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# Exercise Training Normalizes Vascular Dysfunction and Improves Central Adiposity in Obese Adolescents

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**OBJECTIVES** We sought to characterize the impact of obesity on vascular function in adolescents and to determine whether an exercise program reverses abnormalities in endothelial function.

**BACKGROUND** Obesity, a major modifiable risk factor for cardiovascular disease, is epidemic in Western societies, with rapid rates of increase in the young. Atherosclerosis begins in childhood, and endothelial dysfunction is its earliest detectable manifestation.

**METHODS** The influence of eight weeks of circuit training (CT) was examined in 19 obese subjects (14.3 ± 1.5 years), using a randomized, crossover protocol. Functional capacity and muscular strength were assessed by standard techniques. Body composition was examined using anthropometric measures and dual-energy X-ray absorptiometry. Conduit vessel endothelial function was assessed using high-resolution ultrasound and flow-mediated dilation (FMD) of the brachial artery.

**RESULTS** Circuit training decreased abdominal and trunk fat and significantly improved fitness and muscular strength ($p < 0.05$). In the obese group, FMD was significantly impaired relative to control subjects ($n = 20$) at entry (5.3 ± 0.9% vs. 8.9 ± 1.5%, $p < 0.05$) and was normalized after CT (8.8 ± 0.8%, $p < 0.05$).

**CONCLUSIONS** Circuit training improved functional capacity, muscular strength, and body composition in obese adolescents. Furthermore, conduit vessel function was normalized after exercise training. If vascular dysfunction is an integral component of the pathogenesis of vascular disease, this study supports the value of an exercise program in the management of obese adolescents. (J Am Coll Cardiol 2004;43:1823–7) © 2004 by the American College of Cardiology Foundation

Obesity, a major modifiable risk factor for cardiovascular disease, has reached epidemic proportions in affluent Western societies and is associated with substantial health care costs (1). Primary prevention may be the key to decreasing obesity, especially because its prevalence is increasing in children and adolescents (1). This increase in fat mass in adolescents is particularly alarming, as a high proportion of adolescent obesity persists into adulthood, and adolescent obesity predicts a broad range of adverse health effects in adulthood (2).

The importance of the endothelium in maintaining a healthy vasculature has been increasingly recognized, especially regarding release of nitric oxide (NO), which possesses a number of antiatherogenic properties (3). Several studies have detected impaired brachial artery flow-mediated dilation (FMD), a well-validated measure of vascular endothelial function (3), in adolescents with cardiovascular risk factors (4–6). Endothelial dysfunction is particularly relevant given recent studies indicating that it predicts cardiovascular mortality and morbidity and that it may be an early manifestation of atherosclerotic disease (3). In addition, interventions that improve NO-dilator function, including exercise training (7,8), are cardioprotective. Early detection and treatment of endothelial dysfunction may represent a novel primary prevention strategy in adolescents who are at elevated risk of the development of cardiovascular disease in later life. However, no studies have examined any intervention, including exercise training, which may ameliorate the impaired vascular function evident in obese adolescents.

## METHODS

**Subjects and screening measures.** Nineteen obese (9) subjects (9 males and 10 females; mean [±SD] age 14.3 ± 1.5 years; Tanner stages 3 to 5) were recruited. A matched group ($n = 20$) of lean control subjects (9 males and 11 females; age 14.9 ± 2.7 years) were also recruited for a cross-sectional comparison.

Exclusion criteria included systolic blood pressure (BP) >140 mm Hg or diastolic BP >85 mm Hg, smoking, total cholesterol >213 mg/dl or low-density lipoprotein (LDL) cholesterol >116 mg/dl, and all forms of medication, including vitamin supplements and oral contraceptives. Informed consent was obtained from all adolescents and parents. The study was approved by the Ethics Committee of Princess Margaret Hospital.

**Study design.** Familiarization exercise and vascular ultrasound assessments were undertaken before randomization. Subjects were randomized to a crossover study of eight weeks of exercise training or a non-training period. Subjects were specifically requested to desist from activity during

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**Abbreviations and Acronyms**

BMI = body mass index
BP = blood pressure
CT = circuit training
DEXA = dual-energy X-ray absorptiometry
FMD = flow-mediated dilation
$HbA_{1c}$ = glycosylated hemoglobin
HDL = high-density lipoprotein
HR = heart rate
LDL = low-density lipoprotein
NO = nitric oxide

their non-training period, with compliance checked using activity records. Subjects were also requested not to modify their diet, and diet diaries confirmed this.

**Experimental measurements.** BODY COMPOSITION, ANTHROPOMETRIC, AND MUSCLE STRENGTH ASSESSMENTS. Body weight, height, body mass index (BMI), skinfolds (six sites), and waist/hip circumference were obtained before each exercise test. Maximal strength was assessed for five muscle groups, and a dual-energy X-ray absorptiometry (DEXA) scan (Norland, Connecticut) assessed whole-body and regional fat and lean tissue mass.

ASSESSMENT OF EXERCISE CAPACITY. The exercise test involved three consecutive 4-min epochs of exercise on a bicycle ergometer, with subjects cycling at 50 to 60 rpm. Identical exercise intensities were used before and after training, and changes in fitness were assessed by comparing heart rate (HR) responses at these matched workloads.

ASSESSMENT OF BLOOD CHEMISTRY. On a visit separate from the first exercise test, blood samples were collected to determine concentrations of cholesterol (total, LDL, and high-density lipoprotein [HDL]), triglycerides, homocysteine, glycosylated hemoglobin ($HbA_{1c}$), and fasting blood glucose.

ASSESSMENT OF CONDUIT VESSEL FUNCTION. Vascular function was assessed at the same time of the day for individual subjects, after a 4-h fast and abstinence from caffeine and exercise. Brachial artery internal diameter was assessed using high-resolution vascular ultrasonography (Acuson) with a 10-MHz multi-frequency probe. Flow-mediated dilation, induced by reactive hyperemia to a 5-min ischemic stimulus, is a well-established measure of endothelium-dependent vasodilator function, which is largely NO-mediated (10). It provides an index of endothelial dysfunction, an early manifestation of atherosclerotic disease (3). Data were assessed by automated edge-detection software, which is independent of investigator bias (11).

**Exercise training regimen.** The eight-week regimen consisted of three 1-h sessions of circuit training (CT) exercise each week, involving both cycle ergometer and resistance training. Cycle ergometry was maintained at 65% to 85% of maximum HR and resistance training intensity at 55% to 70% of pre-training maximum strength.

**Analysis of data.** Results are expressed as the mean value ± SE. Anthropometric, muscular strength, plasma concentrations, and FMD after exercise training were compared with non-training responses, using the Student paired *t* test or two-way analysis of variance (ANOVA) for variables that possessed several levels. A value $p < 0.05$ was considered significant.

## RESULTS

All subjects completed at least 90% of the 24 exercise sessions, and no significant adverse events occurred.

**Comparison of lean and obese subjects.** No differences were evident between lean and obese subjects in terms of resting BP, HR, fasting blood glucose, and $HbA_{1c}$ (Table 1). Total and HDL cholesterol levels were significantly higher in the lean subjects ($p < 0.05$).

Obese subjects possessed significantly higher body weight, BMI, waist girth, and skinfolds (all $p < 0.0001$) (Table 2). At study entry, FMD was significantly impaired in obese subjects relative to lean controls (5.3 ± 0.9% to 8.9 ± 1.5%, $p < 0.05$) (Fig. 1).

**Effects of exercise training.** There were no significant differences in plasma lipids, homocysteine, $HbA_{1c}$, fasting blood glucose, or resting systolic and diastolic BP after training (Table 2).

ANTHROPOMETRIC ASSESSMENT AND MUSCULAR STRENGTH. Exercise training enhanced muscular strength ($p < 0.01$) (Table 2). Body weight, BMI, segment girths, and skinfolds did not change. The DEXA measures, validated by ensuring that the bone mineral content measures for each body segment were comparable before and after training, revealed significant decreases in body fat in the abdominal and trunk regions ($p < 0.05$).

**Table 1.** Blood Chemistry and Hemodynamic Data on Lean Control Subjects and Obese Subjects in the Untrained or Trained State

| | Lean Controls | Obese Subjects | |
|---|---|---|---|
| | | Untrained | Trained |
| Plasma lipids (mg/dl) | | | |
| Total cholesterol | 177.9 ± 7.7* | 146.9 ± 3.9 | 146.9 ± 7.7 |
| LDL cholesterol | 96.7 ± 11.6 | 81.2 ± 3.9 | 81.2 ± 3.9 |
| HDL cholesterol | 58.0 ± 7.7* | 46.4 ± 3.9 | 42.5 ± 3.9 |
| Triglycerides | 106.3 ± 26.6 | 97.4 ± 8.8 | 106.2 ± 8.8 |
| Glycosylated hemoglobin (%) | 5.2 ± 0.1 | 5.2 ± 0.1 | 5.3 ± 0.1 |
| Fasting blood glucose (mg/dl) | 91 ± 4 | 95 ± 4 | 95 ± 2 |
| Mean arterial pressure (mm Hg) | 80.5 ± 1.7 | 78.8 ± 1.6 | 76.4 ± 2.2 |
| Resting heart rate (beats/min) | 68 ± 4 | 73 ± 2 | 72 ± 2 |

Lean subjects possessed higher HDL cholesterol and total cholesterol (*$p < 0.05$). No significant differences were evident for other variables. Data are presented as the mean value ± SE.

HDL and LDL = high- and low-density lipoprotein, respectively.

**Table 2.** Anthropometric and Muscular Strength Characteristics of the Lean Control Subjects and Obese Subjects During the Trained and Untrained Periods

| | Lean Controls | Obese Subjects | |
|---|---|---|---|
| | | Untrained | Trained |
| Body weight (kg) | 57.5 ± 3.1* | 96.4 ± 3.3 | 96.4 ± 3.2 |
| BMI (kg/m$^2$) | 21.2 ± 0.8* | 34.4 ± 0.8 | 34.1 ± 0.7 |
| Waist girth (mm) | 71.7 ± 2.3* | 97.3 ± 2.4 | 97.9 ± 2.3 |
| Sum of 6 skinfolds (mm) | 102.3 ± 9.5* | 252.5 ± 5.5 | 252.4 ± 6.2 |
| DEXA results | | | |
| Fat (%) | | 42.5 ± 1.3 | 41.9 ± 1.3 |
| Fat mass (kg) | | 41.2 ± 1.9 | 40.5 ± 1.8 |
| Lean body mass (kg) | | 52.9 ± 2.3 | 53.5 ± 2.4 |
| Head region | | | |
| Fat mass (kg) | | 0.9 ± 0.1 | 0.9 ± 0.1 |
| Lean body mass (kg) | | 3.6 ± 0.1 | 3.6 ± 0.1 |
| Trunk region | | | |
| Fat mass (kg) | | 19.0 ± 1.0 | 18.3 ± 1.0* |
| Lean body mass (kg) | | 23.6 ± 1.1 | 23.7 ± 1.3 |
| Abdomen region | | | |
| Fat mass (kg) | | 8.6 ± 0.6 | 8.0 ± 0.4* |
| Lean body mass (kg) | | 9.9 ± 0.5 | 9.6 ± 0.5 |
| Upper limb region | | | |
| Fat mass (kg) | | 7.5 ± 0.5 | 8.0 ± 0.5 |
| Lean body mass (kg) | | 6.5 ± 0.4 | 6.8 ± 0.3 |
| Lower limb region | | | |
| Fat mass (kg) | | 13.8 ± 0.6 | 13.3 ± 0.6 |
| Lean body mass (kg) | | 19.2 ± 0.8 | 19.4 ± 0.7 |
| Muscle strength | | | |
| Sum of 5 maximal contractions (kg) | | 274.2 ± 17.5 | 315.6 ± 16.0* |

Obese subjects possessed higher body weight, BMI, waist girth, and skinfolds than did lean controls (*$p < 0.0001$). Exercise training decreased measures of central adiposity (abdominal and trunk fat mass, $p < 0.05$) and improved muscular strength ($p < 0.01$). No significant differences were evident for other variables. Data are presented as the mean value ± SE.

BMI = body mass index; DEXA = dual-energy X-ray absorptiometry.

**EXERCISE TEST DATA.** Submaximal exercise HR responses were significantly lower at matched workloads after training ($p < 0.05$ by ANOVA) (Fig. 2), indicating a significant fitness improvement.

**FOREARM CONDUIT VESSEL FUNCTION.** Baseline arterial diameter (3.46 ± 0.15 mm) was not altered by training in the obese group (3.42 ± 0.12 mm). Before exercise training, the ischemic stimulus increased the arterial diameter from 3.46 ± 0.15 mm to 3.64 ± 0.16 mm ($p < 0.0001$). After the exercise intervention, the increase was from 3.42 ± 0.12 mm to 3.72 ± 0.14 mm ($p < 0.0001$). Brachial artery FMD therefore significantly increased after exercise training, from 5.3 ± 0.9% to 8.8 ± 0.8% ($p < 0.05$). Although FMD was significantly impaired in obese subjects relative to lean controls at entry ($p < 0.05$), exercise training normalized the response (8.8 ± 0.8% to 8.9 ± 1.5%, p = NS) (Fig. 1).

**EFFECT OF ORDER OF ADMINISTRATION.** Figure 3 depicts trained and nontrained FMD, according to the order of administration of exercise training. The effect of training on FMD was not different between these subgroups ($p = 0.86$) and nontrained FMD did not differ between the groups ($p = 0.98$). The order of training therefore did not influence

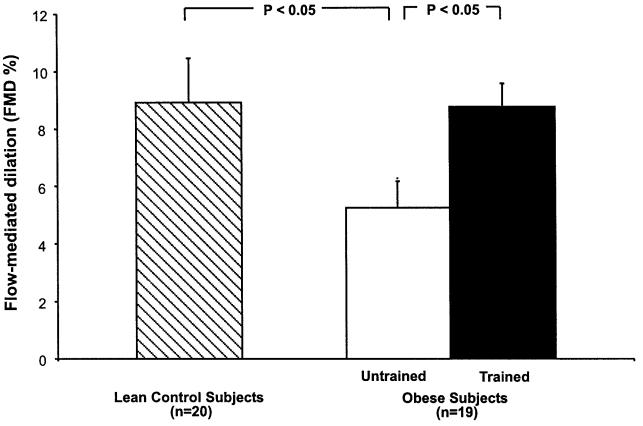


**Figure 1.** Endothelium-dependent flow-mediated dilation (FMD) of the brachial artery in lean control subjects **(lined bar)** and obese subjects after eight weeks of inactivity **(open bar)** and eight weeks of circuit training **(solid bar)**. Data are expressed as the mean value ± SE. Although FMD was significantly impaired in obese subjects relative to matched lean controls at entry ($p < 0.05$), exercise training was associated with normalization of the response ($p < 0.05$).

responses, and the improvement in FMD as a result of training did not persist after eight weeks of sedentary behavior. There was no effect of the order of randomization on the difference between trained and nontrained body composition or other data.

## DISCUSSION

This study indicates that FMD, which was impaired in obese adolescents, significantly improved relative to a group of matched lean control subjects, after exercise training. Flow-mediated dilation is endothelium- and largely NO-dependent (10), and impaired FMD is considered a sentinel event of atherosclerotic disease (3). To our knowledge, this is the first study to demonstrate an improvement in vascular function in obese adolescents as a result of any intervention.

Previous animal studies suggest that exercise training improves NO-dependent vascular function and upregulates

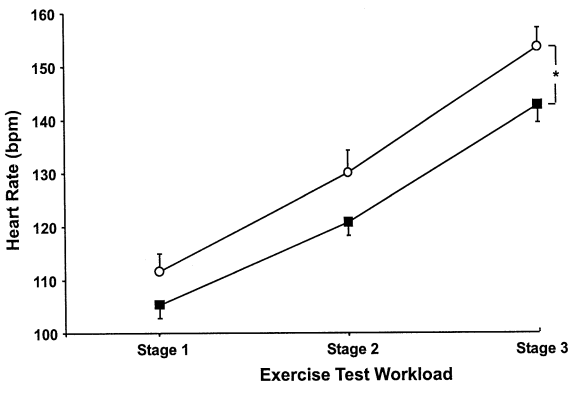


**Figure 2.** Heart rate responses at matched cycle ergometer workloads after eight weeks of inactivity **(circles)** and eight weeks of circuit training **(squares)**. Data are expressed as the mean value ± SE. Submaximal exercise heart rate responses were significantly lower at matched cycle ergometer workloads after training (*$p < 0.05$ by analysis of variance), indicating a significant improvement in cardiorespiratory fitness.

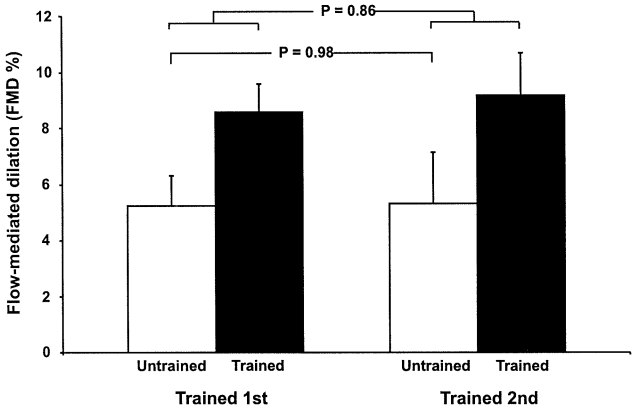


**Figure 3.** Flow-mediated dilation response after eight weeks of inactivity **(open bars)** and eight weeks of circuit training **(solid bars)** in the group trained first and the group trained second. Data are expressed as the mean value ± SE. The order of exercise training did not influence responses, and improvement in flow-mediated dilation (FMD) as a result of training did not persist.

constitutive endothelial NO-synthase expression (12). In addition, exercise programs improve endothelium-dependent function in adults with cardiac failure (7), coronary disease (13), and diabetes (8). Shear stress-mediated upregulation of NO-synthase expression, resulting from increased blood flow across the endothelium, is the likely physiologic mechanism for improvement. Acute changes in flow and shear stress stimulate the release of NO during exercise in animals, and increases in blood flow through conduit arteries are associated with flow-mediated stress on the vessel wall, which, in turn, liberates NO from the endothelium (12). In humans, FMD is attenuated by co-infusion of $N^G$monomethyl-L-arginine (L-NMMA), suggesting that conduit vessel dilation during exercise may, at least in part, be NO-dependent (10). Improvement in vascular function in human training studies is not restricted to the vessels of the exercising musculature (7,8) and occurs in the absence of changes in lipid fractions, BP, or glycemic control (14), consistent with the results of the present investigation. The effect is therefore probably due to the generalized impact of hemodynamic variables acting through vessel wall shear stress (15), but hormonal or other effects accompanying exercise could contribute.

Training was associated with significant improvements in aerobic capacity, strength, and central adiposity in this study. Total body fat decreased by an average of 0.6% (~700 g), the majority of which was lost from the abdominal and trunk regions. Interestingly, subcutaneous fat did not change, even in these regions. This suggests that exercise training modifies body composition, with initial decreases in fat predominantly occurring from the viscera. The lack of change in gross body composition measures (weight, BMI, waist girth), despite countervailing regional changes in fat and lean mass, emphasizes the importance of comprehensive assessment of body composition in future training studies.

Because the nontrained data did not differ between the groups training first or second, it does not appear that the effect of exercise training on FMD or body composition persisted for eight weeks. This is in accordance with the reversal of improvement in FMD of the brachial artery observed six to eight weeks after training cessation in adult populations (7,8). It is therefore likely that continuous training is necessary to maintain the vascular and anthropometric benefits of exercise.

**Study limitations.** Due to ethical considerations, we did not administer nitroglycerine, which is commonly used to assess endothelium-independent vasodilation. We are therefore unable to identify the specific locus of improvement, although previous studies have suggested that NO dilator system improvement in response to exercise training is endothelium-dependent (8,16). A second limitation relates to the effect of estrogen on NO-dilator system function. However, no difference existed in the impact of exercise training on FMD responses between males (5.1 ± 1.5% to 8.7 ± 1.1%) and females (5.4 ± 1.2% to 8.9 ± 1.3%).

**Conclusions.** Exercise training reverses vascular dysfunction associated with obesity in adolescents. The clinical relevance of this finding is highlighted by the critical role of endothelial function in the prevention of atherosclerosis (3), the high levels of cardiovascular mortality and morbidity associated with obesity, and previous findings that interventions which improve endothelial function (13,17,18) are also associated with improved mortality and morbidity (3,19). Although future studies will be required to specifically establish that exercise-induced changes in vascular function translate into long-term clinical benefit, this study supports the value of an exercise program in the management of obese adolescents.

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