High Adipose LPL Activity and Adipocyte Hypertrophy Reduce Visceral Fat and Metabolic Risk in Obese, Older Women

Monica C. Serra1,2, Alice S. Ryan1,2, John D. Sorkin1,2, Knachelle H. Favor1,2, and Andrew P. Goldberg1,2

Objective: To determine whether higher subcutaneous adipose tissue lipoprotein lipase activity (AT-LPLA) is associated with greater triglyceride (TG) storage in subcutaneous adipose tissue (SAT), thereby reducing visceral adipose tissue (VAT) accumulation and metabolic dysfunction.

Methods: Obese postmenopausal women (60 ± 1 years, mean ± SEM; N = 101) had body composition measured by DXA and CT and had fat aspirations to measure fat cell weight (FCW) and AT-LPLA. Women were ranked by visceral to total abdominal fat ratio (VAT/TAF), and the lowest and highest groups (n = 24) matched for % fat and age.

Results: The prevalence of metabolic dysfunction was 7- to 10-fold higher in women with high VAT/TAF (Ps < 0.01). Women with low VAT/TAF had 11% and 6% lower abdominal and gluteal FCW but 28% and 54% higher AT-LPLA/10^6 cells in abdominal and gluteal fat, respectively. Abdominal FCW correlated with AT-LPLA in women with low (r = 0.63, P < 0.01) but not high (r = 0.14, P = 0.52) VAT/TAF, and these lines differed in slope (P < 0.05) and intercept (P < 0.01), suggesting greater capacity for TG storage with low VAT/TAF. There were no relationships between gluteal FCW and AT-LPLA. The relationship between SAT and abdominal AT-LPLA (r = 0.39, P < 0.01) suggests that higher AT-LPLA is associated with SAT adipocyte hypertrophy, which reduces visceral adiposity and metabolic risk in obese, older women.

Conclusions: These results suggest that higher AT-LPLA is associated with SAT adipocyte hypertrophy, which reduces visceral adiposity and metabolic risk in obese, older women.

Introduction

The accumulation of fat in visceral adipose tissue (VAT) is strongly associated with insulin resistance, impaired glucose tolerance (IGT), and metabolic syndrome (MSyn) (1,2). Several mechanisms are proposed to explain the increased uptake and storage of triglycerides (TG) in VAT. One theory posits that the impaired expandability of subcutaneous adipose tissue (SAT) during the development of obesity results in the overflow of lipid into VAT and ectopic sites, such as skeletal muscle, liver, and pancreas (3,4). This is supported by studies that show that reduced lipogenesis and adipogenesis in SAT are associated with greater fat deposition in VAT and metabolic dysfunction in adolescent obesity (5), and in response to weight gain during high-fat overfeeding in adults (6).

Larger adipocytes accumulate more TG and release more free fatty acids (FFA) than smaller adipocytes (7,8). The uptake and storage of TG in adipocytes is primarily regulated by adipose tissue lipoprotein lipase (AT-LPL), the rate limiting enzyme in the clearance of circulating TG-rich lipoproteins. Insulin is a key regulator of AT-LPL, and the hyperinsulinemia and insulin resistance of obesity is associated with decreased sensitivity of adipocyte lipolysis to insulin, higher AT-LPL activity (AT-LPLA) and greater fat cell size (9,10). The higher AT-LPLA and lower basal lipolysis in gluteal (GLT) and abdominal (ABD) SAT in postmenopausal compared to perimenopausal women suggests that regional differences in AT-LPLA may contribute to the higher body weight, central adiposity, and metabolic abnormalities associated with menopause (11,12). This is supported by studies that show that age-associated regional differences in fat deposition correlate with regional AT-LPLA.
Obesity

Central obesity (waist based on the presence of three or more of the following criteria: elevated blood pressure (>130/85 mm Hg or antihypertensive treatment), and dyslipidemia (TG >2 mmol l\(^{-1}\) or HDL-C <0.9 mmol l\(^{-1}\)); none were on a lipid-lowering medication. The diagnosis of MSyn was made if the presence of any two criteria was met.

Approximately 23% of women were matched for % body fat (VAT/TAF ratio) and 24 women with the lowest VAT/TAF were included. Women were ranked by their visceral to total abdominal fat ratio (VAT/TAF), and 24 women with the highest VAT/TAF were matched for % body fat (<20 kg weight change) over the prior 6 months. Women with diabetes (fasting glucose >7 mmol l\(^{-1}\) or 2-h glucose tolerance test glucose >11 mmol l\(^{-1}\)) on oral agents or insulin, TG >400 mg dl\(^{-1}\), overt cardiovascular, renal, or liver disease, or unstable medical conditions were excluded. Women were ranked by their visceral to total abdominal fat ratio (VAT/TAF), and 24 women with the lowest VAT/TAF were matched for % body fat (±2%) and age (±5 years) to 24 women with the highest VAT/TAF. Approximately 23% of women in each group took ACE inhibitors, none took a diuretic, and none were on a lipid-lowering medication. The diagnosis of MSyn was based on the presence of three or more of the following criteria: central obesity (waist >88 cm), impaired glucose metabolism (fasting glucose >5.6 mmol l\(^{-1}\)), elevated blood pressure (>130/85 mmHg or antihypertensive treatment), and dyslipidemia (TG >1.7 mmol l\(^{-1}\) or HDL-C <1.3 mmol l\(^{-1}\)) (18).

Body composition

Body mass index (kg m\(^{-2}\)) was calculated from height and weight measured using a stadiometer and electric scale, respectively. Percent body fat and fat-free mass (FFM) were measured by dual-energy X-ray absorptiometry scan (DXA: DPX-IQ or Prodigy; LUNAR Radiology, Madison, WI). CT scans were performed with a PQ 6000 scanner (Marconi Medical Systems, Cleveland, OH) to quantify VAT, SAT, and mid-thigh low-density lean tissue areas. For SAT and VAT, a single 5 mm scan was taken at the L4-L5 region while the subject was supine, with arms stretched overhead. A second scan performed at the level of the mid-thigh quantified low-density lean tissue area, and data for the right leg are reported (19). CT data are expressed as cross-sectional area of tissue (cm\(^2\)), where muscle area is considered 30-80 Hounsfield units (HU), adipose tissue ~190 to ~30 HU, and low-density lean tissue 0-29 HU (20).

| TABLE 1 Physical characteristics of subjects with low and high VAT/TAF |
| --- | --- | --- |
| Low VAT/TAF (N = 24) | High VAT/TAF (N = 24) | P value |
| Age (years) | 58 ± 1 | 62 ± 2 | 0.07 |
| BMI (kg m\(^{-2}\)) | 30 ± 1 | 33 ± 1 | 0.02 |
| Waist circumference (cm) | 89 ± 2 | 101 ± 3 | <0.01 |
| Body fat (%) | 46 ± 1 | 47 ± 1 | 0.31 |
| Fat-free mass (kg) | 42 ± 1 | 44 ± 1 | 0.04 |
| SAT area (cm\(^2\)) | 459 ± 19 | 421 ± 17 | 0.08 |
| VAT area (cm\(^2\)) | 113 ± 6 | 214 ± 12 | <0.01 |
| VAT/TAF | 0.20 ± 0.01 | 0.34 ± 0.01 | <0.01 |
| Mid-thigh LDLT area (cm\(^2\)) | 16.5 ± 1.5 | 24.7 ± 1.9 | <0.01 |
| Systolic blood pressure (mm Hg) | 122 ± 3 | 126 ± 2 | 0.25 |
| Diastolic blood pressure (mm Hg) | 70 ± 3 | 76 ± 2 | 0.03 |

Values are expressed as means ± SEM. SAT = subcutaneous abdominal adipose tissue; VAT = visceral abdominal adipose tissue; TAF = total abdominal fat (SAT+VAT); LDLT = low-density lean tissue.

(13,14). The purpose of this study was to determine the relationship of subcutaneous AT-LPLA to subcutaneous adipocyte size, visceral adiposity, and metabolic dysfunction in obese, older Caucasian women. We hypothesized that the ability of adipocytes in SAT to hypertrophy, reduces visceral adiposity and cardiometabolic risk in obese, older women.

Methods

Subjects

One hundred one healthy, obese [body fat >35% (15)] Caucasian postmenopausal women who had previously provided University of Maryland IRB approved informed consent and participated in weight loss studies (16,17) were included if they had a DXA scan for body composition, a computed axial tomography (CT) scan to measure SAT and VAT, and a fat aspiration to measure AT-LPLA in ABD and GLT sites. The women were sedentary (<20 min of aerobic exercise two times per week) and weight stable (<2 kg weight change) over the prior 6 months. Women with diabetes (fasting glucose >7 mmol l\(^{-1}\) or 2-h glucose tolerance test glucose >11 mmol l\(^{-1}\)) on oral agents or insulin, TG >400 mg dl\(^{-1}\), overt cardiovascular, renal, or liver disease, or unstable medical conditions were excluded. Women were ranked by their visceral to total abdominal fat ratio (VAT/TAF), and 24 women with the lowest VAT/TAF were matched for % body fat (±2%) and age (±5 years) to 24 women with the highest VAT/TAF. Approximately 23% of women in each group took ACE inhibitors, none took a diuretic, and none were on a lipid-lowering medication. The diagnosis of MSyn was based on the presence of three or more of the following criteria: central obesity (waist >88 cm), impaired glucose metabolism (fasting glucose >5.6 mmol l\(^{-1}\)), elevated blood pressure (>130/85 mmHg or antihypertensive treatment), and dyslipidemia (TG >1.7 mmol l\(^{-1}\) or HDL-C <1.3 mmol l\(^{-1}\)) (18).

Metabolic testing

To minimize the effects of diet composition on metabolism, a registered dietitian weight stabilized the women on a Step I American Heart Association diet (21) for ~4 weeks prior to metabolic testing. Dietary intake compliance was verified by food records, and counseling was provided when saturated fat exceeded 10% of calories and desirable fat intake was >35%. For 2-days prior to all metabolic tests the women were given a weight maintaining diet composed of 50-55% carbohydrate, ~30% fat, and 15-20% protein, based on their food records. Body weight was stable (±0.5 kg) during metabolic tests. Blood was drawn following a 12-h fast for measurement of lipoprotein lipase, as previously described (22), on two separate occasions a week apart and averaged. A 2-h oral glucose tolerance test was performed with measures of glucose and insulin at fasting and 30 min increments following ingestion of 75g glucose. Plasma glucose concentrations were measured using the glucose oxidase method (2300 STAT Plus; YSI, Yellow Springs, OH) and immunoreactive insulin by radioimmunoassay (Linco Research, St. Charles, MO). Subjects were classified as having normal (fasting glucose <7 mmol l\(^{-1}\) or IGT (2-h glucose of 7.8–11.0 mmol l\(^{-1}\)) none were diabetic (23).

Adipose tissue lipoprotein lipase

After an overnight fast, SAT was aspirated under local anesthesia (0.5% xylocaine) from both the ABD and GLT regions using a 10 mm mini-cannula and adipocytes were isolated by collagenase digestion (1 mg ml\(^{-1}\)) and fat cells weights (FCW) and surface areas (FCSA) were calculated from fat cell diameter (10,24). AT-LPLA...
was measured as heparin elutable LPL in 40–50 mg pieces, as previously described (9). To evaluate substrate quality and variability within each assay, 20 μl of a human postheparin plasma pool (stored at −80°C) was incubated with each substrate for 30 min and the percentage of 14C-FFA counts hydrolyzed was calculated. The inter-assay pool variability was 13% for the pool activity.

Glucose metabolism

Values are expressed as means ± SEM.

Table 2: Metabolic measurements of subjects with low and high VAT/TAF

| Metabolic measurement | Low VAT/TAF | High VAT/TAF | P value |
|-----------------------|-------------|--------------|---------|
| Glucose metabolism    |             |              |         |
| Fasting glucose (mmol l⁻¹) | 5.2 ± 0.1  | 5.6 ± 0.1  | <0.01   |
| 2-h glucose (mmol l⁻¹) | 6.4 ± 0.5  | 8.0 ± 0.4  | <0.01   |
| HOMA-IR               | 2.5 ± 0.3   | 4.4 ± 0.3   | <0.01   |
| Lipid metabolism      |             |              |         |
| Triglycerides (mmol l⁻¹) | 1.2 ± 0.1  | 1.8 ± 0.1  | <0.01   |
| Total cholesterol (mmol l⁻¹) | 5.1 ± 0.2  | 5.4 ± 0.2  | 0.24    |
| LDL-C (mmol l⁻¹)      | 3.1 ± 0.1   | 3.4 ± 0.2   | 0.35    |
| HDL-C (mmol l⁻¹)      | 1.4 ± 0.1   | 1.2 ± 0.1   | <0.01   |
| HDL2-C (mmol l⁻¹)     | 0.24 ± 0.04 | 0.14 ± 0.03 | 0.05    |
| HDL3-C (mmol l⁻¹)     | 1.18 ± 0.03 | 1.07 ± 0.04 | <0.01   |
| Metabolic risk        |             |              |         |
| IGT prevalence (%)    | 8           | 58           | <0.01   |
| MSyn prevalence (%)   | 8           | 83           | <0.01   |

Statistics

Standard methods were used to compute means and standard errors of the means (SEM). Analysis of covariance and chi-square tests compared differences in variables of interest between low vs. high VAT/TAF. Pearson and Spearman correlation coefficients were calculated after log transformation of plasma TG, AT-LPLA, FCW, and SA, as appropriate. Linear regression predicting FCW and FCSA from a model including the log of AT-LPLA, an indicator variable for low and high VAT/TAF, and a log AT-LPLA*indicator variable interaction was used to determine if the slope or intercept differed between the two groups. None of these data met criteria for outliers and high leverage data points as calculated using Cook’s distance (25) or were >2 standard deviations from the mean. HOMA-IR was calculated as [(fasting insulin (μU ml⁻¹) × fasting glucose [mmol l⁻¹])/22.5] (26). Data were analyzed using SPSS Version 20 and SAS 9.3. All tests were two-tailed, and P values <0.05 were considered statistically significant.

Results

Subject characteristics

The 24 women with high VAT/TAF were of comparable age, % body fat, and systolic blood pressure, but had higher BMI and waist circumference (P<0.05) than those with low VAT/TAF. As expected, women with high VAT/TAF tended to have 9% lower SAT (P=0.08) and 89% higher VAT (P<0.01), and thus a higher VAT/TAF (P<0.01). Women with high VAT/TAF had a higher mid-thigh low-density lean tissue area (P<0.01), evidence of ectopic fat distribution in muscle (Table 1).

Glucose and lipid metabolism

The women with high VAT/TAF had higher mean fasting and 2-h glucose and approximately twofold higher HOMA-IR than women with a low ratio (all Ps < 0.01) (Table 2). Plasma TG levels were higher and HDL-C, HDL2-C, and HDL3-C were lower (P<0.05) in women with high VAT/TAF; however, total cholesterol and LDL-C did not differ between the groups. The prevalence of IGT was seven times (58% vs. 8%, P<0.01) and MSyn 10 times (83% vs. 8%, P<0.01) higher in women with high compared to those with lower VAT/TAF. VAT/TAF correlated positively with mid-thigh low-density lean tissue area (r=0.58), fasting (r=0.45) and 2-h (r=0.40) glucose, HOMA-IR (r=0.51), and TG (r=0.56) (all Ps<0.01) and negatively with HDL-C (r=−0.29, P<0.05) across the groups (N=48); however, there were no significant relationships within groups.

FCW, FCSA, and AT-LPLA by VAT/TAF group

Women with low VAT/TAF had 11% lower ABD (P<0.05) and 6% lower GLT (P=0.22) FCW, as well as 7% lower ABD (P<0.05) and 4% lower GLT (P=0.23) FCSA than women with high VAT/TAF. This was associated with 28 and 54% higher AT-LPLA when expressed per 10⁶ cells and 40 and 50% higher AT-LPLA when expressed per FCSA in both ABD and GLT subcutaneous tissue, respectively, despite comparable % body fat (Table 3). In the women with low VAT/TAF, increasing FCW (and FCSA data not shown) correlated with ABD AT-LPLA (r_cell=0.63, P<0.01; r_FCSA=0.33, P<0.05, Figure 1A), suggesting that with increasing subcutaneous adipocyte size these women have higher AT-LPLA and greater capacity to store fat and expand their adipocytes. In contrast, women with high VAT/TAF have higher FCW (and FCSA data not shown) correlated with ABD AT-LPLA (r_cell=0.14, P=0.52; r_FCSA=−0.09, P=0.67, Figure 1B), suggesting less adipocyte capacity to store more TG and expand. The significant difference in the lines depicting these relationships in the ABD site by slope (P=0.05) and y-intercept (P<0.01) whether AT-LPLA is expressed per 10⁶ cells or FCSA (data not shown) suggests that adipocytes of women with low VAT/TAF have greater potential to hypertrophy due to higher AT-LPLA/cell than women with high VAT/TAF. The relatively flat relationship of GLT FCW to AT-LPLA in both the low (r_cell=0.29, P=0.18 [Figure 1C]; r_FCSA=−0.21, P=0.34) and high (r_cell=0.05, P=0.82 [Figure 1D]; r_FCSA=−0.32, P=0.14) VAT/TAF groups suggests that GLT stores may not be able to store more TG in these obese women. HOMA-IR did not correlate with FCW, FCSA, or regional AT-LPLA. However, there was a positive relationship between SAT area and ABD AT-LPLA, expressed per 10⁶ cells (r=0.39, P<0.01) and FCSA (r=0.31, P<0.05), but not for VAT area, supporting our hypothesis that higher AT-LPLA may enhance TG storage in SAT, thereby potentially limiting TG “spillover” into VAT.
TABLE 3 Adipose tissue FCW and AT-LPLA by lowest and highest VAT/TAF

|                      | Lowest VAT/TAF  | Highest VAT/TAF | P value |
|----------------------|-----------------|-----------------|---------|
| Abdominal FCW (µg triglyceride/cell) | 0.73 ± 0.03      | 0.82 ± 0.02     | 0.02    |
| Gluteal FCW (µg triglyceride/cell)    | 0.76 ± 0.03      | 0.81 ± 0.03     | 0.22    |
| Abdominal adipocyte surface area (µm²) | 2.4 ± 0.06       | 2.6 ± 0.05      | 0.02    |
| Gluteal adipocyte surface area (µm²)  | 2.5 ± 0.06       | 2.6 ± 0.06      | 0.23    |
| Abdominal AT-LPLA (nmol FFA/min/10⁶ cells) | 3.7 ± 0.7       | 2.9 ± 0.4       | 0.32    |
| Gluteal AT-LPLA (nmol FFA/min/10⁶ cells) | 5.7 ± 0.9       | 3.7 ± 0.7       | 0.09    |
| Abdominal AT-LPLA (nmol FFA/min/µm²)  | 2.0 ± 0.3        | 1.4 ± 0.2       | 0.19    |
| Gluteal AT-LPLA (nmol FFA/min/µm²)    | 3.0 ± 0.4        | 2.0 ± 0.5       | 0.16    |

Values are expressed as means ± SEM.

Discussion

Lipoprotein lipase is the rate-limiting enzyme in the clearance of circulating TG-rich lipoproteins and the uptake and storage of energy stores in adipose tissue (27). AT-LPLA increases with feeding and weight gain, and high levels of AT-LPLA are associated with abdominal (central) body fat distribution and weight regain after diet-induced weight loss (27,28). The results of this study suggest that obese postmenopausal women with a lower ratio of VAT/TAF have greater capacity for adipocyte hypertrophy, and this is evidenced by their higher AT-LPLA and smaller adipocytes than women with high VAT/TAF. The significantly steeper slope of the relationship between ABD FCW and AT-LPLA in women with low compared to high VAT/TAF is compatible with their smaller ABD fat cells having greater lipogenic capacity to store more lipid than women with high VAT/TAF, who seem to have saturated their subcutaneous adipocyte TG stores. The flat relationship of GLT FCW to AT-LPLA in both low and high VAT/TAF groups suggests the GLT storage depot already may be saturated in these obese women. Collectively, these data support the theory that molecular mechanisms (5) regulate the ability of subcutaneous adipocytes to hypertrophy (3,4), increasing their capacity to store more lipid subcutaneously and prevent the metabolic consequences of lipid spillover to visceral and other ectopic sites. The lower VAT area, muscle fat infiltration, and cardiometabolic risk profile of obese women with low VAT/TAF further supports our hypothesis that higher AT-LPLA in SAT prevents ectopic lipid accumulation and metabolic risk factors associated with visceral adiposity. The congruent findings in obese adolescents (5) suggest that, across the age-span, obese individuals may remain metabolically healthy as long as their subcutaneous adipose depots can expand to more efficiently store excess lipid and prevent its accumulation in visceral tissues (29).

The number of preadipocytes, heterogeneity in adipogenesis, lipogenesis, and adipocyte functionality, and the vascular capacity of adipose tissue for de novo angiogenesis can enhance an obese person’s ability to store fat subcutaneously (30,31), thereby avoiding the adverse health consequences of visceral fat accumulation. While we did not examine the contribution of adipocyte hyperplasia to subcutaneous lipid storage capacity, the higher FCW in women with lower compared to higher VAT/TAF makes it likely that there also are more small subcutaneous adipocytes available to hypertrophy in response to weight gain or fat overfeeding, as suggested by Alligier et al. (6) and Kashiwagi et al. (32). However, despite the larger peak diameter of subcutaneous ABD adipocytes in adolescents with high vs. low VAT/TAF, Kursawe et al. (5) found similar fat cell number and a reduced fraction of large fat cells in the high VAT/TAF group. The notion that the ability to expand subcutaneous adipocytes could prevent or treat type 2 diabetes and metabolic dysfunction is supported by the fact that thiazolidinedione (TZD) administration is associated with SAT hypertrophy, reductions in VAT, and improvements in lipid and glucose metabolism in type 2 diabetes. The ability of TZDs to increase PPARγ and other lipogenic gene expression in SAT suggests they stimulate subcutaneous, not visceral, adipocyte hypertrophy and would likely reduce VAT accumulation in obese women with high VAT/TAF (33). This observation suggests that in contrast to visceral fat, subcutaneous fat has beneficial effects on metabolism.

Weight loss and aerobic exercise have tissue specific effects on fat and muscle AT-LPLA. While weight loss does not appear to affect skeletal muscle LPLA (34), the effects of weight loss on AT-LPLA appears to be heterogeneous, with some studies showing increases (28,35), decreases (36), or both (12). This variability may be due to differences in study populations (i.e. gender, pre- vs. postmenopausal women, and moderate vs. morbid obesity) and the amount and duration of weight loss. Further, the amount of weight regained following weight loss appears to be greater in women who increase AT-LPLA with weight loss (12). In contrast, exercise reduces adipose and increases skeletal muscle AT-LPLA, decreasing lipid storage in adipose tissue and increasing muscle fat oxidation (37,38). The effects of these lifestyle interventions on the lipogenic capacity of adipose tissue and muscle, adipogenesis and angiogenesis warrants further investigation in obese individuals with high VAT who are at risk for diabetes and cardiometabolic complications.

Although these results suggest that the impaired ability to store lipid subcutaneously may increase lipid accumulation in VAT and skeletal muscle, similar findings in adipose tissue biopsies from VAT would be conclusive, but this is not possible without biopsies during abdominal surgery. Unfortunately, we did not have enough tissue to measure additional mechanisms regulating fat cell expandability, such as adipocyte hyperplasia, capillarization and biomarkers of angiogenesis and lipogenesis. These results also should be tempered by the cross-sectional nature of this study and female population; it will be valuable to study the effects of exercise and
weight loss on adipose tissue metabolism in comparably obese men who tend to have twice as much VAT and are at higher risk for type 2 diabetes and MSyn than obese women (39), as well as African Americans who tend to be more insulin resistant than Caucasian women, despite less visceral fat (40). These limitations are, however, somewhat balanced by our strong study design that controlled for obesity, age, and race by matching Caucasian women with low and high VAT/TAF for % body fat and age, studied obese postmenopausal women at high risk for type 2 diabetes and cardiovascular disease, monitored diet compliance, and excluded subjects with metabolic dysfunction such as diabetes, hypothyroidism, and renal disease, which could alter adipose metabolism and AT-LPLA (27).

In sum, these results support the hypothesis that the enhanced ability to store TG in SAT reduces lipid accumulation in VAT and skeletal muscle and their associated metabolic abnormalities (1,6). The finding that higher AT-LPLA was associated with a greater ability to expand adipocytes in women with low VAT/TAF, provides a potential mechanism by which excess circulating TG-FFA can be stored, thereby preventing VAT accumulation and metabolic dysfunction. Studies to determine the effects of exercise, weight loss, and pharmacotherapy on the mechanisms regulating fat accumulation in SAT and VAT could reveal therapies that could expand subcutaneous adipocytes, thereby preventing lipid accumulation in ectopic tissues and its cardiometabolic consequences.  

Acknowledgments

Our appreciation is extended to the women who participated in this study. We are grateful to the nurses, exercise physiologists, and registered dietitians of the University of Maryland School of Medicine.
Division of Gerontology and Geriatric Medicine and Baltimore VA GRECC for their assistance in this project. © 2015 The Obesity Society

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