Improvements in Blood Pressure, Glucose Metabolism, and Lipoprotein Lipids After Aerobic Exercise Plus Weight Loss in Obese, Hypertensive Middle-Aged Men

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The clustering of metabolic abnormalities often associated with hypertension, including insulin resistance, glucose intolerance, and dyslipidemia, in middle-aged men may be the result of a decrease in cardiovascular fitness ($\dot{V}O_2$max) and the accumulation of body fat with aging. This study examines the effects of a 6-month program of aerobic exercise training plus weight loss (AEX + WL) on $\dot{V}O_2$max, body composition, blood pressure (BP), glucose and insulin responses during an oral glucose tolerance test (OGTT), glucose infusion rates (GIR) during 3-dose hyperinsulinemic-euglycemic clamps at insulin infusion rates of 120, 600, and 3,000 pmol · m^{-2} · min^{-1}, and plasma lipoprotein levels. Compared with eight non-obese, normotensive, sedentary men (age, 62 ± 2 years; 19% ± 2% fat; BP, 117 ± 4/72 ± 2 mm Hg), the nine obese, hypersensitive, sedentary men studied (age, 56 ± 1 year; 32% ± 1% body fat; BP, 147 ± 3/93 ± 2 mm Hg) initially had a larger waist girth and waist-to-hip ratio (WHR) and were more hyperinsulinemic and insulin resistant with lower GIR at the two lower insulin infusion rates of the clamp and had a 2.9-fold higher EC_{50}, the insulin concentration producing a half-maximal increase in GIR. They had higher triglyceride (TG) and lower high-density lipoprotein cholesterol (HDL-C) levels. The AEX + WL intervention reduced body weight by 9%, percent body fat by 21%, waist girth by 9%, and WHR by 3%, and increased $\dot{V}O_2$max by 16% ($P < .01$ for all). This was associated with decreases of 14 ± 3 mm Hg in systolic and 10 ± 2 mm Hg in diastolic BP, significant changes in GIR at the low (+42%) and intermediate (+39%) insulin infusion rates and EC_{50} (−39%) and in glucose (−21%) and insulin (−51%) responses during OGTT ($P < .02$ for all). AEX + WL also lowered total cholesterol by 14% and TG by 34%, and raised HDL_2−C levels twofold ($P < .01$ for all). Thus, a 6-month AEX + WL intervention substantially lowers BP and improves glucose and lipid metabolism in obese, sedentary, hypertensive men. This suggests that hypertension and the metabolic risk factors for cardiovascular disease associated with it can be ameliorated by AEX + WL in obese, sedentary, middle-aged men.

THE PREVALENCE OF HYPERTENSION increases with age and is greater among obese compared with normal-weight individuals.[1-3] Insulin resistance, hyperinsulinemia, glucose intolerance and dyslipidemia frequently coexist in obese hypertensive individuals.[4,5] This constellation of abnormalities is referred to as the insulin resistance syndrome.[4] Although blood pressure (BP) can be lowered pharmacologically in hypertensive patients, the lipid and glucose metabolic abnormalities associated with hypertension may still persist or be worsened by some antihypertensive agents.[6,7] To our knowledge, the physiological benefits of a nonpharmacologic lifestyle modification of aerobic exercise and weight loss (AEX + WL) in obese, middle-aged men with manifestations of the insulin resistance syndrome have not been examined.

Weight loss (WL) and aerobic exercise (AEX) are advocated as effective, nonpharmacologic treatments for hypertension.[7] In a review of various studies that examined the effects of WL on BP, Staessen et al[8] calculated a decrease in systolic and diastolic BP of 1.6/1.3 mm Hg for every 1-kg decrease in body weight. In a review of studies examining the effects of AEX on BP, Hagberg indicated that AEX reduced systolic and diastolic BP by 10 to 12 mm Hg in mildly to moderately hypertensive subjects.[9] In addition to reducing BP, both WL and AEX training improve lipid profiles and glucose metabolism in older subjects. However, in most of the AEX training studies, there was WL during the AEX training program.[10-14] In general, except for one study in which AEX training in the absence of WL improved lipoprotein lipids,[15] AEX alone tends not to improve glucose tolerance or lipid profiles in obese older men unless there is concomitant WL.[16]

In obese older men, we showed that WL alone improved results on oral glucose tolerance tests (OGTT), but had no effect on insulin sensitivity, while AEX training alone improved insulin sensitivity with no effect on glucose tolerance.[17] In that study, the combined intervention of AEX + WL both improved glucose and insulin responses during OGTT and increased insulin sensitivity. Based on these findings, we hypothesized that a combined AEX + WL program in obese middle-aged men with metabolic abnormalities associated with the insulin resistance syndrome would not only lower BP, but would also improve abnormalities in glucose and lipid metabolism. The results of this study demonstrate that regularly performed AEX combined with WL significantly reduces BP and improves glucose and lipid metabolic abnormalities in obese, hypertensive middle-aged men with the insulin resistance syndrome.

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MATERIALS AND METHODS

Subjects

Healthy, nonsmoking 50- to 70-year-old sedentary hypertensive men who had not engaged in a program of regular physical activity over the past year were recruited from the Baltimore-Washington metropolitan area through newspaper advertisements. Subjects provided written informed consent according to the guidelines of the institutional review boards at the University of Maryland and the Johns Hopkins Bayview Medical Center, Baltimore, MD.

Subjects were screened for disease with a medical history, physical examination, fasting plasma glucose, and routine blood chemistries. Individuals were excluded from participation if they exceeded 170% of ideal body weight,[18] or had poorly controlled or more severe hypertension than stage II by Joint National Committee V (JNC V) criteria (BP > 180/110 mm Hg),[3] a fasting plasma glucose greater than 7.8 mmol · L^{-1}, or other underlying illness. No subject took medications, other than five men who were treated with an antihypertensive drug. Each subject had a resting supine and upright 12-lead ECG and BP measured before undergoing a graded exercise treadmill test[19] to a minimum of 85% of age-predicted maximal heart rate. Subjects who were limited by symptoms or had evidence of cardiovascular decompensation or significant myocardial ischemia during the graded exercise treadmill test were excluded from the study.

Nine hypertensive, sedentary, obese (>25% body fat) men with at least three of the metabolic abnormalities associated with the insulin resistance syndrome underwent metabolic and cardiovascular evaluations before and after participation in a 6-month program of AEX + WL. An additional eight normotensive, sedentary, lean healthy men were recruited as a normal comparison group. To eliminate the effects of changes in diet composition and sodium intake on BP and glucose and lipid metabolism that might be independent of the AEX + WL intervention, all subjects (including the comparison group) were instructed over an 8-week period in the principles of an American Heart Association (AHA) step I diet[20] and stabilized on this diet before baseline testing. The diet consisted of 50% to 55% of calories as carbohydrate, 30% to 35% as fat, 15% to 20% as protein, 300 to 350 mg/d of cholesterol, and 3 g/d of sodium. Subjects were counseled weekly throughout the study to maintain this diet. Adherence was monitored by registered dietitians who reviewed weekly food records and stability of body weight, and calculated diet composition and calorie intake from monthly, 7-day food records (Nutritionist III; N-Squared Computing, Salem, OR, 1991).

The five hypertensive subjects treated with antihypertensive medications were gradually tapered off their medication and studied at baseline after 4 weeks of no drug therapy. During this period, BP was monitored twice weekly and remained below 170/110 mm Hg, consistent with stage I or II hypertension by JNC V criteria.[3] During the AEX + WL intervention, these five subjects were placed back on their antihypertensive medication, but at the end of the AEX + WL program, only two required drug therapy. Antihypertensive drugs were gradually tapered and then discontinued for 4 weeks in these two subjects before reevaluation after AEX + WL. At baseline and after the AEX + WL intervention, subjects were monitored for weight stability and adherence to the AHA diet (7-day food records) for at least 2 weeks before beginning metabolic testing.

Measurement of Body Composition

Body weight was measured (±50 g) using a Homms beam balance (Western, San Francisco, CA). The waist-to-hip circumference ratio (WHR) was calculated as the ratio of the minimal circumference of the abdomen (waist) to the circumference of the buttocks at the maximal gluteal protuberance (hip) in cm. Body density was determined by hydrostatic weighing and corrected for residual lung volume as previously described.[21] Percent body fat was calculated using the Siri equation[22] and fat-free mass (FFM) was calculated as body mass minus fat mass.

Measurement of Maximal Oxygen Consumption

A treadmill maximal oxygen consumption ($\dot{V}O_2$max) test was performed in each subject on at least 2 separate days as previously described.[21] A true $\dot{V}O_2$max was considered to be attained if two of the following three criteria were met: (1) respiratory exchange ratio at maximal exercise greater than 1.10; (2) maximal heart rate greater than 90% of age-predicted maximum (220 − age); and (3) a plateau in $\dot{V}O_2$ (<200 mL · min^{-1} change in $\dot{V}O_2$) during the last stages of exercise. If a true $\dot{V}O_2$max was not attained on the second test or the $\dot{V}O_2$max for the two exercise tests differed by more than 200 mL · min^{-1}, additional $\dot{V}O_2$max tests were performed until these criteria were met.

Measurement of BP

Three random-zero BP measurements were taken 1 week apart by auscultation using the appropriate cuff size. Subjects were seated comfortably for 15 minutes with the cuffed arm supported at heart level before measurements were taken. At each visit, BP was measured three times at 5-minute intervals and the mean recorded. The mean of BP measurements from the three visits is reported. Subjects met JNC V criteria for either stage I or II hypertension.

Metabolic Testing

For 3 days before each metabolic test and during testing, subjects were provided with calculated weight-maintaining AHA step I diets prepared in the metabolic kitchen of the General Clinical Research Center (GCRC). If body weight varied by more than 0.25 kg during periods of testing, research tests were delayed for 48 hours and subjects provided additional days of GCRC-prepared metabolic diets until weight stability (±0.25 kg) was achieved. All metabolic tests were performed in the morning after a 12-hour overnight fast. After the intervention, metabolic testing was performed 24 to 36 hours after the last AEX session.

Hyperinsulinemic-Euglycemic Clamp Protocol

Insulin sensitivity and maximal responsiveness were measured using a three-step modification[23] of the hyperinsulinemic-euglycemic glucose clamp technique.[24] Briefly, an intravenous catheter was inserted into an antecubital vein for infusion of insulin, glucose, and potassium chloride and a second catheter was inserted into a dorsal hand vein for blood sampling. The hand was then placed in a warming box controlled at 70°C to arterialize the blood. The subjects rested for 30 minutes before baseline samples for glucose and insulin were obtained. Insulin (Humulin-R; Eli Lilly, Indianapolis, IN) was administered at three sequential, primed infusion rates of 120 pmol · m^{-2} · min^{-1} for 90 minutes (low dose), 600 pmol · m^{-2} · min^{-1} for 90 minutes (intermediate dose), and 3,000 pmol · m^{-2} · min^{-1} for 120 minutes (high dose). These insulin infusion rates span the range of physiological insulin levels and achieved maximal insulin-mediated glucose disposal based on results of previous studies.[23,25-27] During the clamp, plasma glucose levels were measured at 5-minute intervals using the glucose oxidase method (Beckman Instruments, Fullerton, CA), and the glucose concentration was maintained at basal levels by adjustment of a variable infusion of 20% glucose according to a computerized algorithm. Potassium chloride was infused during the clamp at a rate of 4 mmol/h to prevent hypokalemia. Plasma insulin levels were measured by radioimmunoassay on samples obtained at 10-minute intervals during the clamp.[28]

Glucose infusion rates (GIR) were normalized for FFM and averaged over the last 30 minutes of each insulin dose. Steady-state plasma insulin levels were calculated over the same intervals. Individual and mean dose-response curves relating GIR to plasma insulin levels were

constructed using mean GIR and insulin concentrations at each step of the clamp. These curves were fitted to a logistic regression equation[29] to calculate EC_{50}, the insulin concentration producing a half-maximal response in the GIR. Maximal responsiveness was defined as the GIR during the last 30 minutes of the high-dose insulin infusion.

OGTT

Blood samples were drawn before and at 30-minute intervals for 2 hours after the ingestion of 75 g of glucose. Plasma glucose was measured by a glucose oxidase method (Beckman Instruments) and plasma insulin by radioimmunoassay.[28] The areas under the curves for glucose and insulin responses above the basal level were calculated during the 2-hour OGTT using the trapezoidal model.

Measurement of Lipoprotein Lipids

Blood samples were drawn after a 12-hour overnight fast into chilled tubes containing EDTA (1 mg/mL blood). Plasma was separated by centrifugation at 4°C for analysis of triglyceride (TG) and cholesterol levels by enzymatic methods using an Abbott ABA Series II bichromatic analyzer.[30,31] High-density lipoprotein cholesterol (HDL-C) was measured in the supernatant after precipitation of apolipoprotein B–containing lipoproteins with dextran sulfate in subjects with TG less than 4.5 mmol L^{-1},[32] and low-density lipoprotein cholesterol (LDL-C) was calculated.[33] Following a second precipitation with high–molecular-weight dextran sulfate, the HDL_3–C subspecies was measured and HDL_2–C calculated.[34] In all but one subject, the reported values are the means of at least two samples drawn in the fasted state on different days.

AEX + WL Intervention

Subjects met three times per week for the AEX + WL intervention. Exercise training consisted of walking and jogging on a treadmill, and stationary cycling, starting at 50% to 60% heart rate reserve (HRR) for three 5- to 10-minute periods. Target heart rate was calculated for each individual using the Karvonen equation.[35] Training intensity was gradually increased by 5% to 10% of HRR every month. At 3 months, the $\dot{V}O_2$max test was repeated and the exercise intensity adjusted until subjects trained for 40 minutes per session at an intensity of 75% to 85% of HRR. All training sessions were supervised by research staff. In addition, subjects participated in a behavioral modification WL program conducted once a week by a registered dietitian. Food intake was restricted by 300 to 500 kcal/d and adherence monitored by review of food records and meeting with subjects to discuss eating behaviors on a weekly basis. Body weight was measured weekly and recorded; subjects were counseled individually by the registered dietitian as necessary to promote WL. Adherence to the program was excellent, with subjects attending greater than 85% of the exercise sessions and greater than 75% of the diet classes. Subjects who missed exercise sessions indicated they exercised on their own, and by 4 months most of the men exercised four times per week.

Reevaluation

At the completion of the 6-month AEX + WL intervention, subjects continued to exercise at their current exercise intensity and duration three times per week, had diets reviewed by the dietitian, and stabilized body weights on the AHA step 1 diet for 4 weeks before remeasurement of body composition, $\dot{V}O_2$max, glucose tolerance, lipids, BP, and insulin action. The two subjects on antihypertensive drugs discontinued medication as at baseline testing. Body weights were measured at each exercise session and 7-day food records reviewed at weekly classes with the dietitian. Subjects again were provided calculated, weight-maintaining metabolic diets for 3 days before and during metabolic testing. Subjects' weights varied by less than 0.25 kg before metabolic reevaluation.

Statistical Analysis

Data were analyzed using a standard statistical software package (Statview; Abacus Concepts, Berkeley, CA). An alpha level of 0.05 was accepted for statistical significance. Differences in body composition, $\dot{V}O_2$max, BP, and glucose and lipid metabolism between normal, lean and hypertensive, obese men were tested with ANOVA. Changes in variables in the obese sedentary men resulting from the AEX + WL intervention were compared using Student's paired t tests. Although arithmetic means are reported, the logarithms of TG, plasma insulin, and EC_{50} were used in comparisons. The change in the number of cardiovascular risk factors in the hypertensive, obese sedentary men after the AEX + WL intervention was analyzed using a nonparametric paired-sign test. Pearson product-moment regression analyses and stepwise multiple regression analyses were performed to determine relationships between changes in BP and glucose and lipid metabolism and changes in body composition and $\dot{V}O_2$max. Due to the large number of regression analyses performed and sample size of nine subjects, only correlation coefficients with P values less than .01 were considered statistically significant. In all stepwise analyses, independent variables with P values less than .05 were entered into the model in the hierarchal order of their significance, with the highest one first, etc. All data are reported as the mean ± SEM.

RESULTS

Baseline

Metabolic abnormalities. At baseline, all subjects in the intervention group were obese with more than 25% body fat and had hypertension. In addition, three of the nine hypertensive men had impaired glucose tolerance and two were diabetic,[36] seven were hyperinsulinemic based on a fasting plasma insulin greater than 90 pmol · L^{-1},[37] eight had low plasma levels of HDL-C, and two had high plasma TG levels.[38] Thus, at baseline, each of the nine subjects exhibited at least three, and up to as many as six, of the abnormalities associated with the insulin resistance syndrome (Table 1).

Physical characteristics of subjects. By selection, the hypertensive men were significantly heavier, had a greater percentage of fat, higher WHR, and significantly higher systolic (147 ± 3 v 117 ± 4 mm Hg, $P = .001$), diastolic (93 ± 2 v 72 ± 2 mm Hg, $P = .001$), and mean arterial (111 ± 2 v 87 ± 2 mm Hg, $P = .001$) BP than the normal subjects. The hypertensive and normal men had similar $\dot{V}O_2$max when expressed in L · min^{-1}, but the hypertensive men had a lower $\dot{V}O_2$max than the normal men when expressed in mL · kg^{-1} · min^{-1} (Table 2).

Hyperinsulinemic-euglycemic clamp. The hypertensive men had significantly lower GIR than the normal subjects at the low and intermediate insulin infusion rates, but there was no difference in the GIR at the highest insulin infusion rate. The EC_{50} was significantly greater in the hypertensive men than in the normal men (1,931 ± 352 v 659 ± 72 pmol · L^{-1}, $P = .002$) (Fig 1 and Table 3).

OGTT. At baseline, there was no difference in the fasting plasma glucose between the hypertensive and normal men (5.7 ± 0.3 v 5.0 ± 0.2 mmol · L^{-1}, $P = .10$) or in the glucose area (429 ± 70 v 326 ± 53 mmol · min · L^{-1}, $P = .16$). The hypertensive men had a significantly greater fasting mean plasma insulin concentration than the normal men (125 ± 17 v 50 ± 9 pmol · L^{-1}, $P = .004$), as well as a significantly greater insulin area (92,173 ± 28,574 v 31,460 ± 4,741 pmol · min · L^{-1}, $P < .01$) (Fig 2).

Table 1. Effect of AEX + WL Intervention on Metabolic Abnormalities in Obese Men

Subject No.	Obesity		Hypertension		Glucose Intolerance		Hyperinsulinemia		Low HDL-C		High TG	
	Baseline	After	Baseline	After	Baseline	After	Baseline	After	Baseline	After	Baseline	After
1	X		X	*					X	*		
2	X	*	X				X		X	*	X	
3	X	*	X		X		X	*	X	*		
4	X		X				X		X	*		
5	X	*	X		X	*	X		X			
6	X	*	X		X	*	X		X			
7	X		X						X	*		
8	X	*	X		X	*	X			*		
9	X	*	X	*	X		X		X	*	X	*
Total	9	6	9	2	5	3	7	1	8	7	2	1

NOTE. Metabolic abnormalities are defined as obesity (body mass index >26 kg · m^{-2}); hypertension (systolic BP >140 mm Hg or diastolic BP >90 mm Hg); glucose intolerance (plasma glucose >7.8 mmol · L^{-1} at 120 minutes of the OGTT); hyperinsulinemia (fasting plasma insulin >90 pmol · L^{-1}); low plasma HDL-C (<0.9 mmol · L^{-1}); high plasma TG (>2.3 mmol · L^{-1}). X indicates the presence of risk factor at baseline, and *, the presence after AEX + WL intervention.

Lipid profiles. Plasma TG levels were higher and HDL-C and HDL_3-C levels were lower in the hypertensive compared with the normal men. There were no differences in total cholesterol, HDL_2-C, or LDL-C levels (Table 4).

Effects of AEX and WL Intervention in Hypertensive Men

Changes in physical characteristics. The AEX + WL intervention decreased body weight by 9% (−9.0 ± 1.3 kg, $P = .0001$), percentage body fat by 21% (−6.5% ± 0.8%, $P = .0001$), waist by 11% (−10.1 ± 1.4 cm, $P < .0001$), and WHR by 3% (−0.03 ± 0.01, $P < .01$), and raised $\dot{V}O_2$max by 16% (0.44 ± 0.11 L · min^{-1}, $P = .005$). After completing the AEX + WL intervention, the hypertensive men were still significantly heavier and had a higher percentage body fat and waist circumference than the normal men. However, after the intervention, these two groups no longer differed in WHR, and the hypertensive men had relative $\dot{V}O_2$max (mL · kg^{-1} · min^{-1}) values that were similar to those of the normal men (Table 2).

The AEX + WL intervention in the hypertensive men resulted in 10% decreases in systolic (14 ± 3 mm Hg, $P = .003$), diastolic (10 ± 2 mm Hg, $P = .004$), and mean arterial (11 ± 3 mm Hg, $P = .003$) BP (Fig 3). All but one subject had an improvement in BP following the AEX + WL intervention, and three of the five men on medication no longer required therapy. However, even after 6 months of AEX + WL, the hypertensive men still had significantly higher systolic (133 ± 5 *v* 117 ± 4 mm Hg, $P = .02$), diastolic (82 ± 3 *v* 72 ± 2 mm Hg, $P = .01$), and mean arterial (99 ± 4 *v.* 87 ± 2 mm Hg, $P = .01$) BP than the normal men.

Table 2. Physical Characteristics of Subjects

Variable	Normal Lean Men	Hypertensive Obese Men	
		Baseline	After Intervention
Age (yr)	62.0 ± 1.8	55.8 ± 1.3‡	
Weight (kg)	75.2 ± 2.9	96.6 ± 4.4§	87.5 ± 3.9†‡
Percent body fat (%)	19.2 ± 1.6	31.5 ± 1.1§	25.0 ± 1.4†‡
FFM (kg)	60.8 ± 2.6	66.2 ± 2.9	65.5 ± 2.8
WHR	0.88 ± 0.02	0.96 ± 0.01§	0.93 ± 0.01†‡
Waist girth (cm)	86.3 ± 2.9	106.2 ± 2.9§	96.1 ± 2.5†‡
$\dot{V}O_2$max			
L · min^{-1}	2.60 ± 0.11	2.68 ± 0.16	3.12 ± 0.21†
mL · kg^{-1} · min^{-1}	34.8 ± 1.7	27.5 ± 1.1§	35.6 ± 2.1†

Significantly different from baseline value: †$P < .01$.
Significantly different from normal lean men: ‡$P < .05$; §$P < .01$.

Changes in hyperinsulinemic-euglycemic clamp. In these men, after the intervention the GIR during the hyperinsulinemic-euglycemic clamp increased significantly by 42% at the low insulin infusion rate and 39% at the intermediate insulin infusion rate, but did not change significantly at the high insulin dose. The improvements in glucose disposal rates resulted in a 39% decrease in EC_{50} (1,931 ± 352 to 1,090 ± 135 pmol · L^{-1}, $P = .01$). When compared with the normal subjects, the hypertensive men still had a significantly lower GIR at the low insulin infusion rate and significantly higher EC_{50} (1,090 ± 135 *v* 659 ± 72 pmol · L, $P = .015$) after the AEX + WL intervention (Fig 1 and Table 3).

Changes in OGTT. There was no significant change in fasting plasma glucose after 6 months of AEX + WL, but there was a 21% decrease in the glucose area (429 ± 70 to 310 ± 42 mmol · min · L^{-1}, $P < .05$), a 41% decrease in fasting plasma insulin levels (125 ± 17 *v* 68 ± 7 pmol · L^{-1}, $P = .004$), and a 51% reduction in the insulin area (92,173 ± 28,574 to

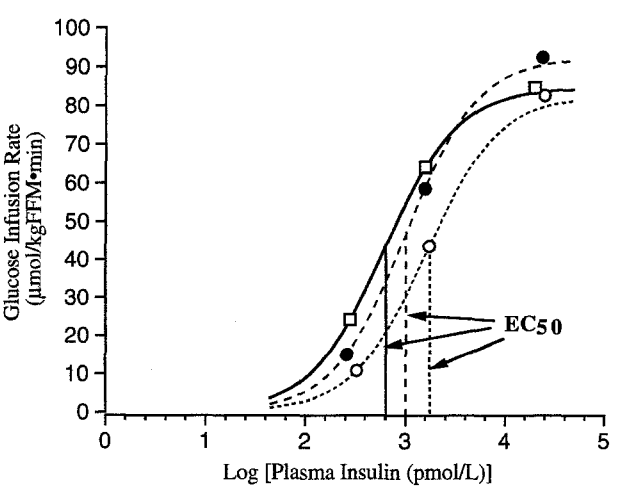

Fig 1. Insulin-mediated glucose disposal dose-response curves (semilogarithmic scale) for normal lean men (□—□) and hypertensive obese men at baseline (○---○) and after 6 months of AEX + WL (●– –●). Vertical lines intersect the abscissa at EC_{50}, the insulin concentration necessary for half-maximal effect.

Table 3. Steady-State Insulin Levels and GIR at Each Step of the Three-Dose Hyperinsulinemic-Euglycemic Glucose Clamp

Variable	Normal Lean Men	Hypertensive Obese Men	
		Baseline	After Intervention
Plasma insulin concentrations (pmol · L^{-1})			
Insulin infusion rate			
120 pmol · m^{-2} · min^{-1}	287 ± 19	342 ± 28	267 ± 19*
600 pmol · m^{-2} · min^{-1}	1,608 ± 99	1,799 ± 159	1,682 ± 92
3,000 pmol · m^{-2} · min^{-1}	21,122 ± 2,503	25,629 ± 2,188	25,184 ± 3,545
Glucose infusion rate (μmol · kg_{FFM}^{-1} · min^{-1})			
Insulin infusion rate			
120 pmol · m^{-2} · min^{-1}	24.2 ± 3.7	10.9 ± 1.1§	15.1 ± 1.7†‡
600 pmol · m^{-2} · min^{-1}	64.2 ± 6.3	43.6 ± 4.7‡	58.6 ± 6.3†
3,000 pmol · m^{-2} · min^{-1}	84.9 ± 6.5	82.9 ± 6.3	92.6 ± 9.3
EC_{50} (pmol · L^{-1})	659 ± 72	1,931 ± 352§	1,090 ± 135†‡

Significant difference between baseline and after intervention value: *$P < .05$; †$P < .01$.
Significant difference between normal lean men and hypertensive obese men: ‡$P < .05$; §$P < .01$.

34,974 ± 3,792 pmol · min · L^{-1}, $P < .01$). After the intervention, there were no differences in the fasting insulin concentration or insulin area during the OGTT between the hypertensive men and the normal comparison group (Fig 2).

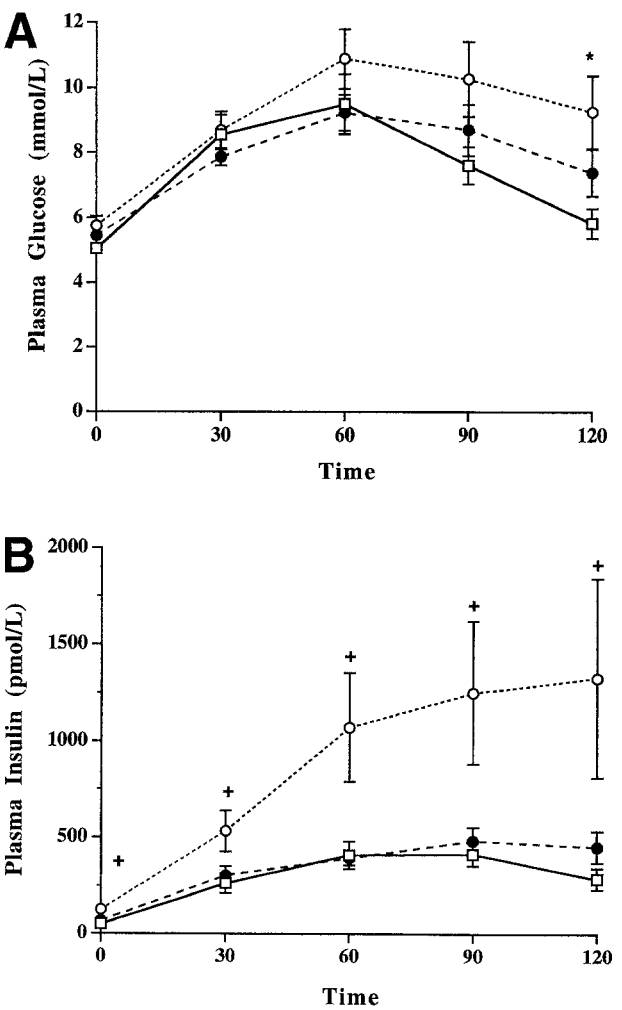

Fig 2. Plasma glucose (A) and insulin (B) responses to an oral glucose load in normal lean men (□—□) and hypertensive obese men at baseline (○---○) and after 6 months of AEX + WL (●– –●). Data are means ± SEM; significant difference between normal lean men and hypertensive obese men at baseline: *$P < .02$, †$P < .01$.

Changes in lipid profile. Six months of AEX + WL was associated with a 14% decrease in total cholesterol (−0.68 ± 0.16 mmol · L^{-1}, $P = .003$) and a 37% reduction in plasma TG (−0.80 ± 0.27 mmol · L^{-1}, $P = .01$). Although there were no significant changes in plasma LDL-C (−0.36 ± 0.24 mmol · L^{-1}, $P = .28$), HDL-C (+0.04 ± 0.04 mmol · L^{-1}, $P = .33$), or HDL_3-C (−0.03 ± 0.04, $P = .70$) levels, there was a significant twofold increase in HDL_2-C levels (0.05 ± 0.01 mmol · L^{-1}, $P = .004$). After the intervention, there was no difference in plasma TG, total cholesterol, HDL_2-C, or LDL-C levels between the hypertensive men and the normal men, but HDL-C levels remained lower in the hypertensive men (Table 4).

Overall changes in risk factors. As a result of the 6-month AEX + WL intervention, there was a 50% reduction in the total number of metabolic abnormalities associated with the insulin resistance syndrome in these obese hypertensive men (40 to 20, $P = .004$). Bivariate regression analyses showed significant relationships between the changes in $\dot{V}O_2max$ (L · min^{-1}) with changes in EC_{50} ($r = .78$, $P = .01$) and fasting insulin ($r = .77$, $P < .02$), and the changes in glucose area during the OGTT with changes in percentage body fat ($r = .83$, $P = .006$). In stepwise multiple regression analyses, with changes in $\dot{V}O_2max$, percentage body fat, and WHR included in the model, none of them added significantly to the predictive equation for the three dependent variables. Thus, changes in $\dot{V}O_2max$ accounted for 64% of the variance in the decrease in EC_{50} and 58% of the variance in the reduction in insulin, while changes in percentage

Table 4. Plasma Lipid Profile of Subjects

Variable	Normal Lean Men	Hypertensive Obese Men	
		Baseline	After Intervention
Total cholesterol (mmol · L^{-1})	4.48 ± 0.23	4.65 ± 0.25	3.97 ± 0.24†
HDL-C (mmol · L^{-1})	1.06 ± 0.07	0.76 ± 0.05§	0.80 ± 0.03§
HDL_2-C (mmol · L^{-1})	0.14 ± 0.04	0.05 ± 0.02	0.10 ± 0.02†
HDL_3-C (mmol · L^{-1})	0.93 ± 0.03	0.71 ± 0.05§	0.69 ± 0.03§
LDL-C (mmol · L^{-1})	3.00 ± 0.17	2.96 ± 0.18	2.60 ± 0.16
TG (mmol · L^{-1})	0.88 ± 0.09	2.05 ± 0.59‡	1.25 ± 0.33†

Significant difference between baseline and after intervention value: *$P < .05$; †$P < .01$.
Significant difference between normal lean men and hypertensive obese men: ‡$P < .05$; §$P < .01$.

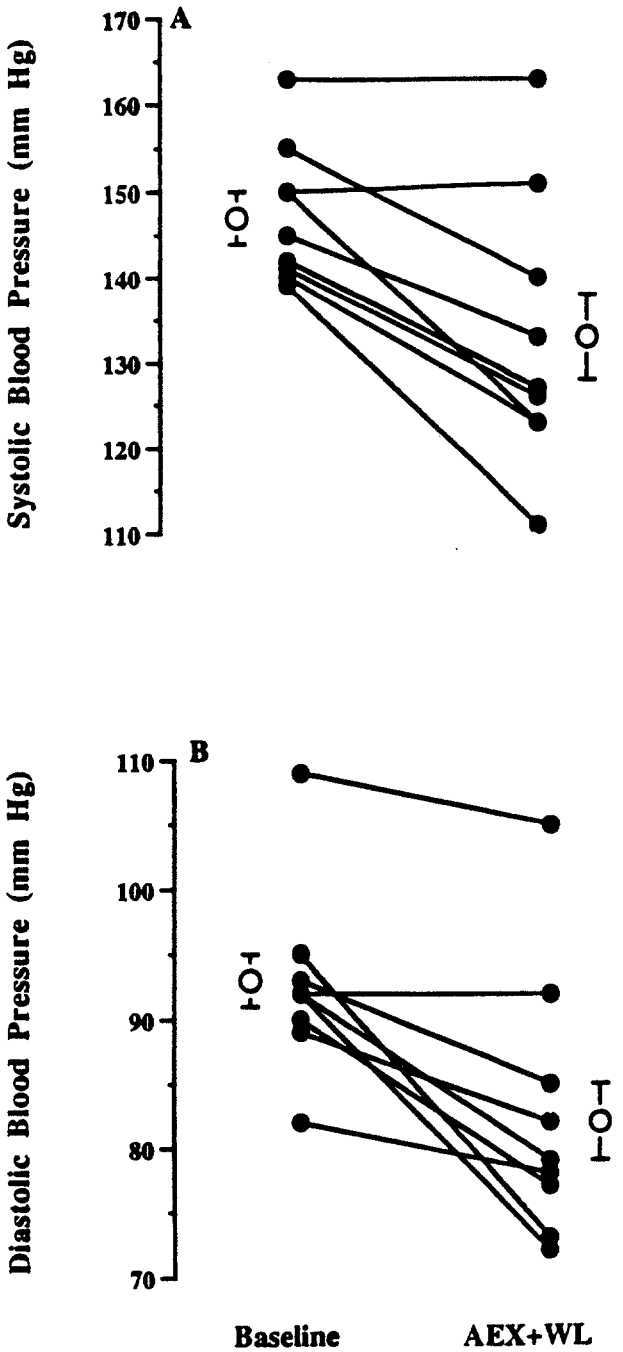

Fig 3. Systolic (A) and diastolic (B) BP of hypertensive obese men at baseline and after AEX + WL. (○) Mean ± SEM BP values at baseline and after AEX + WL.

body fat accounted for 68% of the variance in the decrease in glucose area. None of the other changes in metabolic or BP variables correlated with changes in body composition or $\dot{V}O_2$max in bivariate or stepwise multiple regression analyses.

DISCUSSION

The BP, glucose, and lipoprotein abnormalities associated with insulin resistance are attributable, in part, to genetic factors; however, the results of this study indicate that the increase in body weight and decrease in physical fitness that often accompany aging contribute to the development of these metabolic abnormalities in obese, middle-aged men. A 6-month program of AEX + WL resulted in a significant increase in cardiovascular fitness and decreases in percent body fat and abdominal obesity in these obese, middle-aged men. These changes were associated with significant reductions in BP and improvements in insulin sensitivity, and the glucose and lipoprotein abnormalities associated with the insulin resistance syndrome. The subjects who improved their $\dot{V}O_2$max the most increased their insulin sensitivity and lowered plasma insulin levels the most, while those who lost the most body fat had the greatest improvement in glucose tolerance. This suggests that in middle-aged, obese, hypertensive, sedentary men insulin resistance and its associated metabolic abnormalities are modifiable through changes in exercise and dietary habits. The increase in $\dot{V}O_2$max and reduction in body fat achieved with this AEX + WL intervention significantly reduced the cardiovascular disease risk factor profile in these high-risk patients, and may prevent subsequent cardiovascular disease complications.

In a review of 25 studies that examined the independent effects of AEX on BP in hypertensive patients aged 15 to 70 years, Hagberg[9] reported an average reduction in systolic and diastolic BP of 10.8 and 8.2 mm Hg, respectively. In a review of 11 studies that examined the independent effects of WL on BP in obese hypertensive individuals, Kaplan[39] indicated that an average WL of 9.8 kg was associated with a 15-mm Hg reduction in systolic, and a 10-mm Hg decrease in diastolic blood pressure. In the present study, AEX + WL reduced systolic and diastolic BP by 14 and 10 mm Hg, respectively, and these reductions were independent of medication and dietary sodium intake, which were controlled by discontinuing medications before and after AEX + WL. Even though the hypertensive individuals in the present study had significant reductions in both systolic and diastolic BP and seven of nine normalized their BP, the BPs of these men remained significantly higher than in the normal men. This might be due to the fact that even after the AEX + WL intervention, the hypertensive men were still significantly more obese than the normal men, despite their comparable $\dot{V}O_2$max levels. Further weight loss to achieve desirable body weight might result in normalization of these men's BP. Alternatively, it is possible that genetic factors contribute to the development of hypertension in these individuals, in which case additional reductions in body weight might not lower their BP to normal.

In conjunction with the reduction in BP, the AEX + WL intervention improved glucose and lipoprotein metabolism in these obese, sedentary men. There were significant decreases in both the glucose and insulin responses during the OGTT. The reduction in insulin responses to an oral glucose challenge observed in this study is greater than previously reported in older normotensive individuals.[17,40] This may be related to the fact that several of our subjects were glucose-intolerant before the intervention, and raised $\dot{V}O_2$max and lost more weight than subjects in other studies.[40] An improvement in glucose tolerance that is achieved with a reduction in the plasma insulin response to glucose is compatible with an increase in insulin sensitivity. This is supported by the increase in insulin-mediated glucose disposal achieved by AEX + WL in these men across

the range of physiologic insulin levels achieved during first and second, but not at the supraphysiologic insulin levels achieved during the third dose of the three-dose hyperinsulinemic-euglycemic clamp.

The AEX + WL intervention produced a significant leftward shift in the dose-response relationship between the GIR and insulin levels in the physiologic range, consistent with improved insulin sensitivity. These changes in insulin-mediated glucose disposal are greater than those reported in younger, glucose-intolerant and non–insulin-dependent diabetic subjects in whom a 3-month AEX + WL program produced a 21% increase in glucose disposal at an insulin infusion rate of 240 pmol · m^{-2} · min^{-1}.[41] A longer period of AEX training without WL increased glucose disposal in older individuals during a two-dose hyperinsulinemic-euglycemic clamp performed at 240 and 1,200 pmol · m^{-2} · min^{-1} insulin infusion rates by 13% and 11%, respectively.[42] This greater increase in glucose disposal in our study at the low and intermediate insulin infusion rates and the decrease in EC_{50} are likely the result of the combined effects of AEX + WL, the longer duration of our intervention, and greater magnitude of the increase in $\dot{V}O_2max$ and decrease in body fat than achieved in prior AEX or WL studies. Although we did not measure endogenous (hepatic) glucose production (HGP), it is unlikely that the contribution of HGP to glucose disposal was substantial, since these men had normal fasting plasma glucose levels and HGP is suppressed more than 90% during intermediate and high insulin infusions in normal and mild type 2 diabetic subjects.[26,27] Furthermore, the 42% increase in GIR during the low-dose insulin infusion was greater than could be explained by the suppression of HGP.

The cellular mechanisms for the improvement in insulin-mediated glucose utilization with AEX + WL are not known; but, it is likely that AEX + WL affected the cellular sites relevant in the pathogenesis of the abnormalities in glucose metabolism in these men. These include possible effects on insulin receptor binding and affinity, glucose transporters in muscle (GLUT-4), and increased muscle blood flow and glucose extraction,[43,44] which require further study. Collectively, these results indicate that in hypertensive obese, sedentary middle-aged men, modification of physical inactivity and dietary habits to reduce body fat and improve exercise capacity will improve insulin sensitivity. This suggests that the insulin resistance and hypertension attributed to aging in some obese individuals are modifiable, and not due to primary aging processes.

Abnormal plasma lipoprotein-lipid profiles (ie, high total cholesterol, LDL-C, and TG concentrations and a low HDL-C concentration) are a major risk factor for the development of coronary artery disease.[38] The combination of AEX with WL reduced both total cholesterol and LDL-C and increased HDL_2-C, in obese premenopausal women.[10] Similarly, we showed that the addition of WL to AEX further lowered plasma TG and total and LDL cholesterol, and increased HDL-C and HDL_2-C in middle-aged men.[16] In the present study, the combined intervention of AEX + WL reduced plasma TG and total cholesterol, and increased HDL_2-C levels in obese, sedentary middle-aged men. This would be expected to reduce the risk for cardiovascular disease in these men.

The antidiabetic drug troglitazone decreased insulin resistance and improved glucose tolerance in a comparably obese group of twelve 45-year-old nondiabetic subjects with normal or impaired glucose tolerance.[45] The reductions in glucose and insulin responses during the OGTT and increases in insulin action observed in the present study with AEX + WL are comparable to those achieved with troglitazone, but there were greater improvements in the BP and lipid profiles of our subjects with AEX + WL than in the patients treated with troglitazone. This may be due to the fact that our subjects had hypertension and worse lipid profiles than the patients treated with troglitazone. The results of the Diabetes Prevention Program[46] should determine the effectiveness of lifestyle, as well as drug interventions in the prevention of type 2 diabetes in adults.

In summary, an AEX + WL intervention, which improved insulin sensitivity by 39%, resulted in a 50% reduction in the number of metabolic abnormalities associated with the insulin resistance syndrome in obese, hypertensive, middle-aged men. The mean number of abnormalities associated with insulin resistance decreased from 4.4 to 2.2 per individual. The magnitude of the improvements in these risk factors for CVD in these obese, middle-aged men is encouraging, and demonstrates a need for future studies to determine the long-term effectiveness of this nonpharmacologic intervention in the prevention of CVD in high-risk populations. This suggests that the health benefits of AEX + WL in hypertensive, obese men extend beyond moderate reductions in BP, and indicates that many of the metabolic and physiologic abnormalities associated with the insulin resistance syndrome in obese, middle-aged men can be ameliorated by increasing physical fitness and reducing body weight.

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