Background: Patients with high blood pressure (BP) often exhibit syndrome X, an aggregation of abnormalities in carbohydrate and lipoprotein metabolism associated with increased risk of coronary heart disease (CHD). The present study evaluated the effects of a 6-month intervention involving either aerobic exercise training alone (EX only) or exercise combined with a structured weight loss program (EX+WL) on CHD risk factors associated with syndrome X.

Methods: A total of 53 men and women were selected from a larger behavioral intervention trial, who showed the hyperinsulinemia, dyslipidemia, and high BP characteristic of syndrome X. Participants were randomly assigned to EX only (n=21), EX+WL (n=21), or a waiting list control group (n=11). Before and following treatment, participants underwent measurement of glucose tolerance, lipid levels, and clinical BP.

Results: Hyperinsulinemic responses to glucose challenge were significantly reduced in both the EX+WL group ($P < .001$) and the EX-only group ($P = .003$). Participants who showed the largest amount of weight loss showed the most robust improvements in abnormal insulin responses (EX+WL group, 47% reduction; EX-only group, 27% reduction). Diastolic BP was significantly reduced in the EX+WL group (96±4 to 87±5 mm Hg [mean±SD]; $P = .01$), but not in the EX-only group (93±4 to 89±5 mm Hg [mean±SD]; $P = .08$). Lipid profile was not significantly improved by either intervention.

Conclusion: These results suggest that EX+WL is an effective treatment for hyperinsulinemia and lowering of diastolic BP in patients with the syndrome X.

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lism and lowers BP in men and women with elevated BP. The present study focuses on the effects of EX+WL in a subgroup of patients from this sample, who were characterized by dyslipidemia and elevated 2-hour hyperinsulinemic responses to the oral glucose challenge characteristic of syndrome X. The specific goals of the present study were (1) to compare the effects of EX only and EX+WL on hyperinsulinemia, dyslipidemia, and BP in patients with syndrome X and (2) to examine the degree of aerobic fitness or weight loss necessary to improve hyperinsulinemic responses and dyslipidemia.

METHODS

STUDY SAMPLE

The present study was part of a larger study designed to examine the effects of EX+WL on high BP in patients meeting The Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-VI) criteria for high-normal BP or stage 1 to 2 hypertension. Of this sample, 83% showed BP in the hypertensive range (140-179/90-109 mm Hg) and the remaining 18% had high-normal BP (130-139/85-89 mm Hg). Participants were selected from the larger study sample if they met the following criteria: (1) plasma insulin concentration greater than 80 µU/mL (≥556 pmol/L) 2 hours after the ingestion of 75 g of glucose; (2) dyslipidemia, as defined by high triglyceride levels (≥150 mg/dL [≥1.7 mmol/L]) and/or low HDL-C levels (men, ≤40 mg/dL [≤1.04 mmol/L]; women, ≤50 mg/dL [≤1.3 mmol/L]). As found in previous studies, syndrome X was common in the original sample of hypertensive patients, with approximately 41% (53 of 130) showing dyslipidemia and prolonged insulin responses to oral glucose (mean ± SD insulin concentration at 2-hour post–glucose loading in the selected group was 145 ± 83 µU/mL [1007 ± 576 pmol/L] and in the nonselected group, 51 ± 24 µU/mL [394 ± 167 pmol/L]).

All volunteers were recruited by regional postings and newspaper advertisements. Recruitment criteria excluded individuals younger than 29 years and individuals who engaged in regular aerobic exercise or whose body mass index (calculated as weight in kilograms divided by the square of height in meters) was less than 25. Additional reasons for patient exclusion included history of diabetes, cardiac disease, renal disease, high-grade arrhythmias, chronic obstructive pulmonary disease, orthopedic problems that would preclude exercise, major psychiatric comorbidity, use of any medications known to affect the cardiovascular system (eg, antihistamines and decongestants), or a history of drug abuse or alcoholism. Initial screening procedures included a medical history review and physical examination to rule out secondary hypertension and contraindications to exercise. Participants currently treated for hypertension were included only after antihypertensive medications had been discontinued for at least 6 weeks. All patients read and signed a consent form approved by the Duke University Medical Center Institutional Review Board.

STUDY DESIGN

Patients underwent assessment of BP, lipid level, diet, aerobic fitness, body composition, and glucose tolerance at baseline and after the 6-month intervention. Blood pressure was assessed on 3 separate occasions at 1-week intervals using a stethoscope, random zero sphygmomanometer, and an occlusion cuff of appropriate size. During each session, resting seated BP was taken in triplicate by a trained technician. Following completion of all baseline assessments, subjects were randomized to 1 of 3 treatment conditions for a period of 6 months: (1) EX only, (2) EX+WL, and (3) waiting list control.

GLUCOSE TOLERANCE TESTING

Participants fasted overnight, following which a venous catheter was inserted and blood drawn for assessment of fasting plasma glucose and insulin. Glucose, 75 g, was administered orally, and samples for assessment of plasma glucose and insulin were obtained at 30-minute intervals for 3 hours. For the oral glucose tolerance test (OGTT), glucose was analyzed by Olympus AU 800 (Olympus, Melville, NY, and Irving, Tex). Plasma insulin was analyzed by insulin-specific radioimmunoassay (Linco Research, Inc, St Charles, Mo); mean coefficient of variance for within and between assay variation was 3.2% and 3.9%, respectively.

DIET, WEIGHT, AND BODY COMPOSITION ASSESSMENT

Assessment of dietary content was obtained at baseline and at the conclusion of the intervention. Patients recorded all food intake over 4 consecutive days in a diet diary that was analyzed for caloric and nutritional content using Nutritionist IV software (N-Squared Computing, Salem, Ore). Body fat measurements were performed using the BIA-101Q (Quantum, Highland Heights, Ohio) bioelectrical impedance analyzer in conjunction with bioelectrical impedance analyzer interpretation software (BjL Systems, Inc, Clinton Township, Mich). Fat-free mass was calculated as body weight minus fat mass. Measurements were conducted between 1500 and 1700 hours at ambient temperature using standard right-sided, tetrapolar electrode placement with each subject in a supine position. All participants refrained from food and water for the 3 hours prior to body fat assessment.

Plasma triglycerides, HDL-C, and total cholesterol were measured enzymatically (Lab Corp, Research Triangle Park, NC). High-density lipoprotein cholesterol was estimated by assay of the supernatant remaining after precipitation of serum low-density lipoprotein (LDL) and very-low-density lipoprotein (VLDL) with dextran sulfate plus magnesium chloride. The following equation was used to estimate LDL-C:

\[ \text{LDL (mg/dL)} = [\text{Total Cholesterol (mg/dL)} - \text{HDL (mg/dL)} - \text{Plasma Triglycerides (mg/dL)})]/5 \]

The reported values for plasma lipids are the means from blood samples drawn on 2 separate days under fasting conditions.

MEASUREMENT OF MAXIMAL OXYGEN CONSUMPTION

Maximal oxygen consumption \( (\dot{V}_O_2 \text{max}) \) was determined by exercise stress testing using the Duke-Wake Forest protocol, in which graded exercise began at 3.2 km/h (2.0 miles/h) and 0% grade and workload was increased at a rate of 1 MET/min (MET is the ratio of the metabolic rate during exercise to the metabolic rate at rest). Expired gases were collected for determination of \( \dot{V}_O_2 \text{max} \) using a SensorMedics Metabolic Cart (SensorMedics, Yorba Linda, Calif). To control for differences in fat-free mass, \( \dot{V}_O_2 \text{max} \) is expressed in units of milliliter per kilogram of fat-free mass per minute. Blood pressure was obtained at each workload using a SunTech 4240 BP monitor (Suntech Medical instruments, Raleigh, NC).
INTERVENTIONS

EX-Only Group

Participants exercised 3 to 4 times per week for 26 weeks at a level of 70% to 85% of their initial heart rate reserve determined at the time of the baseline treadmill test. The exercise routine consisted of 10 minutes of warm-up exercises, 35 minutes of cycle ergometry or walking (and eventually jogging), and 10 minutes of cool-down exercises. Most patients spent the 35-minute exercise period walking or jogging; however, any patient with musculoskeletal complaints was allowed to cycle during the full exercise period. The main emphasis was placed on maintaining heart rates at or above target heart rates for at least 30 minutes. All patients were instructed in how to monitor their radial pulses, and a trained exercise physiologist supervised all exercise sessions and performed checks of heart rate at 10-minute intervals to ensure that patients were exercising at a sufficient intensity. Participants were instructed to maintain their usual diets.

EX+WL Group

Patients exercised 3 to 4 times per week using the identical protocol as described in the EX-only group. In addition, patients participated in a weight management program in small groups of 3 to 4 members. The weight management program was a behavioral intervention based on the LEARN manual, which focuses on 5 elements: lifestyle, exercise, attitudes, relationships, and nutrition. The primary goal of the intervention was a weight loss of 0.5 to 1 kg per week, achieved gradually by decreasing calorie and fat intake throughout the entire period. Initial dietary goals were set at approximately 1200 cal for women and 1500 cal for men, with about 15% to 20% of calories coming from fat.

The program format consisted of approximately 26 weekly sessions. Record keeping was a key part of the intervention, and meetings started with each participant recording their weight. This was followed by a review of each member’s food diary and behavior modification targets from the previous week. During the last part of each session, goals for the coming week were developed for each member and strategies to help achieve these goals were assigned.

Waiting List Control

Patients were asked to maintain their usual dietary and exercise habits for 6 months until they were reevaluated. Compliance was monitored monthly, and any patient who reported diet or exercise modifications was encouraged to return to their normal dietary and exercise habits.

DATA ANALYSIS

Baseline differences among treatment groups were assessed using 1-way analysis of variance or continuous variables and χ² tests for categorical variables. Treatment effects were evaluated using a 1-way analysis of covariance, with posttreatment value serving as the dependent variable, pretreatment value as the covariate, and treatment group as the between-subjects factor. Separate analysis of covariance models were evaluated for each variable. Significant findings were evaluated using the Tukey honestly significant difference test to compare each treatment group with the control group, and to compare the EX group with the EX+WL group. The relationship between continuous variables was assessed using correlation analyses. Multiple regression analysis was used to evaluate the independent effects of fitness and weight loss on the insulin responses to glucose.

RESULTS

ADHERENCE

Of the 53 subjects, 41 completed the full intervention (67% of the EX-only group, 76% of the EX+WL group, and 100% of the control group); these 41 subjects were the focus of the present study. There were no differences in baseline characteristics between those who completed the study and those who dropped out of the study prematurely.

Participants who completed the full 26-week exercise program in the EX-only group exercised an average of 3.4 times each week, attending an average of 88 exercise training sessions; no difference in exercise frequency was observed between the EX-only group and the EX+WL group. Both groups exercised at or above their target heart rate training range most of the time (EX only, 90% of time; EX+WL, 86% of time).

Participants who completed the 26-week EX+WL program consumed less fat compared with the control group (P = .03) or the EX-only group (P < .001), and consumed fewer calories compared with the EX-only group (P = .05). Compared with pretreatment levels, estimated daily calorie consumption was reduced by approximately 25% in the EX+WL group and fat consumption was reduced by approximately 50%. Approximately 80% of participants in the EX+WL group reduced their calorie consumption by 15% to 45% and their fat consumption by 35% to 75%.

The control group maintained their dietary and exercise habits, as indicated by monthly adherence ratings as well as by the lack of change in daily calorie, fat, protein, and carbohydrate intake (Table 1) and the lack of change in VO₂max (Table 2) at the end of the 6-month waiting period. There were also no changes in medication use over the 6-month period in the control group.

RESPONSE TO EXERCISE AND WEIGHT LOSS PROGRAMS

Comparisons of the effects of group assignment showed that posttreatment VO₂max, weight, body mass index, waist circumference, and hip circumference were lower in both treatment groups compared with the control group. The degree of improvement in VO₂max was statistically similar in the 2 treatment groups, but the degree of weight loss and change in body mass index was greater in the EX+WL group than in the EX-only group (Table 2). There were no significant differences between the 3 groups in posttreatment percent body fat, waist-hip ratio, peak heart rate, or peak BP.

Comparison of treatment effects revealed that posttreatment 2-hour insulin concentration was significantly reduced in both the EX group (P = .003) and the EX+WL group (P < .001) compared with the control group (Table 2). Compared with pretreatment levels, the 2-hour insulin response to oral glucose was reduced by
Table 1. Effects of Treatment on Dietary Variables

<table>
<thead>
<tr>
<th></th>
<th>EX Only (n = 14)</th>
<th>EX + WL (n = 14)</th>
<th>Control (n = 9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pretreatment</td>
<td>Posttreatment</td>
<td>Pretreatment</td>
<td>Posttreatment</td>
</tr>
<tr>
<td>Protein, g</td>
<td>89 ± 6</td>
<td>103 ± 9</td>
<td>82 ± 6</td>
</tr>
<tr>
<td>Carbohydrates, g</td>
<td>281 ± 19</td>
<td>290 ± 21</td>
<td>251 ± 65</td>
</tr>
<tr>
<td>Fat, g</td>
<td>83 ± 7</td>
<td>92 ± 10</td>
<td>86 ± 5</td>
</tr>
<tr>
<td>Energy, cal</td>
<td>2221 ± 109</td>
<td>2403 ± 157</td>
<td>2038 ± 227</td>
</tr>
</tbody>
</table>

Abbreviations: EX, exercise; WL, weight loss.
*Values represent the mean ± SEM.
†Change from initial value different from EX-only group at P < .05.
‡Change from initial value different from control group at P < .05.

Table 2. Effects of Treatment on Outcome Variables

<table>
<thead>
<tr>
<th></th>
<th>EX Only (n = 14)</th>
<th>EX + WL (n = 14)</th>
<th>Control (n = 9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pretreatment</td>
<td>Posttreatment</td>
<td>Pretreatment</td>
<td>Posttreatment</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>140 ± 10</td>
<td>133 ± 11</td>
<td>130 ± 10</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>96 ± 4</td>
<td>89 ± 5</td>
<td>94 ± 5</td>
</tr>
<tr>
<td>BMI</td>
<td>32.3 ± 3.1</td>
<td>31.6 ± 3.3†</td>
<td>31.9</td>
</tr>
<tr>
<td>% Body fat</td>
<td>33 ± 6</td>
<td>32 ± 9</td>
<td>31 ± 9</td>
</tr>
<tr>
<td>Energy, cal</td>
<td>2277 ± 145</td>
<td>1717 ± 110†‡</td>
<td>2038 ± 227</td>
</tr>
</tbody>
</table>

27% in the EX-only group and by 47% in the EX + WL group. Although there were no significant effects of treatment on 2-hour glucose response to the OGTT, the group who also participated in the weight management program showed a significantly lower glucose response at 30 minutes (P = .02), 60 minutes (P = .02), and 90 minutes (P = .01) post–glucose loading, and tended to show a decreased glucose response at 2-hour post–glucose loading (P = .10), relative to the control group. Posttreatment cholesterol, triglyceride, LDL-C, and HDL-C levels were not significantly different in the active treatment groups compared with the control group (Table 2).

Comparison of posttreatment mean values revealed a significant reduction in diastolic BP (DBP) for the active treatments groups (P < .001) and a marginally significant reduction for systolic BP (SBP) (P = .09). Planned contrasts revealed that the EX + WL group had significantly lower DBP compared with the control group (P = .01); however, posttreatment DBP was not significantly different from controls in the EX-only group (P = .08). Participants in the EX + WL group showed an average reduction in SBP/DBP of 9/9 mm Hg compared with an average reduction of 7/5 mm Hg in the EX-only group and a 3/0 mm Hg reduction in the control group.

Multiple regression analyses of the pooled data (EX-only, EX + WL, and control patients combined) showed that improved VO₂max and reduced body weight independently predicted improvement in hyperinsulinemic OGTT responses (VO₂max change, β = −0.37 [P < .01]; weight change, β = 0.52 [P < .001]). Degree of improvement in VO₂max was correlated with degree of improvement in the 2-hour insulin response (r = −0.61; P < .001) and degree of reduction in DBP (r = −0.38; P = .04) and marginally correlated with improvement in SBP (r = −0.33; P = .07). Improvement in lipid levels was not related to improved VO₂max (cholesterol, r = −0.21 [P = .26]; triglycerides, r = −0.12 [P = .52]; LDL-C, r = 0.12 [P = .51]; and HDL-C, r = −0.10 [P = .56]). In contrast, the degree of weight loss was correlated with the improvement in 2-hour insulin responses (r = 0.61; P < .001), the change in DBP (r = 0.38; P < .001) and SBP (r = 0.37; P = .02), as well as the improvement in cholesterol (r = 0.33; P = .04).
LDL-C ($r=0.34; P=.04$), and triglycerides ($r=0.37; P=.02$). Weight loss was unrelated to improved HDL-C ($r=-0.20; P=.20$).

A tertile split of the pooled data based on percent change in weight showed that weight loss was linearly related to improvement in hyperinsulinemia ($P<.001$), with post hoc analysis showing significantly larger effects with increasing tertile of weight loss (Figure 1). The amount of weight loss required to achieve maximal improvements was marked; patients in tertile 3 (ie, with the greatest weight loss) lost an average of 11 kg (range, 6-19 kg). Most patients from this tertile (12/14) underwent EX+WL and exercised an average of 3.3 times a week for 26 weeks. In contrast, separation of the pooled data based on tertile of the degree of improvement in V̇O₂max showed that although there was an overall effect of exercise on improved maximum oxygen consumption ($P<.001$), insulin responses were not significantly different between the middle and highest tertiles of V̇O₂max improvement ($P=.95$, Figure 2). Thus, improvements in V̇O₂max produce modest improvements in insulin responses to glucose, and these changes are not enhanced with further increases in V̇O₂max.

COMMENT

Previous studies have demonstrated that approximately half of patients with high BP also have hyperinsulinemia and dyslipidemia characteristic of syndrome X. The present study confirms these findings and demonstrates that even individuals with mild elevations in BP are at increased risk of showing the hyperinsulinemia and dyslipidemia characteristic of syndrome X. In addition, the current findings emphasize the importance of weight loss in achieving maximal improvement in hyperinsulinemic responses to oral glucose and demonstrate that the addition of a structured weight loss program to an exercise intervention produces a larger degree of improvement in insulin responses and in DBP reduction compared with exercise alone.

Separation of the pooled sample into tertiles based on degree of weight loss or fitness change was used to evaluate the dose-response nature of the weight loss and fitness effects. The degree of weight loss predicted stepwise increases in improvement in DBP and in the exaggerated insulin responses to oral glucose. In contrast, improvement in V̇O₂max showed a nonlinear relationship with insulin responses; patients who showed moderate improvements in V̇O₂max showed the same degree of improvement as patients with the largest improvements in V̇O₂max. Although these findings reaffirm the importance of weight loss in improving hyperinsulinemia, it should be noted that the weight loss was achieved in the context of an exercise intervention.

The present findings that increased V̇O₂max and decreased body weight independently contributed to improved insulin responses support a synergistic effect of EX+WL. These findings are consistent with evidence that EX+WL improve insulin sensitivity through separate mechanisms of action. Exercise training is thought to im-
prove insulin sensitivity by increasing oxidative enzymes and glucose transporters in muscle.23 Long-term exercise training interventions have therefore been shown to reduce the insulin response to glucose, without altering the plasma glucose response to the OGTT.12,24-26 In contrast, weight loss programs are associated with reduced glucose and insulin responses to the OGTT in sedentary men13,25,26 and in men and women with high BP.16,17 The present findings confirm these earlier findings by demonstrating that participants in the EX-only group showed reduced plasma insulin concentration in the presence of unchanged glucose concentrations and the participants in the EX+WL group showed reduced glucose and insulin responses to the OGTT.

In contrast to the effects on BP and hyperinsulinemia, lipids were resistant to the effects of the interventions, with patients in the active treatment groups showing similar changes as those exhibited by the patients in the waiting list control group. However, findings of a significant correlation between degree of weight loss and improvement in lipid levels in the pooled sample of all 3 groups suggests that the lack of differences in the active groups vs the controls may be due in part to the lack of power to detect relatively small differences in the individual groups. Although, to our knowledge, this is the first study that has evaluated the effects of aerobic exercise training on lipid profile in patients with components of syndrome X, previous studies in other populations have reported mixed findings. Most studies report no significant effects of habitual exercise on lipid levels in middle-aged and older men.11,24,26,27 In contrast, EX+WL interventions have generally been associated with improved lipid levels,16,18,28 although reported effects on triglyceride level are inconsistent, with one study demonstrating that participants in the EX-only group showed reduced plasma insulin concentration in the presence of unchanged glucose concentrations and the participants in the EX+WL group showed reduced glucose and insulin responses to the OGTT.

In summary, the present data are consistent with the Adult Treatment Panel III recommendations that EX+WL is a useful form of therapy for syndrome X34 and suggest that EX+WL will likely reduce both hyperinsulinemia and elevated BP in overweight men and women with high BP, hyperinsulinemia, and dyslipidemia characteristic of syndrome X. Exercise in the absence of weight loss is likely to result in more limited improvements in the CHD risk factors characteristic of syndrome X.

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REFERENCES

3. Reaven GM, Lithell H, Landsberg L. Mechanisms of disease: hypertension and...