Wolever TMS, Chiasson JL, Csima A, et al. Variation of postprandial plasma glucose, palatability, and symptoms associated with a standardized mixed test meal versus 75 g oral glucose. Diabetes Care 1998;21: 336–340
17. Kuczmarski RJ, Ogden CL, Grummer-Strawn LM, et al. CDC growth charts: United States. Adv Data 2000;314:1–27
18. Nunez C, Rubiano F, Horlick M, Thorton J, Heymsfield SB. *Application of Leg-to-Leg Bioimpedance System in Children*. Atlanta, International Life Sciences Institute Center for Health Promotion, 1999
19. 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
20. 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
21. Yeckel CW, Weiss R, Dziura J, et al. Validation of insulin sensitivity indices from oral glucose tolerance test parameters in obese children and adolescents. J Clin Endocrinol Metab 2004; 89:1096–1101
22. Utzschneider KM, Prigeon RL, Faulenbach MV, et al. Oral disposition index predicts the development of future diabetes above and beyond fasting and 2-h glucoselevels. Diabetes Care 2009;32: 335–341
23. Rhee SY, Woo JT, Chon S, et al. Characteristics of insulin resistance and insulin secretory capacity in Korean subjects with IFG and IGT. Diabetes Res Clin Pract 2010;89:250–255
24. Muthen LK, Muthen BO. *Mplus User's Guide*. 6th ed. Los Angeles, Muthen and Muthen, 2010
25. Allison P. *Missing Data*. Thousand Oaks, Sage Publications, 2001
26. Mobley CC, Stadler DD, Staten MA, et al.; HEALTHY Study Group. Effect of nutrition changes on foods selected by students in a middle school-based diabetes prevention intervention program: the HEALTHY experience. J Sch Health 2012;82: 82–90
27. DeStefano RA, Caprio S, Fahey JT, Tamborlane WV, Goldberg B. Changes in body composition after a 12-wk aerobic exercise program in obese boys. Pediatr Diabetes 2000;1:61–65
28. Zeitler P, Hirst K, Pyle L, et al.; TODAY Study Group. A clinical trial to maintain glycemic control in youth with type 2 diabetes. N Engl J Med 2012;366:2247–2256

29. Tamborlane WV, Klingensmith G. Crisis in care: limited treatment options for type 2 diabetes in adolescents and youth. Diabetes Care 2013;36:1777–1778
30. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care 2010;33(Suppl. 1):S62–S69
31. Nowicka P, Santoro N, Liu H, et al. Utility of hemoglobin A(1c) for diagnosing prediabetes and diabetes in obese children and adolescents. Diabetes Care 2011;34:1306–1311
32. Nowicka P, Price G, Suri V, et al. Providing a cost-effective comprehensive weight management program for highly obese children: not a mission impossible. In *Proceedings of Obesity 2010, 28th Annual Scientific Meeting, San Diego, CA, October 2010*, p. 8–12