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Exercise Is Required for Visceral Fat Loss in Postmenopausal Women with Type 2 Diabetes

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This study examined the effects of aerobic exercise without weight loss, a hypocaloric high monounsaturated fat diet, and diet plus exercise (D+E) on total abdominal and visceral fat loss in obese postmenopausal women with type 2 diabetes. Thirty-three postmenopausal women (body mass index, 34.6 ± 1.9 kg/m^2) were assigned to one of three interventions: a hypocaloric high monounsaturated fat diet alone, exercise alone (EX), and D+E for 14 wk. Aerobic capacity, body composition, abdominal fat distribution (magnetic resonance imaging), glucose tolerance, and insulin sensitivity were measured pre- and postintervention. Body weight (~4.5 kg) and percent body fat (~5%) were decreased ($P < 0.05$) with the D and D+E intervention, whereas only percent body fat (~2.3%) decreased with EX. Total abdominal fat and sc adipose tissue (SAT) were reduced with the D and D+E interventions ($P < 0.05$), whereas visceral adipose tissue (VAT) decreased with the D+E and EX intervention, but not with the D intervention. EX resulted in a reduction in total abdominal fat, VAT, and SAT ($P < 0.05$) despite the lack of weight loss. The reductions in total abdominal fat and SAT explained 32.7% and 9.7%, respectively, of the variability in the changes in fasting glucose levels, whereas the reductions in VAT explained 15.9% of the changes in fasting insulin levels ($P < 0.05$). In conclusion, modest weight loss, through either D or D+E, resulted in similar improvements in total abdominal fat, SAT, and glycemic status in postmenopausal women with type 2 diabetes; however, the addition of exercise to diet is necessary for VAT loss. These data demonstrate the importance of exercise in the treatment of women with type 2 diabetes. (*J Clin Endocrinol Metab* 90: 1511–1518, 2005)

NUMEROUS METABOLIC COMPLICATIONS are associated with obesity. The accumulation of fat mass results in the development of impaired fat and glucose metabolism involving both hepatic and peripheral tissues (1, 2). More specifically, intraabdominal visceral adipose tissue (VAT) is positively associated with insulin resistance in obese individuals and individuals with type 2 diabetes (3–5). VAT accumulation results in elevations in plasma free fatty acid (FFA) release into the portal vein, resulting in disturbances in glycemic control (6). Chronic exposure to elevated FFA levels causes resistance to the effects of both insulin and glucose on adipose tissue lipolysis and triglyceride storage (7); in individuals with type 2 diabetes, this response is more deranged, thus potentially causing more deleterious metabolic consequences. Weight loss, whether with diet and/or exercise, results in reductions in abdominal fat, particularly in the visceral depot in healthy obese individuals, and these changes in abdominal fat have also been associated with improvements in insulin sensitivity (8–13). Exercise without weight loss is also effective in reducing visceral adipose tissue (14, 15). However, these earlier studies did not include individuals with type 2 diabetes, in whom disordered fat storage and mobilization occurs, causing dramatic metabolic abnormalities (7). In these individuals the abdominal fat may respond to the weight loss interventions differently than in obese individuals. In obese, nondiabetic individuals the excess adipose tissue with an enhanced FFA flux is under physiological control of high insulin concentrations, but with diabetes this adipose tissue is more resistant to hormonal stimulation (2).

During exercise, a marked increase in lipolysis in abdominal sc adipose tissue (SAT) compared with femoral adipose tissue has been observed (16), and this difference is more pronounced in women than in men (16). Also, greater lipid and lower carbohydrate oxidation is found in women compared with men during moderate intensity exercise (17, 18). Only a few studies examining abdominal fat loss have included women (9, 15), yet a different response to diet and exercise interventions may occur in women than has been observed in men. Because women with type 2 diabetes have altered fat metabolism, they may not have a similar abdominal fat loss as that previously reported in obese men. Because visceral fat is an important predictor of metabolic complications of obesity and insulin resistance (6, 19), we believed it was necessary to understand how abdominal fat is lost in this population.

The purpose of this study was to determine the independent effects of a weight-reducing diet or diet plus exercise on abdominal fat loss and glycemic control in obese, postmenopausal women with type 2 diabetes. We also examined the

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Abbreviations: AUC, Area under the curve; D+E, diet plus exercise; EX, exercise alone; FFA, free fatty acid; GLUT-4, glucose transporter-4; HbA_{1c}, hemoglobin A_{1c}; HDL, high-density lipoprotein; HMF, high monounsaturated fat; HRT, hormone replacement therapy; MRI, magnetic resonance imaging; RMR, resting metabolic rate; SAT, sc adipose tissue; VAT, visceral adipose tissue; $\dot{V}O_2$, O_2 consumption.

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effects of exercise alone, without weight loss, on total abdominal fat and abdominal fat distribution. We hypothesized that a similar energy deficit, independent of treatment (diet or diet plus exercise), would reduce total abdominal fat, particularly VAT, and this would be associated with improvements in insulin sensitivity and glycemic control.

The previous studies (9, 12) examining abdominal fat loss in obese individuals have used the traditionally recommended higher carbohydrate diet; however, in individuals with type 2 diabetes, a high carbohydrate diet may adversely affect glycemic and lipid control (20, 21). A high monounsaturated fat (HMF) diet is now recommended because of its beneficial effects on glucose and lipid levels (20, 22). Unlike previous studies, in this study we prescribed a HMF diet to these women with type 2 diabetes, as is currently recommended.

Subjects and Methods

Subjects

A total of 108 women with type 2 diabetes were initially screened by phone for participation in the study. Forty obese (body mass index, >30 kg/m^2), postmenopausal women, 50–70 yr old, qualified and agreed to participate in this study; they signed an informed consent approved by Syracuse University and State University of New York Upstate Medical University institutional review boards. Thirty-three women completed the study; three women dropped out of the study due to compliance problems, such as inability to attend the exercise sessions or accurately follow the dietary intervention, and four women dropped out due to health problems unrelated to the study. All women were postmenopausal for a minimum of 1 yr. The subjects had been diagnosed with type 2 diabetes for at least 1 yr, based on the American Diabetes Association criteria (23). Twenty-two of the subjects were taking oral hypoglycemic agents [sulfonylureas (n = 3), metformin (n = 14), combination of sulfonylureas and metformin (n = 5)]; all dosages were stable for a minimum of 1 yr before participation, and the dose of these medications did not change over the course of the study period (Table 1). Eleven women were not taking any medication for diabetes. Ten of the 33 women were receiving hormone replacement therapy [HRT; Prempro (Wyeth-Ayerst Labs, Philadelphia, PA) (n = 5), Estrace (Bristol Meyers Squibb Co., Rockaway, NJ) (n = 2), Ogen (Pharmacia, New York, NY) (n = 1), Femhrt (Parke-Davis, Morris Plains, NJ) (n = 1), and Activell (Novo Nordisk Pharmaceutical, Princeton, NJ) (n = 1)] for a minimum of 1 yr (average, 7.6 ± 2.5 yr), and the dose of HRT did not change over the course of the study period. Subjects were excluded if they were taking insulin, thiazolidinediones, β-blockers, or lipid-lowering medications. None of the women was participating in any type of regular physical activity or diet treatment for the year before entry into the study, and all were weight stable. All women were in good health with no major complications related to diabetes, such as cardiovascular disease or neuropathy.

Experimental design

Using a counterbalanced study design, the women were assigned to one of three interventions: HMF diet alone (D), exercise alone (EX), or HMF diet plus exercise (D+E). Before the start of the intervention, women came to the laboratory for testing, which included an exercise stress test, body composition analysis for total and regional body fat, resting metabolic rate (RMR) determination, and a meal test. After the 14-wk intervention, all tests were repeated by the same investigator.

TABLE 1. Oral hypoglycemic drugs taken by the subjects in the D+E, D, and EX intervention groups

	D+E (n = 11)	D (n = 11)	EX (n = 11)
Metformin	5	5	4
Sulfonylureas		2	1
Metformin + sulfonylureas	2	1	2
No medications	4	3	4

Anthropometric and body composition tests

Body weight was measured without shoes on a standing scale that was calibrated to 0.1 kg. Body height was measured without shoes on a wall-mounted stadiometer. Waist circumference was determined from the magnetic resonance imaging (MRI) scan using a single MRI slice at the anatomic site of the umbilicus (NIH software, Bethesda, MD). Standing hip circumference was measured at the widest part of the hips. Total body fat was determined by underwater weighing or the BodPod (Life Measurement, Inc., Concord, CA). All subjects were assessed by the same technology pre- and postintervention.

Exercise stress test

A continuous treadmill exercise stress test was performed to determine aerobic fitness and detect any potential cardiac abnormalities using a protocol previously described (24). Briefly, this was a walking protocol using continuous 2-min stages, starting at 2.0 mph. The speed was increased by 0.5 mph every 2 min to 3.5 mph, followed by a 2% grade increase every 2 min thereafter until volitional fatigue. Using standard, open circuit, spirometric techniques (Quark b^2 metabolic cart, Cosmed, Rome, Italy; calibrated with known gases), metabolic data (O_2 consumption ($\dot{V}O_2$), CO_2 production) were collected. If the test met the previous established criteria (24), the $\dot{V}O_2$ peak was determined as the highest $\dot{V}O_2$ attained. If the subject did not meet the established criteria, the stress test was repeated so that peak $\dot{V}O_2$ could be determined. A continuous 10-lead electrocardiogram recording was performed, and the electrocardiogram was evaluated by a cardiologist for any cardiac abnormalities.

RMR and meal test

Subjects reported to the human performance laboratory at 0700 h after a 12-h overnight fast and a 48-h absence from any type of exercise. RMR measurement was conducted for estimation of 24-h energy expenditure and was used in the estimation of each subject's daily energy requirement. Subjects rested quietly in a supine position in a quiet thermoneutral environment for 30 min. This was followed by 30 min of indirect calorimetry measurements (2900 Metabolic Cart, SensorMedics, Anaheim, CA). After determination of the RMR, a meal test was conducted. A catheter was placed in the anticubital vein of the subject's arm, and a venous blood sample was drawn for fasting blood glucose, insulin, lipids, and hemoglobin A_{1c} (HbA_{1c}) determinations. After the fasting sample was drawn, a meal composed of 66 g carbohydrates, 29 g protein, and 11 g fat (Ensure, Ross Laboratory, Columbus, OH) was administered, and blood samples for glucose and insulin determinations were collected every 30 min for the next 4 h. Women were instructed to take their oral hypoglycemic medications before administration of the RMR and meal tests.

MRI

Measurements of total abdominal fat, VAT, and SAT were conducted by MRI as previously reported (24). MRI scans were obtained using standard T1-weighted spin echo imaging with respiratory compensation (GE Sigma 1.5 T MRI scanner, General Electric, Milwaukee, WI). The MRI scans ranged from the superior portion of the head of the femur to the most superior part of the kidneys, and approximately 40 consecutive slices (1 cm thick) were individually analyzed (24). MRI data were analyzed using an automated fat segmentation program run on a SUN workstation (SUN Microsystems, Santa Clara, CA). Total abdominal fat was calculated for each slice, and VAT was segmented out of each MRI slice using the outer borders of the abdominal wall. SAT was determined by subtracting VAT from total abdominal fat. The calculation of total abdominal fat, VAT, or SAT was the sum of all slices in the scanned region. Test-retest reliability for repeated image analysis was r = 0.9999 ($P < 0.0001$) (24).

Interventions

Diet. The D intervention was an HMF diet comprised of 40% fat (30% monounsaturated, 5% polyunsaturated, and 5% saturated), 40% carbo-

hydrates (15% simple and 25% complex carbohydrates), and 20% protein (20). Olive oil was used as the main dietary source of monounsaturated fat. A 2510-kJ (600 kcal) deficit/d from the subjects' weight maintenance total energy consumption was produced based on the subject's RMR and was adjusted for daily activity. At the start of the diet, subjects participated in a nutritional consultation session, where they were prescribed the dietary intervention. A 7-d diet model was given to the subjects to ensure that they would follow the diet as accurately as possible. Subjects also met once a week for 1 h for motivational support and questions concerning compliance with the diet. A 1-d dietary recall was completed every 2 wk and analyzed (Food Processor 7.81, ESHA Research, Salem, OR) for total energy consumption and relative percentages of nutrients (fat, carbohydrates, and protein) to ensure compliance with the prescribed dietary regimen. Subjects were also asked to refrain from any type of regular physical activity during the 14 wk of the diet treatment.

Exercise. The EX intervention consisted of a supervised walking program three times per week for 50 min at an intensity of 65–70% VO_2 peak. Other activities, such as bicycling and stepping, were included periodically in the exercise program to reduce the risk of injury and also to provide some variety in the workout. Heart rate monitors as well as the ratings of perceived exertion scale were used to help monitor the exercise intensity. Approximately 1050–1250 kJ (250–300 kcal) were expended during each exercise session as determined from the American College of Sports Medicine physical activity energy expenditure equations (25). During the exercise treatment, 1-d dietary recalls were completed every 2 wk and analyzed for nutrient composition and energy intake to ensure that all subjects continued following their usual eating patterns.

D+E. The D+E intervention consisted of the same HMF diet and exercise program as the diet alone and the exercise alone treatments, respectively. A total of 2510 kJ (600 kcal) deficit was used to match the energy deficit of the diet intervention. On the exercise days, an approximately 1460-kJ (400 kcal) deficit was produced from the diet, and an energy expenditure of approximately 1050 kJ (200 kcal) was produced from the exercise; on the nonexercise days, a 2510-kJ (600 kcal) deficit was produced from the diet.

Blood analysis

Blood was collected, centrifuged, and stored at −80 C for later analysis. Blood glucose was measured using the Cholestech LDX analyzer (Hayward, CA). Blood lipids were analyzed by Cardiovascular Specialty Laboratories (Atlanta, GA). Low concentrations of cholesterol and triglycerides were determined using enzymatic methods (Beckman Coulter Diagnostics, Fullerton, CA) using a modified automated method calibrated at 55 mg/dl for cholesterol and 45 mg/dl for triglycerides. Linearity can be demonstrated down to 0.5 mg/dl. Phospholipids and free cholesterol were determined using enzymatic kits (Wako Pure Chemical, Osaka, Japan) adapted for the CX7 chemistry autoanalyzer. Lipoprotein particle size (26) and lipoprotein fractionation (27, 28) were measured as previously described. HbA_{1c} was analyzed by a commercial kit from Diabetes Technologies, Inc. (Thomasville, GA). Plasma insulin concentrations were measured in duplicate using commercial RIA kits (Diagnostic Products Corp., Los Angeles, CA). The sensitivity of the assay was 1.2 μU/liter. Intra- and interassay coefficients of variation for the insulin assay were 3.0% and 14.5%, respectively. Whole body insulin sensitivity was estimated by the equation of Matsuda and DeFronzo (29).

Statistical analysis

Comparison of the descriptive data for the three intervention groups was conducted using a one-way ANOVA. A mixed model, repeated measures ANOVA was used to determine the differences from pre- to postintervention between groups for all dependent variables. Because the lipid data did not have a normal distribution, the data were log-transformed before statistical analysis. Multiple regression analysis using the enter mode was employed to examine whether changes in abdominal fat were independent predictors of changes in glucose and insulin levels. Glucose and insulin areas under the curve (AUCs) were determined by the use of a trapezoid method (version 2.01, GraphPad, Inc., San Diego, CA). The threshold for significance in all tests was set at $P = 0.05$. Statistical analysis was performed with SPSS for Windows, version 11 (SPSS, Inc., Chicago, IL). All values are presented as the mean ± SEM.

Power calculations to determine the number of subjects were based on a 20% difference in the mean using an $\alpha = 0.05$ and a power greater than 0.80. This difference was used because this abdominal fat loss resulted in significant differences in previous studies of healthy obese men.

Results

Baseline characteristics

The baseline anthropometric, metabolic, and abdominal fat measurements were not different among groups (Fig. 1 and Table 2). The women were similar in age (~57 yr), body weight (~92 kg), percent body fat (~36%), and cardiovascular fitness (~19.8 ml/kg·min). The average duration of diabetes was approximately 3 yr in these women. The relative abdominal fat distribution was approximately 34.5% VAT and about 66% SAT, and the size of the abdominal fat depots was not different between groups at baseline (Fig. 1). At baseline, plasma total cholesterol, low-density lipoprotein cholesterol, and triglycerides were slightly elevated in these women with diabetes, whereas high-density lipoprotein (HDL) cholesterol was within the desirable range. No significant difference was found in the baseline characteristics of the women receiving HRT and those who were not; thus the data were not analyzed by HRT use.

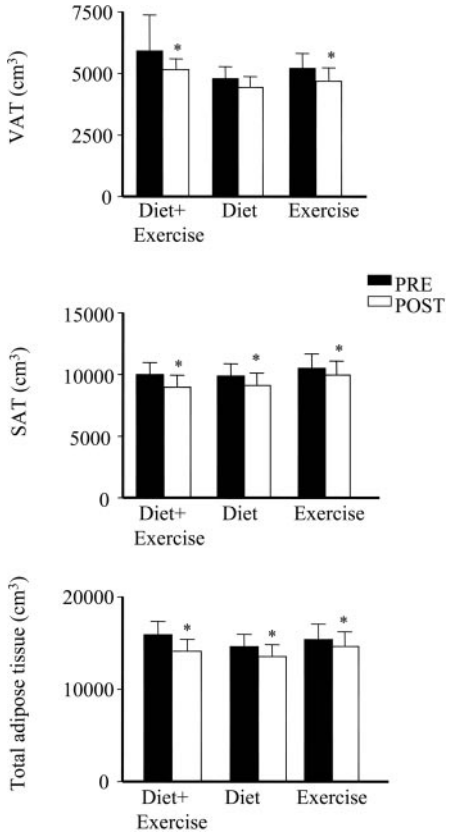

FIG. 1. Changes in total abdominal adipose tissue, VAT, and SAT before and after 14 wk of diet and/or exercise intervention. *, $P < 0.05$ *vs.* pretreatment.

TABLE 2. Changes in anthropometric, abdominal fat distribution, and metabolic variables from pre- to postintervention in the D, EX, and D+E intervention groups

	D+E (n = 11)		D (n = 11)		EX (n = 11)	
	Pre	Post	Pre	Post	Pre	Post
Anthropometric						
Body weight (kg)	89.5 ± 5.9	84.1 ± 5.7[a]	92.4 ± 5.9	88.8 ± 5.7[a]	92.9 ± 6	91.2 ± 5.6
Body mass index (kg/m^2)	33.7 ± 1.7	31.7 ± 1.7[a]	34.3 ± 1.8	32.9 ± 1.6[a]	35.9 ± 2.2	35.3 ± 2.1
Waist (cm)	115 ± 3.4	111 ± 3.3[a]	115 ± 4	111 ± 5[a]	120 ± 4.5	117 ± 4.5[a]
% Body fat	36.5 ± 1.1	31.1 ± 1.1[a]	35.5 ± 1.2	30.3 ± 1.2[a]	36.8 ± 1.0	34.5 ± 1.4[a]
Fat-free mass (kg)	55.5 ± 15	53.3 ± 14[a]	53.1 ± 6.7	51.5 ± 6.3[a]	50.1 ± 2.7	50.1 ± 2.2
VO_2 peak (ml/min)	1850 ± 106	1987 ± 95[a]	1589 ± 134	1561 ± 163	1877 ± 236	2193 ± 292[a]
Metabolic						
HbA_{1c}	6.8 ± 0.5	6.3 ± 0.7	7.3 ± 0.5	7.8 ± 0.6	6.4 ± 0.8	6.6 ± 0.3
Fasting glucose (mmol/liter)	9.0 ± 0.9	6.7 ± 0.7[a]	9.5 ± 0.8	8.2 ± 0.8[a]	8.2 ± 0.6	8.7 ± 0.8
Fasting insulin (pmol/liter)	97.2 ± 21.6	46.9 ± 11.6	34.7 ± 22.7	27.9 ± 12	61.2 ± 20.2	49.6 ± 19.1
Total cholesterol (mg/dl)	5.4 ± 0.4	4.8 ± 0.3[a]	5.8 ± 0.4	5.5 ± 0.3[a]	5.6 ± 0.4	5.7 ± 0.2
Low-density lipoprotein cholesterol (mg/dl)	3.1 ± 0.3	2.8 ± 0.2	3.5 ± 0.3	3.4 ± 0.2	3.6 ± 0.4	3.6 ± 0.2
HDL cholesterol (mg/dl)	1.2 ± 0.1	1.1 ± 0.1[a]	1.3 ± 0.1	1.1 ± 0.1[a]	1.3 ± 0.1	1.3 ± 0.1
Triglycerides (mg/dl)	2.4 ± 0.5	2.2 ± 0.3	2.7 ± 0.5	2.0 ± 0.3	1.7 ± 0.2	1.9 ± 0.3
Total cholesterol/HDL cholesterol	4.26 ± 0.3	4.35 ± 0.3	4.58 ± 0.3	4.9 ± 0.3	4.7 ± 0.5	4.9 ± 0.4

Values are the mean ± SE.
[a] $P < 0.05$ *vs.* pre.

Diet and exercise adherence

One-day dietary recalls were submitted by all 33 participants every other week. Analysis of the dietary records revealed that the energy deficit remained stable throughout the 14-wk intervention period, with an average energy deficit of 2386 ± 63 kJ/d (570 ± 15 kcal/d) for the D intervention, 2595 ± 71 kJ/d (620 ± 17 kcal/d) for the nonexercise days, and 1653 ± 50 kJ/d (395 ± 12 kcal/d) for the exercise days for the D+E intervention [1050–1250 kJ (250–300 kcal) were estimated for the exercise session]. The monounsaturated fat intake was maintained at the recommended levels (~39%) and ranged between 35–42% of the total fat consumed. No significant differences were found in the energy deficit and fat intake between the D and D+E group. In the EX group, analysis of the 1-d dietary records showed that both total dietary intake and dietary composition remained stable during the 14-wk intervention period.

Exercise adherence, as evident from the percent attendance, duration, and intensity of exercise, was not different between the EX and D+E groups ($P > 0.05$). Exercise attendance averaged 96%, with a duration of 48 min/session, and the intensity of each exercise session was approximately 79% of the heart rate maximum.

Aerobic capacity

Exercise training resulted in similar improvements in aerobic fitness measured by $\dot{V}O_2$ peak in the EX and D+E intervention groups ($P < 0.05$). $\dot{V}O_2$ peak was significantly increased from approximately 1860 ml/min at baseline to about 2090 ml/min at the end of the EX and D+E interventions ($P < 0.05$), whereas there was no change in $\dot{V}O_2$ peak after the D intervention ($P > 0.05$; Table 2).

Anthropometric and body composition

Similar reductions in body weight were found with the D and D+E interventions (−4.5 kg; $P < 0.05$), whereas only a minimal reduction in body weight (−1.7 kg) was found in the EX group. Total body fat decreased by 14.7% with D+E, 14.6% with D, and 6% with EX ($P < 0.05$). No significant differences were found in any of the anthropometric and body composition changes between the D and D+E interventions ($P > 0.05$). A decrease in fat-free mass was found with the D and D+E interventions (~2 kg; $P < 0.05$), whereas no change in fat free mass was observed with EX alone.

Abdominal fat distribution

Regardless of the intervention, changes in abdominal fat distribution occurred. With all interventions, a reduction of about 4 cm in waist circumference was found ($P < 0.05$). The MRI analysis revealed that total abdominal fat and SAT were significantly reduced with the D and D+E interventions ($P < 0.05$), with no significant differences between the two groups (Fig. 1). VAT decreased significantly from pre- to postintervention with the EX and D+E interventions (5204 ± 598 *vs.* 4675 ± 550 cm^3 and 5912 ± 484 *vs.* 5152 ± 439 cm^3, respectively; $P < 0.05$), but no change in VAT was found with the D intervention (4785 ± 480 *vs.* 4425 ± 435 cm^3). The relative changes in the VAT and SAT depots were −12.8% and −10.7%, respectively, with the D+E intervention. Similar to the D+E intervention, EX also resulted in reductions in total abdominal fat and SAT ($P < 0.05$).

Metabolic variables

Fasting glucose and insulin concentrations. The D and D+E interventions resulted in similar reductions in fasting plasma

glucose concentrations ($P < 0.05$; Table 2). At baseline, fasting insulin concentrations were higher in the D+E group. In response to all interventions, a nonsignificant decrease in fasting insulin concentrations was found ($P = 0.06$). HbA_{1c} did not change over the course of the study with any of the interventions.

Meal test. The glucose AUC was significantly reduced ($P < 0.05$) in response to the D and D+E interventions, with no group differences, and no change was found in the glucose AUC with the EX intervention (Fig. 2). The insulin AUC was significantly reduced with the EX and D+E interventions ($P = 0.05$), whereas the D intervention did not cause a significant reduction ($P > 0.05$). Both exercise interventions resulted in a greater change in insulin AUC ($P < 0.05$) than was seen with the D intervention. Calculated insulin sensitivity [D: pre, 10.5 ± 2.1; post, 14.2 ± 2.4; D+E: pre, 3.6 ± 2.1; post, 6.9 ± 2.4 $(mg/dl \cdot mU/ml)^2$; $P < 0.05$] improved with the D and D+E interventions. Exercise also improved calculated insulin sensitivity from pre- to postintervention ($P < 0.05$), with no differences between groups.

Lipid profile. HDL cholesterol levels fell in the D and D+E groups, but were preserved in the EX group (Table 2). There were no group differences between the D and D+E interventions. Triglyceride levels (log-transformed) were significantly lower with the D and D+E interventions ($P < 0.05$), but no significant change was found with the EX intervention. The changes in triglycerides were also associated with decreases in HDL triglycerides and low density lipoprotein triglycerides (log-transformed) in the D and D+E groups ($P < 0.05$; Table 3). HDL subfractions and particle size were also not altered with the interventions. Lipoprotein(a) significantly increased from pre- to postintervention with EX, but not with the other interventions ($P < 0.05$). No differences in apolipoproteins CIII, E, A-I, and B were found among interventions (data not shown). There were no differences between the D and D+E groups for any of the lipid variables.

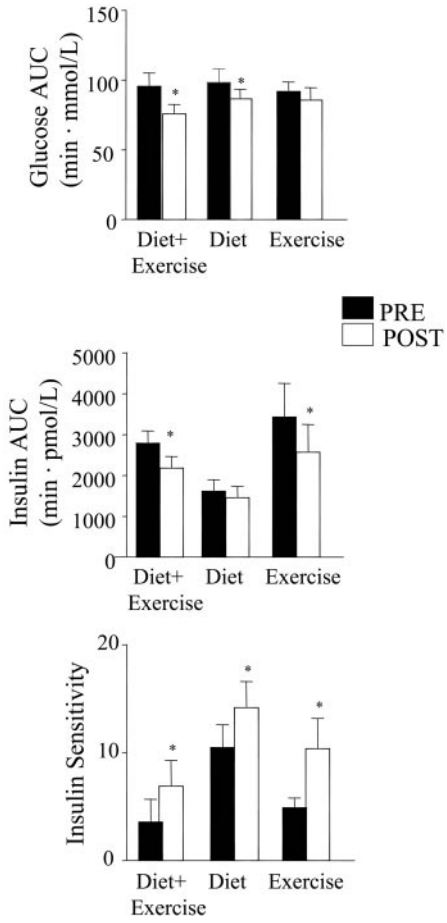

FIG. 2. Insulin AUC, glucose AUC, and insulin sensitivity (29) in each group after the 14-wk intervention period. *, $P < 0.05$ *vs.* pretreatment.

Relationship between metabolic status and abdominal fat changes

To examine the relationship between metabolic status and abdominal fat changes, a multiple regression analysis was employed (Table 4). Alterations in abdominal fat distribution were a significant predictor of the reductions in glucose levels and insulin resistance in these postmenopausal women with type 2 diabetes. Changes in total abdominal fat and SAT were independent predictors of the changes observed in fasting glucose concentration ($P < 0.01$), explaining 32.7% and 9.7% of the variance, respectively, whereas changes in total abdominal fat and VAT were independent predictors of the change in glucose AUC (22.1% and 14.1% of the variance, respectively). VAT change was the only significant predictor of the change in fasting insulin (16%) and insulin AUC (19.4%). Total abdominal fat, VAT, and SAT decrements had no predictive value on the reduction in calculated insulin sensitivity ($P > 0.05$).

Discussion

Previous work in healthy obese individuals (8–10, 12, 13) has demonstrated that diet- and/or exercise-induced weight loss reduces abdominal adiposity, which, in turn, contributes to a decrease in insulin resistance. However, this previous work did not include women with type 2 diabetes. This is a unique population to study, because type 2 diabetes results in more serious derangements in glucose and fat metabolism than typically seen in obese, nondiabetic individuals (1, 7) and because earlier work had shown that during exercise women have a greater lipid and a lower carbohydrate oxidation than those observed in men (17, 18). This may result in differences in abdominal fat loss with lifestyle interventions. The current study was the first to employ an HMF diet in the investigation of the effects of a weight reduction diet and/or exercise on the distribution of abdominal fat loss and insulin sensitivity in obese, postmenopausal women with type 2 diabetes. The findings reveal that 1) both an HMF diet and D+E intervention reduce total and sc abdominal fat and improve metabolic control in obese, postmenopausal women with type 2 diabetes; 2) exercise is required for a reduction in VAT, because the HMF diet alone did not reduce this fat depot; and 3) changes in VAT are necessary for changes in fasting and postmeal (AUC) insulin levels.

Diet studies using an HMF diet have reported improve-

TABLE 3. Changes in log-transformed lipid data for each intervention

	D+E (n = 11)		D (n = 11)		EX (n = 11)	
	Pre	Post	Pre	Post	Pre	Post
LDL size	1.41 ± 0.005	1.41 ± 0.003	1.41 ± 0.005	1.41 ± 0.003	1.06 ± 0.006	1.05 ± 0.006
HDL2 size	1.06 ± 0.006	1.06 ± 0.008	1.07 ± 0.007	1.06 ± 0.009	0.98 ± 0.006	0.98 ± 0.006
HDL3 size	0.99 ± 0.006	0.99 ± 0.005	0.99 ± 0.006	0.99 ± 0.005	0.75 ± 0.03	0.75 ± 0.03
HDL2 (%)	1.61 ± 0.06	1.67 ± 0.05	1.51 ± 0.07	1.57 ± 0.05	1.74 ± 0.03	1.76 ± 0.03
HDL3a (%)	1.76 ± 0.03	1.72 ± 0.03	1.81 ± 0.03	1.78 ± 0.04	0.85 ± 0.05	0.86 ± 0.02
Cholesterol	2.23 ± 0.04	2.22 ± 0.04	2.23 ± 0.04	2.23 ± 0.04	2.25 ± 0.08	2.27 ± 0.07
TG	2.38 ± 0.06	2.31 ± 0.06[a]	2.32 ± 0.06	2.29 ± 0.06[a]	2.27 ± 0.07	2.26 ± 0.04
HDL	1.65 ± 0.03	1.64 ± 0.03	1.61 ± 0.03	1.62 ± 0.03	1.65 ± 0.04	1.69 ± 0.03
LDL	2.02 ± 0.05	1.99 ± 0.05	2.01 ± 0.05	2.00 ± 0.05	1.99 ± 0.04	2.07 ± 0.03
Lp(a)	0.79 ± 0.5	0.87 ± 0.6	0.77 ± 0.5	0.86 ± 0.5	1.10 ± 0.3	1.33 ± 0.2[a]
VLDL cholesterol	1.36 ± 0.06	1.33 ± 0.07	1.46 ± 0.06	1.49 ± 0.06	1.26 ± 0.09	1.31 ± 0.09
VLDL TG	1.92 ± 0.07	1.89 ± 0.08	2.02 ± 0.07	1.99 ± 0.08	1.80 ± 0.1	1.83 ± 0.09
VLDL plasma	1.26 ± 0.03	1.23 ± 0.05	1.43 ± 0.03	1.41 ± 0.05	1.23 ± 0.07	1.19 ± 0.1
LDL cholesterol	1.97 ± 0.04	1.94 ± 0.04	1.93 ± 0.04	1.92 ± 0.04	1.95 ± 0.03	1.98 ± 0.03
LDL TG	1.84 ± 0.07	1.72 ± 0.09[a]	1.71 ± 0.07	1.65 ± 0.08[a]	1.73 ± 0.08	1.67 ± 0.07
LDL plasma	1.73 ± 0.05	1.64 ± 0.08	1.84 ± 0.05	1.82 ± 0.08	1.82 ± 0.03	1.86 ± 0.03
HDL cholesterol	1.68 ± 0.03	1.67 ± 0.03	1.60 ± 0.03	1.60 ± 0.03	1.61 ± 0.04	1.62 ± 0.02
HDL TG	1.62 ± 0.08	1.55 ± 0.08[a]	1.48 ± 0.07	1.38 ± 0.82[a]	1.45 ± 0.09	1.34 ± 0.09[a]
HDL plasma	2.06 ± 0.04	1.99 ± 0.06	2.05 ± 0.04	2.04 ± 0.06	2.02 ± 0.04	2.07 ± 0.06

All data are log transformed. LDL, low-density lipoprotein; Lp(a), lipoprotein(a); TG, triglycerides; VLDL, very low-density lipoprotein.
[a] $P < 0.05$.

ments in glycemic and lipid control in type 2 diabetes, unlike the deterioration observed in the lipid profile with a high carbohydrate diet (21, 30, 31). Consistent with these findings, we found improvements in glycemic and lipid control with the HMF diet in postmenopausal women with type 2 diabetes, supporting the use of this dietary intervention for this population. In particular, an approximately 20% decrease in fasting glucose levels as well as an approximately 17% decrease in glucose AUC during the meal test were observed in the women on the HMF diet regardless of whether they exercised. Although dramatic decreases in blood lipids were not found, changes in triglyceride and HDL triglyceride levels occurred, and in many subjects these were clinically significant changes. There were no negative ramifications of the HMF diet on HDL cholesterol, HDL subfractions, or HDL particle size. This supports previous research (20) indicating that the HMF diet does not result in a worsening of the lipid profile. Also, the responses of HDL cholesterol and its subfractions to exercise training have been found to be dependent on endothelial lipase genotype, which may explain why in our sample we found no significant change with exercise alone (32). Lipoprotein(a) increased slightly in the EX group, which has been shown to occur in some previous studies using exercise interventions (33).

Because there is a strong association between abdominal fat, especially VAT, and type 2 diabetes, the goal of most weight loss programs is to try to reduce this fat depot. The addition of aerobic exercise to the diet intervention augmented the abdominal fat loss, causing a 13% reduction in VAT, compared with a 7.5% reduction with the diet alone intervention. In contrast to our findings, Janssen *et al.* (9) observed similar reductions in VAT in healthy men and women with both D and D+E interventions when using a hypocaloric diet with dietary fat intake restricted to less than 30%. Exercise was necessary to reduce VAT in the present study, suggesting that exercise alters adipose tissue metabolism in individuals, possibly by mobilizing FFA from VAT. The greater visceral fat loss observed with the exercise intervention could be attributed to the higher sensitivity of the omental and mesenteric adipocytes to lipolytic stimulation in response to catecholamines (34). The dramatic increase in catecholamines during exercise could stimulate β-adrenoreceptors in the VAT depot, resulting in greater FFA release and oxidation. The disordered fat storage and mobilization with type 2 diabetes may require increased lipolytic stimulation for the VAT to respond. Thus, exercise may be necessary to use this adipose tissue depot effectively. It is also possible that the HMF diet may affect VAT differently than the standard diet that has been used in previous studies (9, 12). Summers *et al.* (35) reported a greater decrease in abdominal sc fat in obese individuals when they were fed a diet higher in polyunsaturated fat than a diet higher in saturated

TABLE 4. Regression results for the prediction of blood glucose and insulin change (Δ) measures using abdominal fat distribution changes

Dependent variable	Independent variable	β	Beta	*P*	sr^2	Multiple r	r^2	Overall *P*
Fasting glucose Δ	Total abdominal fat Δ	0.0214	0.572	0.001	0.327	0.572	0.327	0.001
	sc fat Δ	0.0188	0.351	0.06	0.097	0.485	0.235	0.018
Glucose AUC Δ	Total abdominal fat Δ	0.009	0.471	0.006	0.221	0.471	0.221	0.006
	Visceral fat Δ	0.0157	0.422	0.024	0.141	0.496	0.246	0.015
Fasting insulin Δ	Visceral fat Δ	0.046	0.448	0.022	0.159	0.433	0.188	0.044
Insulin AUC Δ	Visceral fat Δ	2.838	0.495	0.011	0.194	0.443	0.197	0.037

Total abdominal fat change was an independent variable in a single linear regression model; visceral fat change and sc fat change were entered in a separate multiple regression model.

fats. In our study the use of HMF may have resulted in a slightly greater loss of SAT than that observed previously. More research needs to be conducted comparing the effects of different diets on abdominal fat loss. Lastly, the differences in abdominal fat loss reported in this study may be due to differences in MRI data acquisition. Previous studies have used approximately five abdominal slices (9, 12, 15) when determining changes in abdominal fat loss, whereas in the present study the entire abdominal region was included in the analysis (~35 slices). It has been reported that analyzing only a few slices does not yield as precise results a analyzing the total abdominal region, probably explaining the discrepancy with previous reports (36).

In this study we demonstrated that exercise alone, without weight loss, is sufficient to produce a reduction in waist circumference and improvements in VAT, SAT, and total abdominal fat in women with type 2 diabetes. Exercise also protected the fat-free mass in this group, unlike both the D and D+E groups where approximately 2 kg was lost. Our findings of decreases in total abdominal fat, VAT, and SAT are consistent with those by Mourier and colleagues (37), who noted a similar change in men with type 2 diabetes after 4 months of aerobic training and supplementation with branched chain amino acids. In a healthy population, Ross *et al.* (12, 15) also demonstrated a similar reduction in VAT with 12 wk of aerobic exercise training. In comparison with previous studies of healthy, young, obese individuals and those with type 2 diabetes, in whom a preferential reduction in VAT was noted (8–10, 12, 13), we found that both VAT and SAT decreased in postmenopausal women with type 2 diabetes after with and/or exercise training. Thus, we demonstrated that exercise training can cause decreases in waist circumference and abdominal fat loss in both VAT and SAT depots, indicating that metabolic changes are occurring before weight loss can be detected. This finding in women supports the earlier report in men and women (12, 15).

Dietary and exercise interventions are frequently prescribed in an effort to improve both insulin resistance and insulin sensitivity in individuals with type 2 diabetes. In the present study, calculated insulin sensitivity increased by about 44% in all groups. Pooling the data from all subjects, the multiple regression analysis revealed that VAT accounted for 20% of the change in insulin AUC. Similarly, some studies (37) found that VAT accounts for changes in insulin sensitivity, but unlike other studies (38, 39) we found no association between changes in SAT and those in insulin AUC. However, SAT loss was associated with improvements in fasting plasma glucose levels in these women, similar to findings in premenopausal women (40). It should be noted that exercise alone, without weight loss, also resulted in changes in insulin sensitivity. Exercise training has previously been shown to increase muscle glucose transporter-4 (GLUT-4) transcription and GLUT-4 content, increase the number of muscle membrane GLUT-4 receptors, and increase nonoxidative glucose disposal (41). Despite the improvements in insulin levels, exercise alone did not significantly improve fasting glucose levels. In the present study, glycemic control was assessed 48 h after the last exercise session. It is possible that the lack of improvement in fasting glucose levels with the exercise alone intervention can be attributed to the time of measurement. Overall, our data indicate that in women with type 2 diabetes, loss of VAT is important for metabolic improvement, and exercise is essential for this VAT loss.

This study demonstrated that a 14-wk, home-based, lifestyle intervention can improve insulin sensitivity, providing additional evidence that the loss in abdominal fat affects metabolic control in women with type 2 diabetes. Unlike previous studies of healthy obese individuals, we studied individuals with type 2 diabetes who were taking oral hypoglycemic medications. Potentially, these medications could affect the magnitude and distribution of abdominal fat loss. In the present study, lower total abdominal fat and SAT levels were observed in the women taking sulfonylureas compared with women taking metformin, the combination of sulfonylureas and metformin, or no hypoglycemic medication; however, a similar pattern of fat loss was seen regardless of the oral hypoglycemic drug taken. Patients taking thiazolidinediones, which are known to affect VAT and SAT, were excluded from our study. Limited information is available on the impact of these oral hypoglycemic agents on abdominal fat loss with weight loss interventions.

Our data add to the current literature by demonstrating that moderate weight loss (~4.5 kg) results in abdominal fat loss in women with type 2 diabetes; however, exercise is essential for a decrease in the VAT depot in this population. Exercise alone, without weight loss, is sufficient to result in abdominal fat loss and improved insulin sensitivity. Because changes in insulin levels are associated with the changes in abdominal fat loss, particularly in the VAT depot, this finding emphasizes the need for exercise in the treatment of women with type 2 diabetes.

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