International Journal of Obesity (2006) 30, 1211–1216
 0307-0565/06 $30.00
www.nature.com/ijo

ORIGINAL ARTICLE

Addition of aerobic exercise to dietary weight loss preferentially reduces abdominal adipocyte size

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Objective: To determine if hypocaloric diet, diet plus low-intensity exercise, and diet plus high-intensity exercise differentially influence subcutaneous abdominal and gluteal adipocyte size in obese individuals.
Design: Longitudinal intervention study of hypocaloric diet, diet plus low-intensity exercise, and diet plus high-intensity exercise (calorie deficit = 2800 kcal/week, 20 weeks).
Subjects: Forty-five obese, middle-aged women (BMI = 33.0 ± 0.6 kg/m^2, age = 58 ± 1 years).
Measurements: Body composition testing and adipose tissue biopsies were conducted before and after the interventions. Subcutaneous abdominal and gluteal adipocyte size was determined.
Results: All three interventions reduced body weight, fat mass, percent fat, and waist and hip girths to a similar degree. Diet only did not change subcutaneous abdominal adipocyte size, whereas both diet plus exercise groups significantly reduced abdominal adipocyte size. Changes in abdominal adipocyte size in the diet plus exercise groups were significantly different from that of the diet group. Gluteal adipocyte size decreased similarly in all three groups.
Conclusion: Addition of exercise training to dietary weight loss preferentially reduces subcutaneous abdominal adipocyte size in obese women. This may be of importance for the treatment of health complications associated with subcutaneous abdominal adiposity.
International Journal of Obesity (2006) **30,** 1211–1216. doi:10.1038/sj.ijo.0803245; published online 31 January 2006

Keywords: exercise training; hypocaloric diet; abdominal fat; gluteal fat; fat cell size

Introduction

Obesity is a risk factor for type 2 diabetes and cardiovascular disease.[1–2] However, not all obese people develop these diseases and some may have normal glucose tolerance and lipid profile.[3] Location of body fat is one risk factor that differentiates obese persons with and without metabolic complications,[3,4] and obese people with more upper-body (abdominal) fat are under a higher metabolic risk than those with more lower-body (gluteal-femoral) fat.[5–7] In fact, abdominal obesity, including subcutaneous and visceral fatness, is an accepted component of the clustering of metabolic risk factors known as the metabolic syndrome.[8]

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Received 30 August 2005; revised 14 October 2005; accepted 29 October 2005; published online 31 January 2006

In addition to total and abdominal obesity, adipose cellularity is another potential factor that contributes to elevated metabolic risk. For example, obese women with larger subcutaneous abdominal adipocytes are more likely to have hyperinsulinemia and glucose intolerance.[5,9,10] Moreover, subcutaneous abdominal adipocyte size predicts type 2 diabetes, independent of obesity and insulin resistance.[11] Interestingly, subcutaneous gluteal adipocyte size may be more sensitive for predicting metabolic syndrome in African-American than Caucasian older women.[12]

Life style modifications, such as dietary weight loss and increasing physical activity are advocated for the treatment of total and central obesity and prevention of diabetes and cardiovascular disease.[8,13] Although both diet and exercise interventions reduce total body fat mass, exercise may be more efficient in decreasing abdominal adiposity.[14–19] Results from observational studies indicate that abdominal adiposity is inversely related to aerobic fitness[14] and physical activity.[15] Interventional studies show that exercise-induced weight loss preferentially reduces abdominal fat.[16–19] Although one study did not show an effect of exercise

intensity on changes in body composition and fat distribution in response to exercise training alone,[20] it is not known if exercise intensity is a factor to influence abdominal fat distribution during dietary weight loss.

It has been reported that the fat-reducing effect of both diet and exercise is through a decrease in fat cell size.[21,22] As elevated metabolic risk is highly linked with adipocyte size, especially in the abdominal region,[5,9–11] identification of the most effective treatment to reduce abdominal adipocyte size is of clinical significance. Thus, we tested the hypothesis that dietary weight loss combined with high-intensity aerobic exercise training would be more effective in selectively reducing abdominal adipocyte size, compared to weight loss with low-intensity exercise training or weight loss alone in obese older women.

Methods

Subjects

All women were recruited from the Piedmont Triad area of North Carolina, and enrolled in the study based on the following inclusion/exclusion criteria: (1) overweight or obese (BMI = 25–40 kg/m^2 and waist girth >88 cm), (2) older (age = 50–70 years, and at least 1 year without menses), (3) nonsmoking, (4) not on hormone replacement therapy, (5) sedentary (<15 min of exercise, two times/week) in the past 6 months, and (6) weight-stable (<5% weight change) for at least 6 months before enrollment. All women provided informed consent to participate in the study according to the guidelines of the Wake Forest University Institutional Review Board for Human Research.

Initial screening included a medical history review, physical examination, fasting blood profile (lipoprotein lipids and glucose) and 12-lead resting electrocardiogram. Participants with evidence of untreated hypertension (blood pressure >160/90 mmHg), hypertriglyceridemia (triglycerides >400 mg/dl), insulin-dependent diabetes, active cancer, liver, renal or hematological disease, or other medical disorders were excluded. On a second screening visit, the subjects underwent a graded exercise test to exclude those with an abnormal cardiovascular response to exercise.[23] Forty-nine women were enrolled in the study and randomly assigned to either a hypocaloric diet only (Diet), a diet plus low-intensity exercise (Diet + LE), or a diet plus high-intensity exercise (Diet + HE) intervention for a period of 20 weeks.

Study design

Baseline measurements of body composition, body fat distribution, maximal aerobic capacity (VO_2max) and adipocyte sizes were performed after at least 2 weeks of weight stability before the interventions. Subjects reported to the facility on the first day for the measurement of body composition, body fat distribution and VO_2max. The subjects were asked to remain sedentary and the fat biopsies were performed at least 5 days after the VO_2max test. The fat biopsies took place at the same time of morning (0700–0900 hours) after an overnight fast. After the 20-week interventions, the women were retested at their lower body weight in the same manner as at baseline. The diet plus exercise groups continued to exercise during this testing period, but the postintervention fat biopsies occurred at least 36 h after an exercise session.

Study interventions

During the 20-week interventions, all women were provided food for their lunch and supper, which was prepared by the Wake Forest University General Clinical Research Center (GCRC) metabolic kitchen staff. These meals were prepared individually after women chose from a hypocaloric menu designed by a registered dietitian (RD). Women purchased and prepared their breakfast meal, in consultation with the GCRC dietitian, from this same menu. They were allowed 2 free days per month, during which they were given guidelines for diet intake and asked to report all intake. They were also allowed to consume as many noncaloric, noncaffeinated beverages as they liked. In addition, all women were provided with a daily calcium supplement (1000 mg/day).

The diet only group was asked not to alter their physical activity habits during the study. Both diet plus exercise groups walked on a treadmill 3 days/week at a target heart rate calculated from the Karvonen equation ((HRR × (intensity) + resting heart rate),[24] where heart rate reserve (HRR) is maximal heart rate minus resting heart rate obtained from each subject's VO_2max test. The duration and intensity of the exercise progressed from 15 to 20 min at 45–50% of HRR during the first week to 55 min at 45–50% HRR for the low-intensity group, and 30 min at 70–75% HRR for the high-intensity group by the second month. The calorie deficits of all women were adjusted to ~2800 kcal/week. The deficits for the diet only group resulted totally from reduction in dietary intake, whereas deficits for the diet plus exerciser groups resulted from both reductions in dietary intake (~2400 kcal/week) and in exercise expenditure (~400 kcal/week). The average daily calorie intake recorded by all women was 99.4 ± 0.3% of the provided calorie level. The exercise compliance was 92.3 ± 1.7% for the low-intensity exercise group, and 87.9 ± 2.3% for the high-intensity exercise group.

Body composition

Height and weight were measured to calculate BMI (kg/m^2). Waist (minimal circumference) and hip (maximal circumference) was measured and waist-to-hip ratio was calculated. Fat mass, lean mass and percent body fat were measured by dual energy X-ray absorptiometry (Hologic Delphi QDR, Bedford, MA, USA).

Maximal aerobic capacity

VO_2max was measured on a motor-driven treadmill (Medical Graphics Corporation, Minneapolis, MN, USA) during a progressive exercise test to voluntary exhaustion. A ramp treadmill protocol was used for the exercise test. The speed of the treadmill was set at a constant rate according to individual ability, and the incline increased at small intervals continuously throughout the test. Each test was set for a duration of 12 min with a goal of 12 metabolic equivalents, and the treadmill self-adjusted the incline to reach that goal. A valid VO_2max was obtained when a respiratory exchange ratio (RER) of 1.10 had been reached. If the participant did not reach a RER of 1.10, the test was repeated.

Adipocyte size

Subcutaneous adipose tissue from both the abdominal and gluteal regions was taken by aspiration with a 16-gauge needle under local anesthesia (2% xylocaine) after an overnight fast. Adipocytes were isolated in a Krebs-Ringer *N*-2-hydroxyethylpiperazine-*N*′′-2-ethanesulfonic acid buffer (pH 7.4, KRH) containing 4% bovine serum albumin, 5 mM glucose, 0.1 mM ascorbic acid, 200 nM adenosine, and 1 mg/ml collagenase, and in a shaking water bath at 100 r.p.m., 37°C for 45 min.[25] Isolated cells were filtered through 400-μM nylon mesh and washed three times with enzyme-free KRH buffer and resuspended to a final concentration of 20 000–30 000 cells/ml. An aliquot of the final cell suspension was placed on a glass slide and diameters of 100 cells per site were measured using a microscope equipped with a graduated ocular. The average cell diameter and standard deviation were calculated and the average cell weight for each site was determined as described.[26]

Statistics

Statistical analyses were performed using SPSS 10.1. for Windows (Chicago, IL, USA). First, within-group differences between preintervention and postintervention measures of all variables were determined using a paired *t*-test. Differences among the intervention groups at baseline and over-time changes in response to the interventions were determined using one-way ANOVA. The Fisher's LSD *post hoc* test was used to determine any group differences if an overall group effect was ascertained. All data are presented as means ± standard error, and the level of significance was set at $P<0.05$ for all analyses.

Results

Subject characteristics

Forty-five (Diet: $n=15$, Diet + LE: $n=14$, Diet + HE: $n=16$) of the initial 49 women completed the interventions. Four women dropped out of the program owing to personal reasons and time constraints. Of the 45 women who completed the study, three women did not complete the VO_2max test. Owing to insufficient adipose tissue yield obtained from the biopsies, four women did not have measures of abdominal adipocyte size and seven women did not have measures of gluteal adipocyte size. There were no differences in age, years postmenopause, or percent of African Americans among the three groups.

Effects of diet, diet plus low-intensity exercise, and diet plus high-intensity exercise on body composition and aerobic fitness

Body composition measures before and after the interventions in the three groups are shown in Table 1. At baseline, there were no group differences in weight, fat mass, lean mass or percent body fat. After the 5-month interventions, all three groups lost a similar amount of body weight (Diet: −11.3 ± 0.8%; Diet + LE: −12.8 ± 1.4%; Diet + HE: −10.0 ± 1.2%), consisting of approximately 70–80% adipose tissue. Likewise, there were similar reductions in lean mass and percent body fat in all three groups.

At baseline, there were no group differences in absolute or relative VO_2max (Table 1). All three interventions did not change absolute VO_2max, but increased relative VO_2max (Diet: 8.8 ± 2.0%; Diet + LE: 12.6 ± 2.3%; Diet + HE: 20.8 ± 6.6%). There were no significant group differences among changes in absolute or relative VO_2max.

Table 1 Body composition and aerobic fitness in the Diet, Diet+LE, and Diet+HE groups before and after interventions and over-time changes

	Pre	*Post*	*Change*
Weight (kg)			
Diet ($n=15$)	91.2 ± 2.2	80.9 ± 2.0***	−10.4 ± 0.8
Diet+LE ($n=14$)	86.6 ± 2.3	75.7 ± 2.8***	−10.9 ± 1.2
Diet+HE ($n=16$)	85.8 ± 3.8	77.0 ± 3.2***	−8.8 ± 1.2
Fat mass (kg)			
Diet ($n=15$)	39.9 ± 1.7	32.8 ± 1.7***	−7.0 ± 0.8
Diet+LE ($n=14$)	37.7 ± 1.3	29.7 ± 1.6***	−8.0 ± 0.9
Diet+HE ($n=16$)	38.2 ± 2.1	31.2 ± 1.9***	−7.0 ± 0.7
Lean mass (kg)			
Diet ($n=15$)	51.4 ± 0.9	47.3 ± 0.9***	−4.1 ± 0.5
Diet+LE ($n=14$)	49.3 ± 1.5	45.8 ± 1.5***	−3.5 ± 0.4
Diet+HE ($n=16$)	48.6 ± 1.5	45.6 ± 1.4***	−3.0 ± 0.4
Percent body fat (%)			
Diet ($n=15$)	42.4 ± 1.1	40.0 ± 1.2***	−2.8 ± 0.6
Diet+LE ($n=14$)	42.2 ± 0.8	38.0 ± 1.1***	−4.2 ± 0.7
Diet+HE ($n=16$)	42.6 ± 0.8	39.1 ± 1.0***	−3.5 ± 0.4
Absolute VO_2max (l/min)			
Diet ($n=14$)	1.76 ± 0.07	1.72 ± 0.07	−0.04 ± 0.07
Diet+LE ($n=13$)	1.83 ± 0.07	1.78 ± 0.05	−0.05 ± 0.04
Diet+HE ($n=15$)	1.67 ± 0.09	1.68 ± 0.08	0.01 ± 0.04
Relative VO_2max (ml/min/kg)			
Diet ($n=14$)	19.9 ± 0.8	21.6 ± 0.9**	1.7 ± 0.4
Diet+LE ($n=13$)	20.8 ± 0.8	23.2 ± 0.6***	2.4 ± 0.4
Diet+HE ($n=15$)	19.2 ± 1.0	22.4 ± 0.7**	3.3 ± 0.9

All data are means ± s.e. **$P<0.01$, ***$P<0.001$ compared with baseline.

Table 2 Body fat distribution and regional adipocyte size in the Diet, Diet+LE, and Diet+HE groups before and after interventions and over-time changes

	Pre	*Post*	*Change*
Waist girth (cm)			
Diet ($n=15$)	100.9±2.0	92.1±2.1***	−8.8±1.0
Diet+LE ($n=14$)	100.2±2.2	90.7±2.8***	−9.4±1.3
Diet+HE ($n=16$)	96.4±2.5	87.1±2.2***	−9.3±1.4
Hip girth (cm)			
Diet ($n=15$)	118.8±2.2	111.5±2.2***	−7.3±1.3
Diet+LE ($n=14$)	116.7±2.2	107.1±2.2***	−9.7±1.4
Diet+HE ($n=16$)	116.6±2.4	108.4±2.4***	−8.2±0.8
Waist-to-hip ratio			
Diet ($n=15$)	0.85±0.02	0.83±0.02	−0.02±0.01
Diet+LE ($n=14$)	0.86±0.02	0.85±0.02	−0.01±0.02
Diet+HE ($n=16$)	0.83±0.02	0.80±0.01	−0.02±0.01
Abdominal adipocyte size (μg)			
Diet ($n=12$)	0.83±0.06	0.80±0.04	−0.04±0.04
Diet+LE ($n=14$)	0.82±0.03	0.66±0.03***	−0.16±0.04†
Diet+HE ($n=15$)	0.89±0.04	0.73±0.04***	−0.16±0.04†
Gluteal adipocyte size (μg)			
Diet ($n=12$)	0.96±0.07	0.81±0.03*	−0.15±0.05
Diet+LE ($n=11$)	0.88±0.04	0.75±0.05*	−0.13±0.04
Diet+HE ($n=15$)	0.95±0.03	0.77±0.05***	−0.19±0.04
Abdominal-to-gluteal size ratio			
Diet ($n=12$)	0.88±0.05	0.99±0.04**	0.11±0.03
Diet+LE ($n=11$)	0.93±0.06	0.90±0.02	−0.03±0.06
Diet+HE ($n=15$)	0.94±0.04	0.98±0.04	0.04±0.06

All data are means±s.e. *$P<0.05$, **$P<0.01$, ***$P<0.001$ compared with baseline. †$P<0.05$ compared with diet only.

Effects of diet, diet plus low-intensity exercise, and diet plus high-intensity exercise on body fat distribution and regional adipocyte size

At baseline, there were no group differences in waist girth, hip girth, or waist-to-hip ratio (Table 2). The interventions reduced waist and hip girths to a similar degree in all three groups, but did not significantly change waist-to-hip ratio in any group.

There were no group differences in abdominal or gluteal adipocyte size at baseline (Table 2). Diet alone did not decrease abdominal adipocyte size; however, diet plus low-intensity exercise and diet plus high-intensity exercise significantly reduced abdominal adipocyte size. Changes in abdominal adipocyte size in the two exercise groups (Diet + LE: -18.4±3.9%; Diet + HE: −16.8±3.5%) were significantly different from that of the diet only group (−0.8±6.2%). Gluteal adipocyte size decreased similarly in all three groups (Diet: −12.4±5.3%; Diet + LE: −13.8±4.5%; Diet + HE: −19.8±4.4%) (Figure 1). Diet only increased abdominal-to-gluteal adipocyte size ratio (14.2±3.8%). Diet plus low-intensity exercise and diet plus high-intensity exercise did not change adipocyte size ratio. There were no group differences among changes in adipocyte size ratio.

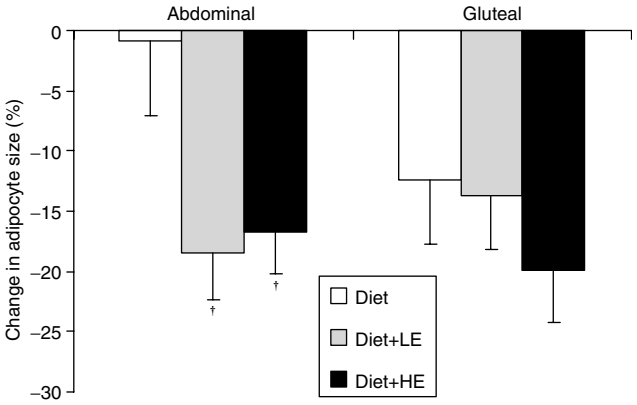

Figure 1 Percent changes in regional adipocyte size in all three intervention groups. †$P<0.05$ compared with diet only.

Discussion

This study investigated whether dietary weight loss plus high-intensity aerobic exercise training would be more effective in reducing abdominal adipocyte size, compared to weight loss plus low-intensity exercise training or weight loss alone in obese older women. The findings showed that addition of either high-intensity or low-intensity aerobic exercise training to dietary weight loss significantly reduced subcutaneous abdominal, but not gluteal, adipocyte size. However, diet plus high-intensity exercise and diet plus low-intensity exercise did not differ in their effects on abdominal adipocyte size.

Our results showed that weight loss alone decreased both waist and hip girths; however, there were no changes in waist-to-hip ratio. These results were similar to our earlier findings in overweight and obese women,[27,28] but different from findings of another study showing that 4 weeks of very-low-calorie-diet (VLCD) treatment decreased waist-to-hip ratio in android obese women.[29] The possible reason for the different findings might be the different subject characteristics, diet types and intervention terms. In obese men, 4 months of exercise training reduced body weight, fat mass, and waist-to-hip ratio, but did not change fat-free mass, indicating that exercise training could preferentially reduce abdominal fat and maintain muscle mass.[19] However, another study investigated effects of exercise amount/intensity on body fatness and found exercise amount affected the degree of weight loss and fat mass loss, but neither exercise amount nor intensity influenced regional fat distribution.[20]

Hypocaloric diet and exercise training can reduce body fat through a decrease in fat cell size, but not cell number.[21,22] Although both diet and exercise treatments reduce total body fatness, it has been suggested that exercise training preferentially reduces abdominal adiposity.[14–19] The current study further demonstrates that addition of aerobic exercise

training to dietary weight loss results in a larger decrease in abdominal, but not gluteal, adipocyte size. These results support those of an earlier observational study that endurance-trained premenopausal women had lower abdominal, but not femoral, adipocyte size than sedentary premenopausal women.[30] Moreover, our results indicate that both high-intensity and low-intensity exercise training are beneficial to at-risk obese women undergoing dietary weight loss.

Weight loss through the current approach may not evenly influence adipocyte size in different regions. This is supported by our findings that diet alone increased abdominal-to-gluteal adipocyte size ratio. This may be due to regional differences in metabolic adaptations of adipocytes to the hypocaloric diet, including a greater reduction in hormone-sensitive lipase (HSL, enzyme for triglyceride hydrolysis) activity and increase in lipoprotein lipase (LPL, enzyme for triglyceride accumulation) activity in abdominal, compared to gluteal adipocytes. In addition, regional difference in estrogen receptor activity may be a possible mechanism to influence lipolysis and adipocyte size.[30] More studies are needed to investigate the mechanism underlying the unparallel changes in the regional adipocyte sizes of the abdominally obese women in response to hypocaloric diet. Similarly, changes in regional adipoctyte size in response to exercise training were likely through modulations on lipid metabolism. As previously described,[31] endurance-trained women have lower subcutaneous abdominal adipocyte size than sedentary women, which may be due to a preferential lipid mobilization from subcutaneous abdominal, compared to femoral, adipose tissue in endurance-trained women. These changes may involve both the HSL and LPL pathways. Moreover, it is not known if exercise training could differentially influence estrogen receptor activity in these fat regions.

We previously conducted two intervention studies to measure abdominal and gluteal adipocyte size in obese postmenopausal women.[27,28] Although one study[27] showed both hypocaloric diet alone and diet plus exercise training reduced abdominal and gluteal adipocyte size, the other study[28] found diet plus exercise, but not diet alone, decreased abdominal and gluteal adipocyte size. In both studies, intervention-induced adipocyte size changes were similar between abdominal and gluteal regions. There are two possible reasons for the different findings between the current study and the two previous studies. First, although subjects in the earlier studies were also overweight or obese postmenopausal women, some of them did not have abdominal obesity. In the current study, all subjects were abdominally obese (waist girth >88 cm) postmenopausal women. Enlarged subcutaneous abdominal adipocytes may be more resistant to dietary treatment in women with more severely abdominal obesity. Second, the two earlier studies used a behavioral approach for dietary weight loss. The current study provided food to the subjects through the metabolic kitchen, which resulted in better compliances in caloric intake and greater amounts of weight loss compared to the earlier studies. Variation in diet compliance and amount of weight loss may influence findings of these studies.

It is notable that changes in waist and hip girths do not exactly reflect changes in subcutaneous gluteal and abdominal adipocyte sizes in response to diet and exercise. This can be explained by the influence of visceral fat, intramuscular fat and fat-free mass. In addition, sample sizes among these intervention groups are relatively small, which might influence the statistical power of data analysis. Larger studies need to be conducted to confirm our findings. Moreover, adipocyte metabolic properties were not tested in this study, although such data would help clarify the mechanisms for changes in regional adipocyte size in response to diet and exercise.

In summary, addition of either high-intensity or low-intensity aerobic exercise training to dietary weight loss preferentially reduces subcutaneous abdominal adipocyte size, whereas dietary weight loss with or without exercise similarly reduces gluteal adipocyte size in abdominally obese women. These findings are consistent with other research showing that exercise training selectively decreases abdominal fat. Considering the health problems associated with enlarged subcutaneous abdominal adipocytes, addition of exercise to dietary weight loss may be important for the treatment of these complications. Future studies need to focus on the link between metabolic biomarkers and regional adipocyte size in response to diet and exercise training.

Acknowledgements

We are grateful to the study coordinators, dietitians, exercise physiologists, nurses, and laboratory technicians of the Section of Gerontology and Geriatric Medicine, and the General Clinical Research Center at Wake Forest University School of Medicine for their assistance in the conduct of this study. We also thank all women who voluntarily participated in this study. This study was supported by NIH Grant R01-AG/DK20583, Wake Forest University Claude D. Pepper Older Americans Independence Center (P30-AG21332), and Wake Forest University General Clinical Research Center (M01-RR07122).

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