Reversal of early abnormalities in glucose metabolism in obese youth: results of an intensive lifestyle randomized controlled trial

Short/Running Title: Effects of lifestyle intervention on obese youth with pre-diabetes

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Background: The childhood obesity epidemic has been accompanied by an increasing prevalence of type 2 diabetes (T2D), particularly in minority children. 20-30% of obese youth have “pre-diabetes” a precursor to diabetes marked by insulin resistance, β-cell dysfunction and impaired glucose tolerance (IGT). The Diabetes Prevention Program (DPP) demonstrated that T2D could be prevented/delayed by intensive lifestyle modification in adults with pre-diabetes, but efficacy of similar interventions in youth has not been established. Therefore, we evaluated the effects of the Bright Bodies Healthy Lifestyle Program on 2-hr OGTT glucose in comparison to adolescents receiving standard of care.

Methods: Parallel-group randomized controlled trial comparing Bright Bodies (BB) with standard clinical care (CC) in obese adolescents (10-16 yo, Tanner stage >2) with elevated OGTT 2-hr blood glucose (130-199 mg/dl) from a racial/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 CC group received clinical care from their pediatrician. Primary outcome was change in 2-hr OGTT glucose and % conversion from elevated 2-hr blood glucose to non-elevated (<130 mg/dl) 2-hr blood glucose. Changes in outcomes were compared between groups using an analysis of covariance with adjustment for baseline outcome and multiple imputation for missing data.

Results: Reductions in 2-hr glucose were more favorable in BB compared to CC (-27.2 vs. -10.1 mg/dl; diff=-17.1, 95% CI ;p= 0.005). Moreover, greater conversion to <130 mg/dl 2-hr glucose occurred in BB than CC (p=0.003) and other insulin sensitivity indices were significantly improved.

Conclusions: Compared to standard of care, the Yale Bright Bodies Program is a more effective means of reducing the risk of T2D in obese adolescents with elevated 2-hour glucose levels.
The epidemic of childhood obesity has been accompanied by an increasing prevalence of type 2 diabetes (T2D), particularly African American and Hispanic children. 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. Previous studies indicate that 20-30% of obese youth have IGT and that progression from IGT to T2D may be more rapid in children than adults, due to continued excessive weight gain. Although IGT has been defined as a 2-hour glucose of 140-199 mg/dl during an oral glucose tolerance test (OGTT), obese adolescents with 2-hour 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-hour glucose >140 mg/dl. Follow-up of these adolescents indicates that impaired β-cell function relative to insulin sensitivity is a strong predictor of progression from NGT to IGT. The Diabetes Prevention Program demonstrated that T2D could be prevented or delayed by an intensive lifestyle program in adults with pre-diabetes but the efficacy of similar interventions in reversing early abnormalities in glucose tolerance in youth with pre-diabetes has not been established.

Yale’s Bright Bodies 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 Bright Bodies Program was remarkably successful in limiting weight gain and improving body composition, insulin sensitivity and lipids compared to a control group who received conventional dietary counseling. In a 2-year follow up with no intervention after 12 months, treatment effects were sustained. Moreover, results of OGTTs in a small subset of subjects in the trial suggested that the Program also improved oral glucose tolerance. These
studies prompted us to develop a new randomized trial whose primary aim was to compare the effects of the Bright Bodies Program and standard clinical care on glucose tolerance in obese adolescents with elevated 2-hour 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 impaired glucose tolerance in obese children and adolescents being cared for in community general pediatric practices in the New Haven area. Youth who were found to have pre-diabetes on OGTT were referred to the Yale Pediatric Obesity Clinic for further evaluation and then the Yale Center for Clinical Investigation’s (YCCI’s) Research Unit for possible enrollment in this study. Eligibility criteria were age 10-16 yrs, 2-hour OGTT plasma glucose between 130-199 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 six 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 Bright Bodies Program with standard clinic care. 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**

**Bright Bodies (BB) Program**

Participants in this group attended the program twice a week for 6 months, offered in the evening at two separate locations (one Spanish-speaking with bilingual instructors). As previously described, the program consisted of two 50-minute exercise sessions per week, one weekly weigh-in, and a 40-minute 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 Bright Bodies “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. 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 (SFBT) were utilized by a psychologist or dietitian. SFBT tools included strength cards (picture cards that indicate positive personal characteristics) to help the parent identify their and their child’s constructive characteristics.

The exercise component was facilitated by an exercise physiologist or physical therapist. Each 50-minute 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®.

**Standard Clinic Care (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 lunch 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 YCCI 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, pre-challenge samples were obtained for measurement of plasma glucose, insulin, lipids, alanine aminotransferase (ALT), and hemoglobin A1c (HgA1c). Flavored glucose (Orangedex; Custom Laboratories, Baltimore, MD) in a dose of 1.75g/kg body weight (maximum 75 g) was then given orally, and blood samples were obtained for the measurement of glucose and insulin every 30 minutes for 2 hours. 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 radiommunoassay (Linco Laboratories, St Charles, MO). Co-efficients of variation for fasting and 2-hour glucose have been demonstrated to be 6.9% and 12.7%, respectively.\textsuperscript{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. Body mass index 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.\textsuperscript{17} Percent 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 absorptometry in children.\textsuperscript{18} Blood pressure was measured automatically with a sphygmomanometer (Model 01-752, American Diagnostics, Hauppauge, NY) twice after participants sat for ten minutes, 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.\textsuperscript{19} The whole-body insulin sensitivity index (WBISI),\textsuperscript{20} was derived from glucose and insulin levels from the OGTT. The index is calculated as follows:

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

This index correlates with M values derived from the hyperinsulinemic-euglycemic clamp in obese children.\textsuperscript{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 minutes after ingestion of glucose. Oral Disposition Index (DI\textsubscript{O}) was calculated as the product of WBISI and IGI obtained during the OGTT.\textsuperscript{22,23} HgA1c was measured by the DCA Vantage Analyzer (Siemens Healthcare Diagnostics, Tarrytown, NY).

**Other Outcomes**
Plasma total cholesterol, high-density lipoprotein, low-density lipoprotein, and triglyceride levels were measured with an autoanalyzer (Model 747-200, Roche-Hitachi, Indianapolis, In). ALT was measured with an ACE Autoanalyzer (Alfa Wassermann Incorporated).

**Statistical Analysis.**

Sample size estimates were based on detecting a difference in the primary outcome, 6-month change in 2-hr plasma glucose. In our previous trial we observed 12-month reductions in 2-hr 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. 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 chi-square 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 analysis of covariance with adjustment for the baseline outcome and body weight. Analyses were also adjusted for baseline factors associated with dropout (HgA1c, HOMA-IR, AST and DI). For positively skewed variables, log transformations were used prior to analysis. Least Squares Means and 95% confidence intervals were estimated for changes in outcomes. The gender by treatment group interaction was also estimated to determine whether the magnitude of the treatment difference was modified by gender. Path analysis using MPLUS 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.\textsuperscript{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 analysis of covariance described above and parameter estimates were averaged across the data sets. Variance estimates included both a within- 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 (SUPPLEMENTAL FIGURE, S1), 432 did not meet the primary inclusion criteria of a 2-h OGTT plasma glucose between 130-199 mg/dl. Of 145 who met this primary inclusion criteria, 53 were excluded, 44 because of their treatment 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 post-randomization anthropometric data were available to carry forward: 2 had transportation issues, 1 broken ankle, 1 psychiatric hospitalization, and 1 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 HgA1c and HOMA-IR and lower DI (data not shown).

**Effects of the Bright Bodies Intervention**

**Glucose and Insulin Outcomes**

Significant reductions from baseline in 2-hour glucose were observed in both BB (-27.2 mg/dl) and CC (-10.1 mg/dl) groups (FIGURE 1 and TABLE 2). Improvements were significantly greater in BB compared to CC (difference=-17 mg/dl, 95% CI [-29, -5], p=0.005). As shown in FIGURE 1 and TABLE 2, significantly greater improvements were observed in the BB group for changes in fasting plasma insulin (p=0.026), 2-hour plasma insulin (p<0.001), HOMA-IR (p=0.03), and WBISI (p=0.02). HgA1c, insulinogenic (IGI) and Disposition Index (DI) showed non-significant changes between groups. Mediation analysis revealed that 12.6, 11, 38 and 27% of the treatment-
related changes in 2-hour glucose, 2-hour 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-hr 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 to CC with respect to changes in weight (difference=-3.1 kg, p=0.006), BMI (-1.1 kg/m², p=0.005), BMI z-score (-0.10, p=<0.001), percent 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 gender were detected (i.e. interactions of gender with treatment group for all outcomes were not significant; p>0.05, SUPPLEMENTARY TABLE, S1).
CONCLUSIONS

The Bright Bodies Program significantly decreased 2-hour glucoses in children at high risk for diabetes after 6 months in comparison to standard of care. We included subjects with 2-hour glucose levels between 130-139 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 beta cell function as youngsters with 2 hour glucose levels between 140- 199 mg/dl.6,7,8

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 to 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 kg versus >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 genders, 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 beta-cell function may have also contributed to metabolic improvement, insulin sensitivity is likely to have played a role in the lowering of two-hour 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 hour 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 pre-diabetes. The BB program also had a favorable effect on other cardio-metabolic risk factors.

The recent results of the TODAY and other studies have served to illustrate the challenges in managing T2D during adolescents. The success of our intensive life-style 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 Bright Bodies program in comparison to standard of care were sustained for up to 2 years, 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 pre-diabetes by more active OGTT screening. Although the OGTT is more labor-intensive and commitment-intensive for families, the use of the HgA1c as a more practical alternative lacks sensitivity in the pediatric population, particularly in a short-term study such as this. 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 United States 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 paper, we have completed such an analysis after an initial one-year efficacy trial and demonstrated that the program is cost-effective in spite of its intensity.

In summary, obese youth with altered glucose tolerance should be followed closely because of vulnerable \( \beta \)-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 non-pharmacological treatment approach that is free from serious side effects. Moreover, behavior modification strategies can have long-lasting positive effects.
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The authors state that there are no conflicts of interest. Ms. Savoye had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

MS designed and supervised the study and wrote the manuscript; SC helped design the study and contributed to the manuscript; JD helped design the study, analyzed the data, and contributed to the manuscript; AC, GG, and GS helped design the study and recruited subjects; FL analyzed the data and created tables/figures; MShaw obtained and managed data and edited manuscript; PN helped design the study and edited manuscript; RK managed data and created figures; FD helped design the study and edited manuscript; GK edited manuscript; and WVT helped design and supervised study and edited manuscript.
References


FIGURE 1. OGTT Data at Baseline and Follow-up Between BB and CC Groups

P value is from comparing area under curve (AUC 120) using t-test.

TABLE 1. Baseline characteristics of children randomized to intervention and control group

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>All Randomized Participants</th>
<th>Compliers</th>
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<tbody>
<tr>
<td></td>
<td>BB Group (n=38)</td>
<td>CC Group (n=37)</td>
</tr>
<tr>
<td>Demographic</td>
<td></td>
<td></td>
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<tr>
<td>Race, n (%)</td>
<td></td>
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<tr>
<td>Non-Hispanic White</td>
<td>12 (31.6)</td>
<td>13 (35.1)</td>
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<tr>
<td>Hispanic White</td>
<td>15 (39.5)</td>
<td>12 (32.4)</td>
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<tr>
<td>Black</td>
<td>11 (29.0)</td>
<td>10 (27.0)</td>
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<tr>
<td>Other</td>
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<td>2 (5.4)</td>
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<tr>
<td>Sex, n (%)</td>
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<td></td>
</tr>
<tr>
<td>Male</td>
<td>12 (31.6)</td>
<td>14 (37.8)</td>
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<tr>
<td>Female</td>
<td>26 (68.4)</td>
<td>23 (62.2)</td>
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<tr>
<td>Age, year</td>
<td>12.7(1.9)</td>
<td>13.2 (1.8)</td>
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<tr>
<td>Glucose and Insulin Metabolism</td>
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<tr>
<td>2 hr Glucose, mg/dL</td>
<td>153.6 (18.2)</td>
<td>148.6 (14.8)</td>
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<tr>
<td>2hr Insulin, µIU/mL ‡</td>
<td>269.2 (1.3)</td>
<td>302.0 (1.9)</td>
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<td>Fasting Glucose, mg/dL</td>
<td>92.9 (7.0)</td>
<td>92.4 (8.0)</td>
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<tr>
<td>Fasting Insulin, µIU/mL ‡</td>
<td>38.0 (1.6)</td>
<td>40.7 (1.6)</td>
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<tr>
<td>HOMA-IR ‡</td>
<td>8.7 (1.7)</td>
<td>9.3 (1.6)</td>
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<td>WBISI</td>
<td>1.2 (0.8)</td>
<td>1.1 (0.5)</td>
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<td>HgbA1c (%)</td>
<td>5.7 (0.4)</td>
<td>5.6 (0.4)</td>
</tr>
<tr>
<td>IG1</td>
<td>4.4 (3.3)</td>
<td>4.3 (2.4)</td>
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<tr>
<td>DIo</td>
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<td>4.2 (2.6)</td>
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<tr>
<td>Anthropometric</td>
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<tr>
<td>Weight, kg</td>
<td>83.7 (19.0)</td>
<td>92.0 (24.0)</td>
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<tr>
<td>Height, cm</td>
<td>160.9 (10.3)</td>
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<td>BMI</td>
<td>32.1 (5.2)</td>
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<td>2.2 (0.4)</td>
<td>2.3 (0.4)</td>
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<tr>
<td>% Body Fat</td>
<td>43.1 (6.3)</td>
<td>43.1 (7.4)</td>
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<tr>
<td>Fat Mass (kg)</td>
<td>36.3 (11.6)</td>
<td>40.9 (16.2)</td>
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<tr>
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<tr>
<td>Blood Pressure – Systolic, mmHg</td>
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<tr>
<td>Blood Pressure – Diastolic, mmHg</td>
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<tr>
<td>Cholesterol – Total, mg/dL</td>
<td>151.1 (34.0)</td>
<td>159.2 (35.9)</td>
</tr>
</tbody>
</table>
Mean (SD) are presented for baseline characteristics.

Data are presented as geometric means and geometric SDs.

HOMA-IR: Homeostasis Model Assessment of Insulin Resistance; WBISI: Whole Body Sensitivity Index; IGI: Insulinogenic Index; DIo: Disposition Index, oral

**TABLE 2.** Comparison of 6-month changes in outcomes between BB and CC groups. Adjusting for baseline outcome, weight, HgbA1c, HOMA-IR and DI.

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>BB Group</th>
<th>CC Group</th>
<th>Treatment Effect (BB – CC)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Glucose and Insulin Metabolism</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 hr Glucose, mg/dL</td>
<td>-27.2 (-35.2 to -19.1)</td>
<td>-10.1 (-18.4 to -1.8)</td>
<td>-17.1 (-29.0 to -5.1)</td>
<td>0.005</td>
</tr>
<tr>
<td>2 hr Insulin, µIU/mL‡</td>
<td>-108.6 (-137.9 to -73.4)</td>
<td>-15.7 (-66.2 to 46.6)</td>
<td>-92.9 (-131.2 to -43.9)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Fasting Glucose, mg/dL</td>
<td>-0.5 (-3.1 to 2.0)</td>
<td>2.5 (-0.7 to 5.7)</td>
<td>-3.0 (-7.3 to 1.2)</td>
<td>0.16</td>
</tr>
<tr>
<td>Fasting Insulin, µIU/mL‡</td>
<td>-4.9 (-10.0 to 1.1)</td>
<td>5.2 (-1.3 to 12.9)</td>
<td>-10.1 (-17.1 to 1.4)</td>
<td>0.03</td>
</tr>
<tr>
<td>HOMA-IR‡</td>
<td>-1.2 (-2.4 to 0.3)</td>
<td>1.4 (-0.3 to 3.4)</td>
<td>-2.6 (-4.3 to 0.4)</td>
<td>0.03</td>
</tr>
<tr>
<td>WBISI</td>
<td>0.41 (0.17 to 0.64)</td>
<td>-0.01 (-0.24 to 0.22)</td>
<td>0.42 (0.08 to 0.76)</td>
<td>0.02</td>
</tr>
<tr>
<td>HgbA1c</td>
<td>-0.16 (-0.27 to -0.05)</td>
<td>-0.05 (-0.17 to 0.07)</td>
<td>-0.11 (-0.27 to 0.05)</td>
<td>0.19</td>
</tr>
<tr>
<td>IGI</td>
<td>2.1 (-0.3 to 4.5)</td>
<td>-0.1 (-2.6 to 2.4)</td>
<td>2.2 (-1.2 to 5.6)</td>
<td>0.20</td>
</tr>
<tr>
<td>DIo</td>
<td>4.7 (0.5 to 8.8)</td>
<td>0.4 (-3.2 to 4.1)</td>
<td>4.2 (-0.8 to 9.3)</td>
<td>0.10</td>
</tr>
<tr>
<td><strong>Anthropometric</strong></td>
<td></td>
<td></td>
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<tr>
<td>-------------------</td>
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</tr>
<tr>
<td><strong>Weight, kg</strong></td>
<td>0.6 (-0.9 to 2.1)</td>
<td>3.7 (2.1 to 5.2)</td>
<td>-3.1 (-5.3 to -0.9)</td>
<td>0.006</td>
</tr>
<tr>
<td><strong>Height, cm</strong></td>
<td>1.9 (1.2 to 2.5)</td>
<td>1.7 (1.0 to 2.3)</td>
<td>0.1 (-0.7 to 1.0)</td>
<td>0.73</td>
</tr>
<tr>
<td><strong>BMI (kg/M²)</strong></td>
<td>-0.37 (-0.86 to -0.11)</td>
<td>0.67 (0.13 to 1.21)</td>
<td>-1.05 (-1.78 to -0.32)</td>
<td>0.005</td>
</tr>
<tr>
<td><strong>BMI-Z</strong></td>
<td>-0.05 (-0.09 to -0.01)</td>
<td>0.04 (0.00 to 0.08)</td>
<td>-0.09 (-0.14 to -0.04)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td><strong>Body Fat (%)</strong></td>
<td>-3.3 (-4.8 to -1.8)</td>
<td>0.4 (-1.5 to 2.4)</td>
<td>-3.8 (-6.3 to 1.3)</td>
<td>0.003</td>
</tr>
<tr>
<td><strong>Fat Mass (Kg)</strong></td>
<td>-2.7 (-4.5 to -0.9)</td>
<td>2.3 (-0.2 to 4.8)</td>
<td>-5.0 (-8.2 to 1.8)</td>
<td>0.002</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Cardiovascular</strong></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Blood Pressure – Systolic, mmHg</strong></td>
<td>-6.2 (-9.1 to -3.2)</td>
<td>-0.7 (-3.4 to 2.1)</td>
<td>-5.5 (-9.3 to 1.7)</td>
<td>0.005</td>
</tr>
<tr>
<td><strong>Blood Pressure – Diastolic, mmHg</strong></td>
<td>-0.9 (-8.4 to 6.6)</td>
<td>8.3 (-0.1 to 16.8)</td>
<td>-9.2 (-19.9 to 1.5)</td>
<td>0.09</td>
</tr>
<tr>
<td><strong>Cholesterol – Total, mg/dL</strong></td>
<td>-10.8 (-21.9 to 0.5)</td>
<td>-2.1 (-11.4 to 7.3)</td>
<td>-8.7 (-23.1 to 5.7)</td>
<td>0.24</td>
</tr>
<tr>
<td><strong>HDL, mg/dL</strong></td>
<td>-2.8 (-5.8 to 0.3)</td>
<td>-3.9 (-6.9 to 0.9)</td>
<td>1.1 (-3.1 to 5.3)</td>
<td>0.60</td>
</tr>
<tr>
<td><strong>LDL, mg/dL</strong></td>
<td>-1.3 (-9.5 to 6.9)</td>
<td>3.5 (-3.8 to 10.8)</td>
<td>-4.8 (-15.2 to 5.6)</td>
<td>0.37</td>
</tr>
<tr>
<td><strong>Triglycerides, mg/dL ‡</strong></td>
<td>-28.4 (-38.9 to -16.4)</td>
<td>-4.6 (-17.3 to 9.9)</td>
<td>-23.9 (-37.2 to 7.9)</td>
<td>0.005</td>
</tr>
<tr>
<td><strong>ALT</strong></td>
<td>-3.9 (-6.8 to 0.9)</td>
<td>-6.7 (-9.1 to 4.2)</td>
<td>2.8 (-0.9 to 6.6)</td>
<td>0.14</td>
</tr>
</tbody>
</table>

‡Data are presented as geometric mean