The Effect of the PREMIER Interventions on Insulin Sensitivity

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OBJECTIVE — This ancillary study of PREMIER sought to determine the effects on insulin sensitivity of a comprehensive behavioral intervention for hypertension with and without the Dietary Approaches to Stop Hypertension (DASH) dietary pattern.

RESEARCH DESIGN AND METHODS — Participants were assigned to one of three nonpharmacologic interventions for blood pressure (group A, advice only; group B, established; and group C, established plus DASH). The established intervention included weight loss, reduced sodium intake, increased physical activity, and moderate alcohol intake; the DASH dietary pattern was added to the established intervention for those in group C. The DASH dietary pattern is high in fruits, vegetables, and low-fat dairy products while being lower in total fat, saturated fat, and cholesterol. It is abundant in nutrients such as magnesium, calcium, and protein, which have been associated with improved insulin sensitivity. Insulin sensitivity was measured at baseline and at 6 months using the frequently sampled intravenous glucose tolerance test with minimal model analysis.

RESULTS — Both intervention groups decreased total calories, percentage of calories from fat, and sodium intake to similar levels, with similar amounts of energy expenditure and weight loss. Covariate differences seen only in group C included increased intake of protein, potassium, calcium, and magnesium. Compared with control subjects, insulin sensitivity improved significantly only in group C, from 1.96 to 2.95 ($P = 0.047$). Group B did have a significant decrease in fasting insulin and glucose, but the changes in insulin sensitivity did not reach statistical significance when compared with control subjects.

CONCLUSIONS — These results suggest that including the DASH dietary pattern as part of a comprehensive intervention for blood pressure control enhances insulin action beyond the effects of a comprehensive intervention that does not include DASH.

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Insulin resistance is associated with an increased risk of hypertension and coronary artery disease (1–4). Although there is no clear cause-and-effect relationship between insulin resistance and hypertension, there is definitive evidence that abnormal insulin sensitivity is associated with a higher prevalence of hypertension. Among individuals with essential hypertension, there is a high prevalence of insulin resistance (2,5,6). In addition, high levels of fasting insulin can predict the development of hypertension, as seen in the San Antonio Heart Study. Over 8 years of follow-up, those with fasting insulin in the highest quartile had a relative risk of developing hypertension of 2.04 ($P = 0.021$) (7).

High blood pressure is routinely treated with nonpharmacologic interventions that include weight loss, increased physical activity, sodium reduction, and decreased alcohol intake. Beyond their effects on blood pressure, each one of these interventions has a varied effect on insulin action, ranging from positive to negative or even no effect at all (8–12). With only 7 days or less of vigorous exercise, significant improvements in insulin sensitivity can be achieved (8). Weight loss of 10% of body weight has been shown to improve insulin sensitivity (9,10). Severe sodium reduction can worsen insulin action. Reduction of sodium intake from 200 to 100 mmol/day did not result in any significant changes in insulin sensitivity; however, further sodium reduction to 30 mmol/day resulted in decreased insulin sensitivity (11). A recent study (12) of the effects of reducing alcohol intake on insulin sensitivity showed no change in the insulin sensitivity index. Although these interventions are commonly combined for the management of hypertension, the aggregate effect of these interventions on insulin action has not been studied.

Another recommended nonpharmacologic intervention for lowering blood pressure is the Dietary Approaches to Stop Hypertension (DASH) dietary pattern (13). Unlike other nonpharmacologic interventions, the effect of the DASH dietary pattern on insulin sensitivity has not been studied in any randomized clinical trials, even though the profile of the DASH dietary pattern suggests that it should improve insulin action in humans. The DASH dietary pattern is distinctly different from typical American intake in several nutrients, including higher levels of potassium, magnesium, calcium, and fiber (14). Several studies in hypertensive and/or obese humans have demonstrated that diets low in these nutrients can lead to or are associated with insulin resistance, and dietary supplementation with calcium and magnesium improves insulin sensitivity (15–20). Because the DASH dietary pattern is higher in these nutrients, consumption of this dietary pattern may

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Abbreviations: CRU, Clinical Research Unit; DASH, Dietary Approaches to Stop Hypertension.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

lead to an improvement in insulin sensitivity independent of weight loss or physical activity.

As the DASH dietary pattern is implemented as a routine part of nonpharmacologic management of hypertension, it will be important to know the effects on insulin action of a comprehensive behavioral program that includes the DASH dietary pattern. If the addition of the DASH dietary pattern adds to a lifestyle intervention (i.e., weight loss, moderate sodium reduction, and increased physical activity) by increasing insulin sensitivity, such a finding would provide added evidence for the need to recommend the DASH dietary pattern as part of a comprehensive lifestyle intervention for treatment of hypertension and overall cardiovascular risk reduction. This study reports the effect of the PREMIER interventions on insulin sensitivity.

RESEARCH DESIGN AND METHODS

This study was ancillary to the PREMIER study, and as such, was designed, conducted, and analyzed by the coauthors only. It was approved by the Institutional Review Board of Duke University Medical Center. Details of the PREMIER study design, interventions, and results have been published elsewhere (21). In brief, PREMIER was a multicenter, randomized clinical trial that studied the effects of three different interventions designed to reduce blood pressure without medication.

Participants enrolled in the PREMIER study at the Duke clinical site were eligible to participate in this ancillary study. Eligibility requirements for the PREMIER study included age 25 years and older, above optimal blood pressure through stage 1 hypertension, and a BMI of 18.5–45 kg/m^2. Individuals that used antihypertensive medications, weight loss medications, or oral steroids on a routine basis were excluded. Other exclusion criteria included diabetes, a history of a cardiovascular event (stroke, myocardial infarction, percutaneous transluminal coronary angioplasty, coronary artery bypass grafting, or other therapeutic procedure for coronary heart disease), congestive heart failure, current symptoms of angina or peripheral vascular disease by Rose Questionnaire, cancer diagnosis or treatment in past 2 years (except for nonmelanoma skin cancer), renal insufficiency, or a psychiatric hospitalization within the last 2 years.

Interventions and data collection

There were three treatment arms in PREMIER: advice only (group A), established (group B), and established plus DASH (group C). Participants assigned to group A received advice at a single individual visit to follow the guidelines established by the National High Blood Pressure Educational Program for patients with above optimal blood pressure and stage 1 hypertension. These recommendations included weight loss if overweight, limiting alcohol and dietary sodium intake, regular physical activity, and eating a healthful diet. Group B had an intensive behavioral intervention during the study, which was focused on behavioral modification to control hypertension. During group and individual sessions, participants received counseling on low-sodium/low-fat diets, weight loss (if overweight, BMI ≥25 kg/m^2), moderating alcohol intake, and increasing physical activity. Intervention goals for group B included sodium intake of 2.4 g/day or less, 30% of calories from fat, weight loss of at least 15 pounds if overweight, and 180 min of moderate physical activity per week. Group C received a similar behavioral intervention; however, their counseling also included information about the DASH dietary pattern. Intervention goals for group C were similar to those of group B, with the exception of goals for 25% of calories from fat, with ≤7% of calories from saturated fat; 9–12 servings of fruits and vegetables per day; and 2–3 servings of low-fat dairy per day. The intervention meeting schedules for groups B and C were the same during the first 6 months—14 group sessions and 4 individual sessions. Clinical measurements including blood pressure, weight, fasting lipids, physical activity, and dietary intake were measured at baseline (before randomization) and after 6 months.

After participants completed screening and qualified for the PREMIER study at the Duke site, they were recruited into the insulin sensitivity ancillary study. Informed consent was obtained, and a baseline intravenous glucose tolerance test was completed at the Duke Clinical Research Unit (CRU) before randomization. At the end of 6 months, participants returned to the CRU to complete the follow-up intravenous glucose tolerance test. Participants were compensated $50 for each CRU visit.

Measurements

We assessed insulin sensitivity using the frequently sampled intravenous glucose tolerance test (22,23) with minimal model analysis (24). We used the reduced sampling protocol, which requires 12 samples of glucose and insulin. A 50% glucose solution at 0.3 g/kg and regular human insulin at 0.03 units/kg were injected through an intravenous line at 0 and 20 min, respectively. Blood (~4 ml) was collected at each of 12 intervals over a 3-h period (−5, 2, 4, 8, 19, 22, 30, 40, 50, 70, 100, and 180 min) through a second intravenous line. Participants fasted for 12 h before initiation of the testing. Serum glucose levels were measured on the Roche Cobas Mira Plus using the Hexokinase/G-6-PD methodology, and insulin levels were measured using a human insulin–specific radioimmunoassay kit (Linco Research, St. Louis, MO). An insulin sensitivity index (S_i) was calculated using the MINMOD program (version 2.0; R.N. Bergman, USC, Los Angeles, CA).

Certified study staff measured weight, height, and waist circumference using calibrated scales, wall-mounted stadiometers, and anthropometric measuring tape, respectively, according to the PREMIER study protocol. Blood pressure was measured at two clinic visits, using random-zero mercury sphygmomanometers with participants in the seated position for 5 min before measurement. Blood pressure was measured twice on each clinic visit with a 30-s rest period between each measurement. Nutrient intake was determined from two unannounced, nonconsecutive 24-h dietary recalls conducted by telephone. The Diet Assessment Center of Pennsylvania State University performed the recalls. The Nutrition Data System was used to generate the estimates of individual nutrient intake from the recalls. The 7-Day Physical Activity Recall (25,26) was used to assess physical activity. This questionnaire estimates total daily energy expenditure by asking participants to estimate the number of hours spent in sleep and in "moderate," "hard," and "very hard" activities during the previous 7 days. Hours spent doing "light activity" are calculated as the remaining time. The amount of time spent in each category is multiplied by the average metabolic equivalent (METs, or kcal · kg^{-1} ·

Table 1—*Baseline characteristics of the ancillary study population compared with all PREMIER participants*

	Insulin sensitivity participants	All PREMIER participants
n	52	810
Age (years)	51.7 ± 9.2	50 ± 8.9
Female	69.2	61.7
Race		
African American	30.7	34.4
Non-Hispanic white	67.3	63.1
BMI (kg/m^2)	32.6 ± 5.8	33.1 ± 5.8
Systolic blood pressure (mmHg)	137.5 ± 10.2	134.9 ± 9.6
Diastolic blood pressure (mmHg)	83.4 ± 4.3	84.8 ± 4.2
Hypertensive	36.5	37.5
Energy expenditure (kcal · kg^{-1} · day^{-1})	34.7 ± 5.9	33.7 ± 2.9
Education		
Completed high school	5.8	7.8
Some college	26.9	33.8
College degree	26.9	24.9
Post grad work	40.4	32.1

Data are means ± SD or percent.

h^{-1}) of each category and summed to calculate energy expenditure in terms of kcal · kg^{-1} · day^{-1}.

Statistical analysis

Sample size calculations were based on an estimated SD for the change in insulin sensitivity index (S_i min^{-1} · μU^{-1} · ml^{-1} × 10^{-4}) of 1.1, obtained from studies with similar populations of obese, sedentary, and hypertensive patients. Consistent with the main study design, the primary hypothesis for this ancillary study was that there would be a difference in the change in insulin sensitivity between each dietary intervention and the advice-only group (group B versus group A and group C versus group A). The secondary hypothesis was that there would be a difference in the change in insulin sensitivity between the active intervention groups (group C versus group B). Calculations indicated that ~18 participants in each group would be needed to detect a 50% difference in insulin sensitivity index, with 80% power at a significance level of 0.05. ANCOVA with the baseline measure as a covariate was used to compare the treatment groups with the control group for all outcomes. Pairwise comparisons between each treatment group and control as well as between treatment groups were tested using Fisher's protected least significant difference procedure (i.e., proceeding with post hoc comparisons only after establishing that the overall *F* statistic comparing all three groups simultaneously is significant) at the standard significance level of 0.05. All statistical analyses were based on intention to treat and conducted using the SAS System for Windows version 8.2 (SAS, Cary, NC).

RESULTS — A total of 55 participants had a baseline intravenous glucose tolerance test and were randomized to treatment groups in the PREMIER study. The results of the intravenous glucose tolerance tests were reviewed for outliers. We identified outliers by using standard boxplots and determining values that were 1.5 to 3 times the interquartile range. Once outliers were identified, the records from each participant's protocol were reviewed for any irregularities. Three participants identified as outliers had irregularities in their baseline measures of insulin sensitivity due to technical difficulties with the intravenous glucose tolerance test. This resulted in S_i values that significantly influenced respective group means. Consequently, the three participants were excluded from the analysis (one from each treatment group). Results are reported for the remaining 52 participants.

Baseline demographics for the study participants are presented in Tables 1 and 2. The sample of participants who chose to participate in the ancillary study was very similar to the overall PREMIER study population (Table 1). There were no significant differences between the participants based on their group assignments (Table 2).

Intervention results

Thirty percent of the participants in this sample achieved the 15-pound weight loss recommendation (A = 2, B = 5, and C = 9 participants). Twelve participants from group B (75%) decreased their percentage of calories from fat to ≤30%, while 8 participants from group C (44%) decreased their percentage of calories from fat to the DASH goal of ≤25%. Alcohol intake was low and did not change for any group. Table 3 shows some of the key intervention differences and similarities between treatment groups after 6 months of the intervention. All participants lowered their caloric intake. Groups B and C lowered their sodium and fat intake, decreasing both to lower levels than the intervention targets for their respective groups. Percentage of calories

Table 2—*Baseline characteristics of insulin sensitivity study participants by treatment group*

	Group A	Group B	Group C
n	18	16	18
Age (years)	49.9	51.6	53.6
Female (%)	66.7	75	66.7
Race (%)			
African American	16.7	37.5	38.9
Non-Hispanic white	77.8	62.5	61.1
BMI (kg/m^2)	32.8	31.1	33.7
Systolic blood pressure (mmHg)	137.5	138.9	136.1
Diastolic blood pressure (mmHg)	83.3	84.2	82.9
Hypertensive (%)	38.9	37.5	33.3
Energy expenditure (kcal · kg^{-1} · day^{-1})	34.0	33.8	36.1

Table 3—*Nutrient outcomes*

Outcome	A	B	C	*P* value for overall group comparison*	B–A	C–A	C–B
Calories (kcal)							
Baseline	2,072.84 ± 645.13	1,928.79 ± 650.30	1,940.08 ± 657.06	0.002	−196.03 (0.2134)	−170.36 (0.2559)	25.67 (0.869)
6 Months	1,826.51 ± 616.96	1,569.24 ± 507.18	1,599.71 ± 406.78				
Change	−246.33 ± 751.74	−359.55 ± 342.17	−340.37 ± 524.88				
Fat intake (g/day)							
Baseline	81.29 ± 31.83	68.50 ± 38.55	72.25 ± 34.92	<0.001	−17.19 (0.0070)	−19.96 (0.0012)	−2.76 (0.649)
6 Months	66.54 ± 24.37	44.83 ± 19.33	43.39 ± 18.78				
Change	−14.76 ± 33.14	−23.67 ± 24.84	−28.86 ± 25.70				
Sodium (mg/day)							
Baseline	3,351.46 ± 1,093.50	3,139.71 ± 1,365.99	3,101.00 ± 1,516.40	<0.001	−833.59 (0.0025)	−744.86 (0.0044)	88.73 (0.735)
6 Months	2,793.54 ± 993.47	1,891.38 ± 777.62	1,970.49 ± 757.12				
Change	−557.93 ± 1,291.95	−1,248.33 ± 911.14	−1,139.51 ± 1,215.93				
Soluble fiber (g/day)							
Baseline	6.54 ± 2.84	6.44 ± 3.25	6.04 ± 2.40	0.004	0.15 (0.8262)	0.37 (0.5722)	0.219 (0.754)
6 Months	6.78 ± 2.39	6.87 ± 3.50	6.83 ± 2.19				
Change	0.25 ± 2.11	0.43 ± 1.99	0.79 ± 2.39				
Calories from fat (%)							
Baseline	34.66 ± 5.98	30.84 ± 9.72	32.14 ± 6.90	<0.001	−5.49 (0.0104)	−8.02 (0.0001)	−2.52 (0.217)
6 Months	32.92 ± 7.24	25.49 ± 6.62	23.62 ± 6.66				
Change	−1.74 ± 5.89	−5.34 ± 8.19	−8.52 ± 6.41				
Animal protein (g/day)							
Baseline	54.89 ± 22.56	49.41 ± 28.24	46.94 ± 24.70	<0.001	−8.25 (0.5726)	11.03 (0.0502)	14.289 (0.016)
6 Months	47.99 ± 17.10	43.05 ± 18.26	56.58 ± 18.36				
Change	−6.90 ± 25.99	−6.36 ± 21.11	9.64 ± 23.34				
Potassium (mg/day)							
Baseline	2,834.03 ± 1,051.73	2,974.23 ± 1,219.53	2,503.69 ± 1,056.85	<0.001	−133.51 (0.6465)	653.45 (0.0229)	786.95 (0.01)
6 Months	2,767.90 ± 840.06	2,703.68 ± 1,133.72	3,258.10 ± 982.37				
Change	−66.13 ± 894.85	−270.55 ± 767.8	754.41 ± 1,218.18				
Magnesium (mg/day)							
Baseline	298.15 ± 116.13	295.25 ± 122.80	261.93 ± 105.77	<0.001	−9.46 (0.7527)	52.04 (0.0762)	61.497 (0.046)
6 Months	288.33 ± 85.91	277.45 ± 127.09	322.65 ± 91.15				
Change	−9.82 ± 104.63	−17.80 ± 97.51	60.73 ± 104.98				
Calcium (mg/day)							
Baseline	936.29 ± 435.89	756.71 ± 342.36	738.65 ± 393.42	<0.001	−13.18 (0.9060)	196.25 (0.0715)	209.42 (0.061)
6 Months	759.08 ± 350.70	665.54 ± 412.77	866.89 ± 307.03				
Change	−177.22 ± 386.36	−91.16 ± 379.88	128.24 ± 368.58				

Data are means ± SD or difference (*P* value). Contrasts are adjusted for baseline differences. **P* values are generated from an *F* statistic comparing all groups simultaneously in an ANCOVA model.

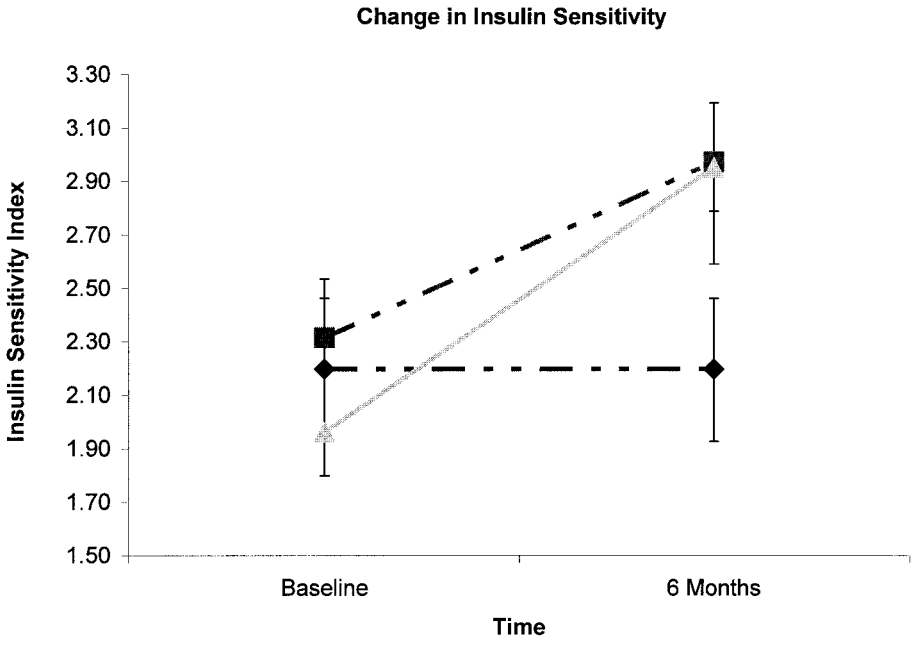

Figure 1—*Change in insulin sensitivity.* ◆, *group A;* ■, *group B;* ▲, *group C.*

from fat for group B was 25, while group C decreased their calories from fat to 23.6%. Sodium intake was reduced from ~3,100 to 1,900 mg/day. Dietary fiber increased marginally in both B and C. Dietary potassium intake, a key component of the DASH dietary pattern, was higher for group C at 6 months, while the average potassium intake for group B decreased. Dietary magnesium, calcium, and protein, which are also key DASH diet nutrients, showed similar patterns to dietary potassium.

Insulin sensitivity

Figure 1 depicts the increase in insulin sensitivity associated with the established plus DASH intervention (group C). Table 4 shows the magnitude of this effect. Group C had a 50% increase in S_i from baseline over the 6-month intervention period, whereas group B had a 28% increase in S_i from baseline ($P = 0.047$ for C vs. A, $P = 0.146$ for B vs. A). Groups B and C had similar S_i measures at the end of the 6-month follow-up. However, after adjusting for baseline differences, Group C showed a 35% greater increase in S_i compared with group B (0.616). Fasting insulin and glucose also changed differentially, with group B having larger decreases than group C in both measures compared with group A. Despite the fact that the absolute decreases in insulin and glucose were larger for group B, the ratio of change for insulin to glucose (change in insulin divided by change in glucose) was ~1:1. For group C, the ratio of change for insulin to glucose was nearly 3:1. This ratio suggests that as a result of the increased effectiveness of the circulating insulin, participants were able to maintain a slightly lower fasting glucose even though they had lower serum insulin. Table 4 also shows that, relative to the usual care group, both groups experienced similar amounts of weight loss (B vs. C, 5.69 vs. 6.56 kg, respectively) and small increases in energy expenditure. Waist circumference decreased for the two active treatment groups. While group B had a mean decrease in waist circumference of 5.5 cm ($P = 0.06$) compared with group A, group C had a mean decrease of 7.96 cm ($P = 0.005$) compared with group A. The differences in weight loss and waist circumference between group B and group C were not statistically significant ($P = 0.672$ and 0.399, respectively).

CONCLUSIONS — Because insulin resistance and hypertension are closely associated, understanding the impact of nonpharmacologic therapy for hypertension on insulin action has important implications for cardiovascular health. Until this study, the nonpharmacologic interventions recommended by the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC) reports VI and VII had not been tested to determine their combined impact on insulin action. The addition of the DASH dietary pattern to these recommendations and its impact on insulin action had not been studied either. We were able to show that a comprehensive behavioral intervention targeted at achieving established recommendations (group B), i.e., weight loss of at least 15 pounds, 180 min of moderate physical activity per week, a sodium intake of 2.4 g/day, and a low-fat diet (30% of calories from fat), improved fasting insulin and glucose. These changes in fasting insulin and glucose did not result in improvements in insulin sensitivity to a level that was statistically different from an advice-only control group. However, the addition of the DASH dietary pattern to this behavioral intervention (group C) led to a statistically significant improvement in insulin sensitivity compared with the control group. Both groups had similar weight loss (5.69 vs. 6.56 kg), calories from fat (25.49 vs. 23.62%), total calories (1,569 vs. 1,599 kcal), sodium intake (1,891 vs. 1,970 mg/day), and energy expenditure (34.3 vs. 36.3 kcal · kg^{-1} · day^{-1}). The established plus DASH intervention group had higher intakes of protein and potassium as compared with the control group. Other key DASH nutrients such as magnesium and calcium were higher for the established plus DASH group but did not reach statistical significance when compared with the control group.

Table 4—*Primary/secondary outcomes*

Outcome	A	B	C	*P* value for overall group comparison*	B–A	C–A	C–B
Insulin sensitivity index							
Baseline	2.20 ± 1.13	2.32 ± 0.65	1.96 ± 0.94	0.022	0.69 (0.146)	0.93 (0.047)	0.24 (0.616)
6 Months	2.20 ± 1.12	2.97 ± 1.74	2.95 ± 1.62				
Change	0 ± 1.06	0.66 ± 1.63	0.99 ± 1.39				
Systolic blood pressure (mmHg)							
Baseline	137.47 ± 10.81	138.94 ± 10.65	136.13 ± 9.49	0.135	−2.98 (0.3122)	−6.36 (0.0294)	−3.38 (0.256)
6 Months	127.27 ± 12.81	125.74 ± 14.37	119.57 ± 12.60				
Change	−10.2 ± 6.36	−13.2 ± 9.56	−16.55 ± 9.07				
Diastolic blood pressure (mmHg)							
Baseline	83.29 ± 4.41	84.16 ± 4.46	82.90 ± 4.31	0.357	−0.22 (0.9253)	−3.26 (0.1495)	−3.04 (0.194)
6 Months	77.83 ± 7.19	78.54 ± 8.96	74.15 ± 8.19				
Change	−5.46 ± 4.64	−5.62 ± 8.17	−8.75 ± 6.78				
Weight (kg)							
Baseline	94.19 ± 21.55	88.61 ± 22.70	93.18 ± 18.11	0.008	−5.69 (0.0077)	−6.56 (0.0044)	−0.871 (0.672)
6 Months	93.02 ± 22.07	82.20 ± 22.31	85.53 ± 14.81				
Change	−1.18 ± 3.16	−6.4 ± 6.21	−7.65 ± 7.75				
Waist circumference (cm)							
Baseline	109.40 ± 16.23	103.26 ± 14.37	109.93 ± 13.02	0.040	−5.50 (0.0628)	−7.96 (0.0051)	−2.46 (0.399)
6 Months	110.37 ± 19.07	99.05 ± 16.65	102.92 ± 11.60				
Change	0.97 ± 7.04	−4.22 ± 9.56	−7.01 ± 7.70				
BMI (kg/m^2)							
Baseline	32.85 ± 6.31	31.49 ± 5.96	33.72 ± 5.24	0.009	−1.95 (0.0090)	−2.29 (0.0016)	−0.333 (0.646)
6 Months	32.45 ± 6.67	29.23 ± 6.15	30.98 ± 4.44				
Change	−0.40 ± 1.09	−2.26 ± 2.12	−2.75 ± 2.66				
Estimated energy expenditure ($kcal \cdot kg^{-1} \cdot day^{-1}$)							
Baseline	33.95 ± 2.07	33.83 ± 2.75	36.10 ± 9.42	0.0566	0.16 (0.8593)	0.26 (0.7702)	0.098 (0.914)
6 Months	34.26 ± 1.96	34.32 ± 1.91	36.30 ± 8.97				
Change	−0.31 ± 1.79	−0.49 ± 3.24	−0.20 ± 3.08				
Fasting insulin (μU/ml)							
Baseline	16.65 ± 9.05	14.14 ± 5.23	15.65 ± 7.99	0.0941	−6.32 (0.0144)	−3.81 (0.1105)	2.51 (0.315)
6 Months	18.41 ± 12.55	10.00 ± 3.35	13.76 ± 8.84				
Change	1.76 ± 7.45	−4.14 ± 5.88	−1.88 ± 6.98				
Fasting glucose (mg/dl)							
Baseline	104.94 ± 16.31	102.25 ± 12.16	102.11 ± 9.63	<0.0001	−6.64 (0.0215)	−1.32 (0.6297)	5.32 (0.06)
6 Months	100.50 ± 9.41	93.00 ± 5.97	98.28 ± 10.74				
Change	−4.44 ± 11.56	−9.25 ± 14.27	−3.83 ± 9.91				

Data are means ± SD or difference (*P* value). Contrasts are adjusted for baseline differences. **P* values are generated from an *F* statistic comparing all groups simultaneously in an ANCOVA model.

Few studies have evaluated the effect of providing nutrient supplementation to improve insulin action. Using the euglycemic-hyperinsulinemic clamp, Sanchez et al. (19) found that 1,500 mg/day of oral calcium provided as supplements to nondiabetic, essential hypertension patients improved the S_i from 2.89 to 4.0 $mg \cdot kg^{-1} \cdot min^{-1}$. Paolisso et al. (15) demonstrated that magnesium supplementation improved insulin action in elderly patients. Using 4.5g/day of oral magnesium for 4 weeks, the elderly patients had improved insulin action measured by the euglycemic glucose clamp (15). There is also a small amount of published data that implies the potential effects of dietary potassium and protein on insulin action. A study by Norbiato et al. (27) suggested that maintaining normal potassium levels using oral supplementation during a fast led to improved peripheral glucose utilization. Piatti et al. (28) compared a 45% protein diet with one that contained 20% protein and determined that the lower protein diet led to a larger decrease in fat-free mass, whereas the higher protein diet preserved fat-free mass and was associated with improved glucose utilization and insulin action.

The DASH dietary pattern is not based on any one nutrient; however, it utilizes a healthy array of food sources that contain a combination of the aforementioned nutrients to create a synergistic effect on cardiovascular disease risks such as blood pressure, serum homocysteine, and lipids (29–31). The results of this study suggest that the DASH dietary pattern, when incorporated into a multicomponent behavioral intervention, also improves insulin sensitivity. As a part of the DASH intervention, group C participants had higher intakes of fruits, vegetables, low-fat dairy, and lean protein,

leading to higher intakes of potassium, magnesium, calcium, and animal protein. The increased fruit and vegetable intake contributed dietary potassium, magnesium, and fiber. In addition, the increase in fruit and vegetable intake allowed participants to displace foods from energy-dense sources, thereby decreasing fat intake. The low-fat dairy and calcium intake may have been important from a weight loss standpoint as well, as evidence grows in support of a role for calcium in the regulation of adiposity (32,33). The increase in lean protein may have served to preserve lean mass during weight loss, leading to improvements in glucose disposal (28). This combination of foods and nutrients may have an effect on a variety of different cellular targets that ultimately promotes changes in body composition during weight loss, resulting in a favorable impact on insulin action. This hypothesis may account for the unexpected differences we observed between groups B and C in key areas that impact insulin sensitivity. These included differences in weight loss (0.87 kg, $P = 0.67$), BMI (0.34 kg/m^2, $P = 0.64$), and waist circumference (2.46 cm, $P = 0.39$). Although the differences were not statistically significant, the combination of these differences may have a clinically significant impact on insulin action.

One significant limitation of this study is that the changes in insulin action seen with the comprehensive intervention alone may be clinically important changes; however, the study was not powered to detect this degree of change in insulin sensitivity. On the other hand, the large change seen in insulin sensitivity with the comprehensive plus DASH intervention suggests that as we make recommendations for behavior modification to improve cardiovascular health, we must give special consideration to the dietary pattern. Simply employing a low-fat hypocaloric diet with the overall goal of improving cardiovascular health as a result of weight loss may not be the optimal strategy. Another limitation of this study concerns the use of two nonconsecutive dietary recalls to estimate nutrient intake. While the 24-h dietary recall is a reliable methodology to estimate nutrient intake for large cohorts, this procedure will have less accuracy for a smaller subset of that population. However, we have noted that the changes in nutrient profiles were similar to what would be expected for individuals within their respective dietary interventions, and the participants in this ancillary study had changes in nutrient intake similar to the overall study sample from which they were recruited.

This study demonstrates that there are additional benefits that patients can receive if the proper dietary regimen is prescribed. Because many patients will have a difficult time modifying behavior in the short term and maintaining the new behaviors long term, it is extremely important that we determine the dietary strategies that provide optimal results for a given effort. The findings from this study suggest several areas of future investigation that include determining the potential mechanism of action for improvements in insulin action seen with the DASH dietary pattern and evaluating the impact of the DASH dietary pattern on progression of impaired fasting glucose to diabetes. Based on the results of this study, including the DASH dietary pattern as a basic part of a hypocaloric dietary plan can lead to significant improvements of up to 50% in insulin sensitivity.

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