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Sex differences in insulin action and body fat distribution in overweight and obese middle-aged and older men and women

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Abstract

Controversy exists as to whether there are differences in insulin action between older men and women, and what factors contribute to these differences. This study tests the hypothesis that sex differences in regional fat distribution contribute to a disparity in insulin sensitivity in older men vs. older women. Healthy, older (50–71 years), sedentary men ($n = 28$) and women ($n = 29$) were recruited to participate in the study. Body fat, fat-free mass (FFM), and visceral (VAT) and subcutaneous abdominal (SAT) adipose tissue areas were measured by DXA and computed tomography (CT). For measurements of insulin-stimulated glucose disposal (M), insulin was infused at a constant rate of $240 \text{ pmol} \cdot \text{m}^{-2} \cdot \text{min}^{-1}$, and M was calculated between the 90th and 120th min of the hyperinsulinemic–euglycemic clamp. The men weighed 16% more and had 16% higher waist and 4% lower hip circumferences than women ($p < 0.05$ for all). Total fat mass and SAT were 21% and 33% lower and FFM was 49% higher in men than in women, whereas waist-to-hip ratio (WHR) and VAT:SAT ratio were 21% and 56% higher in men than in women ($p < 0.05$ for all). Although insulin concentrations during the glucose clamp were higher in men, M was 47% lower in men vs. women (21.7 ± 1.1 vs. $46.7 \pm 3.1 \text{ } \mu\text{mol} \cdot \text{L}^{-1} \cdot \text{kg}_{\text{FFM}}^{-1} \cdot \text{min}^{-1}$, $p < 0.05$). The sex-related differences in M persisted after controlling for insulin concentrations during the glucose clamp, for waist, WHR, and VAT:SAT. Older men are more insulin resistant than women, despite lower body fat and subcutaneous abdominal fat. This difference in insulin sensitivity is not explained by abdominal fat distribution, therefore other metabolic factors contribute to the sex differences in insulin sensitivity.

Keywords

obesity; fat distribution; insulin sensitivity; gender; aging

Introduction

The age-related decline in physical activity and muscle mass and the increase in body fat contribute to the worsening of insulin sensitivity with aging in men and women (Coon et al. 1992; Goldberg et al. 1996; Kohrt et al. 1993). Controversy exists as to whether there are differences in insulin action in older men compared with older women, and what factors might contribute to the sex-related differences in insulin action. Despite significantly lower percent body fat, some investigators show that middle-aged and older men tend to be more

insulin resistant than middle-aged and older women (Cnop et al. 2003; Ryan et al. 2001a), whereas others report that older men and women have comparable levels of insulin resistance (Lee et al. 2005). A better understanding of the mechanisms underlying the differences in insulin action between older men and women and the factors that might contribute to these differences could result in more effective preventive measures for the development of type 2 diabetes and its cardiovascular complications.

Past research suggests the importance of the amount and the distribution of fat mass, as opposed to the amount of muscle mass, in contributing to insulin sensitivity. Central (abdominal) obesity, as assessed by waist circumference and waist-to-hip ratio (WHR), is a strong predictor of insulin sensitivity in older people (Coon et al. 1992; Kohrt et al. 1993; Pratley et al. 1995). Indeed, a number of cross-sectional studies have shown that the decline in insulin sensitivity with aging is related to higher abdominal obesity and overall fatness (Basu et al. 2003; Coon et al. 1992; Goodpaster et al. 2003; Imbeault et al. 2003). In addition, high levels of upper body fat are associated with an increased risk of cardiovascular disease (CVD), insulin resistance, and diabetes (Anderson et al. 1988; Freedman et al. 1990; Kissebah et al. 1982). In studies that use computed tomography (CT) to assess abdominal adiposity and body fat distribution, lower insulin sensitivity is associated with higher subcutaneous abdominal fat (SAT) in young and middle-aged men and women (Goodpaster et al. 1997), and with higher visceral abdominal fat (VAT) in postmenopausal women (Ryan et al. 2001b) and older men (Ross et al. 2002). In addition, previous studies suggest that higher accumulation of VAT in men may contribute to their higher incidence of CVD vs. women (Freedman et al. 1990; Kotani et al. 1994; Lemieux et al. 1994).

Sex differences in the amount and distribution of body fat are well established (Lee et al. 2005; Goodpaster et al. 2003; Cnop et al. 2003; Freedman et al. 1990). Although women tend to have lower body mass, the percentage of body fat is significantly higher in women than in men. In addition, using either WHR or the ratio of VAT:SAT to determine degree of abdominal adiposity, women tend to have lower levels of abdominal adiposity than men (Shimokata et al. 1989; Cnop et al. 2003; Lee et al. 2005). Higher levels of abdominal adiposity have been significantly associated with a higher risk of insulin resistance and cardiovascular disease (Meyers et al. 1991; Bonora et al. 1992). The contribution of differences in regional fat distribution to sex-related differences in insulin action in older men and women is not well established.

Thus, the primary aim of this study was to examine the contribution of sex differences in regional fat distribution to differences in insulin sensitivity in older, overweight, and obese men and women. We hypothesized that sex differences in regional fat distribution, specifically visceral and subcutaneous abdominal fat accumulation and WHR, contribute to lower insulin sensitivity in sedentary older obese and overweight men compared with women of similar age and body mass index (BMI).

Materials and methods

Subjects

We recruited 57 healthy, Caucasian, non-smoking, sedentary, overweight and obese (BMI 25–40 kg·m⁻²), middle-aged and older (50–71 y) men (*n* = 28) and postmenopausal women (*n* = 29) from the community. The postmenopausal women had not menstruated for at least 1 year and had plasma follicle-stimulating hormone levels > 30 mIU·L⁻¹. None of the women were currently or had a history of taking hormone replacement therapy. All subjects were weight stable (<2 kg weight change) and sedentary (<20 min of aerobic exercise twice per week) for the previous 6 months. Written informed consent was obtained from all

individuals according to the guidelines of the University of Maryland Institutional Review Board for Human Research.

All subjects underwent initial screening evaluations, including a medical history, physical examination, fasting blood profile, and 12-lead resting electrocardiogram. Individuals with evidence of diabetes by history, fasting plasma glucose $\geq 7.0 \text{ mmol}\cdot\text{L}^{-1}$, or 2 h plasma glucose during an oral glucose tolerance test (OGTT) $\geq 11.1 \text{ mmol}\cdot\text{L}^{-1}$ (Report of the Expert Committee 2002), hypertension (blood pressure higher than 160/90 mm Hg), hyperlipidemia (triglycerides $\geq 4.5 \text{ mmol}\cdot\text{L}^{-1}$), heart disease, cancer, liver, renal, or hematological disease were excluded. Subjects were also excluded if they were being treated with an antihypertensive, lipid-lowering, oral hypoglycemic or other medication known to affect glucose metabolism.

Body composition measurements

Height (in centimetres) and mass (in kilograms) were measured to calculate BMI. Circumference measurements of the waist (at the narrowest point superior to the hip) and the hip (at the greatest gluteal protuberance) were measured in duplicate. All participants underwent a total-body scan using dual-energy X-ray absorptiometry (DXA, Model DPX-L, Lunar Corp., Madison, Wis.) to determine percent body fat, fat mass, and fat-free mass (FFM, total body bone mineral content plus lean tissue mass). A single-slice CT taken at the intervertebral space between L4 and L5 was performed using a PQ6000 scanner (General Electric) to measure visceral and subcutaneous abdominal adipose tissue areas (Hounsfield units (HU): -190 to -30) (Ryan and Nicklas 1999). WHR and VAT:SAT were calculated from anthropometric and CT measurements.

Hyperinsulinemic–euglycemic glucose clamp

For 2 days before the clamp study, subjects were provided with a prepared, weight-maintaining, American Heart Association Step I diet (American Heart Association Steering Committee 1988) by the dietary staff of the Baltimore Geriatric Research, Education, and Clinical Center (GRECC). The number of calories given to each subject was estimated from the 7 d food record previously completed by the subject and standard estimates of energy expenditure (Harris and Benedict 1919). The composition of the diet was 50%–55% carbohydrate ($>200 \text{ g}\cdot\text{d}^{-1}$ complex carbohydrates), 15%–20% protein, $<30\%$ fat, and $300\text{--}400 \text{ mg}\cdot\text{d}^{-1}$ cholesterol, with a polyunsaturated – saturated fat ratio of between 0.6 and 0.8. All tests were performed in the morning after a 12 h overnight fast. All subjects were weight-stable within 1 kg for at least 2 weeks before metabolic testing.

Whole-body insulin-stimulated glucose disposal (M) was measured using the hyperinsulinemic–euglycemic glucose clamp technique (DeFronzo et al. 1979). Briefly, an intravenous catheter was inserted into an antecubital vein for infusion of insulin and glucose, and a second catheter was inserted into a dorsal hand vein for blood sampling. The hand was then placed in a warming box thermostatically controlled at 70°C to arteriaize the blood. After a priming dose of insulin, Humulin insulin (Eli Lilly, Indianapolis, Ind.) was infused at a constant rate of $240 \text{ pmol}\cdot\text{m}^{-2}\cdot\text{min}^{-1}$ for 2 h. Plasma glucose levels were measured at 5 min intervals using the glucose oxidase method (Beckman Instruments, Fullerton, Calif.) and maintained at basal levels with a variable infusion of 20% glucose, which was adjusted according to a computerized algorithm. Samples were obtained at 10 min intervals during the clamp for subsequent measurement of plasma insulin levels by radioimmunoassay (Millipore, Linco Research, Inc., St. Charles, Mo.).

Calculations

The mean plasma glucose levels were 5.7 ± 0.1 and 5.5 ± 0.1 mmol·L⁻¹ (mean $\pm$ SEM), which was $98.8\% \pm 0.3\%$ and $97.5\% \pm 0.2\%$ of the desired goal for men and women, respectively. Mean glucose disposal rates (M, $\mu\text{mol}\cdot\text{L}^{-1}\cdot\text{kg}_{\text{FFM}}^{-1}\cdot\text{min}^{-1}$) were calculated at 30 min intervals, with the average over the last 30 min of a 120 min infusion used as the individual's mean glucose disposal rate. Steady-state plasma insulin levels were averaged over the same interval.

Statistical analyses

Data were analyzed using Statview for Windows and SAS (both from SAS Institute Inc., Cary, N.C.). All data were normally distributed. Differences between groups were determined by unpaired Student's *t* tests. Selected variables with statistically significant differences in men compared with women were used in subsequent analyses of covariance. Pearson's correlation coefficients were calculated between M and selected measures of body composition. Statistical significance was set at $p \leq 0.05$. All data are presented as the means $\pm$ standard error of the mean (SEM).

Results

Physical characteristics

The men and women were of similar age (range 50–71 y, 63 ± 2 vs. 60 ± 1 y, respectively, $p > 0.05$) (Table 1). Because the men were 9% taller and weighed 16% more than the women ($p < 0.05$), there was no difference in BMI between the 2 groups. The waist circumference was 16% higher, whereas the hip circumference was 4% lower and WHR was 21% higher in the men than in the women ($p < 0.05$). Percent body fat and fat mass were 32% and 21% lower, whereas FFM was 49% higher in the men ($p < 0.05$). The SAT area was 33% lower in the men than in the women ($p < 0.05$), but the 9% greater VAT area in the men did not differ significantly from that in the women. Thus, ratio of VAT:SAT was 56% higher in the men, due to their lower amount of SAT ($p < 0.0001$).

Metabolic characteristics

The study included 9 men and 7 women with impaired glucose tolerance by OGTT (Report of the Expert Committee 2002). Fasting insulin concentrations were 36% higher in the men ($p < 0.05$), with no differences in fasting glucose concentrations. The men had a 47% lower M ($\mu\text{mol}\cdot\text{L}^{-1}\cdot\text{kg}_{\text{FFM}}^{-1}\cdot\text{min}^{-1}$), despite 22% higher insulin concentrations during the clamp compared to the women ($p < 0.05$, Table 2). Analyses of covariance were utilized to examine whether differences in M remained after controlling for sex-related differences in body composition. Three separate analyses of covariance were performed, with differences in M controlled for differences in insulin concentrations during the glucose clamps, and for differences in VAT:SAT, waist, or WHR. Since the interaction terms in these analyses were not statistically significant, only main effects were examined. These analyses demonstrated that the sex-related differences in M persisted after controlling for the insulin concentrations during the glucose clamps and for the differences in VAT:SAT, waist, or WHR.

Correlations between M and body fat distribution are displayed in Table 3 and Fig. 1. There was a significant negative relationship between M and waist circumference in both the men and women (Fig. 1). There was also a significant negative relationship between M and VAT and M and WHR in the women, but not in the men. M was not related to SAT or VAT:SAT in either the men or the women.

Discussion

The age-associated decline in cardiovascular fitness and muscle mass and the increase in body fat contribute to the worsening of insulin sensitivity with aging in both men and women (Coon et al. 1992; Goldberg et al. 1996; Kohrt et al. 1993). Insulin resistance in older individuals is often associated with the components of the metabolic syndrome, including increased abdominal obesity, hypertension, and hyperlipidemia. Results of this study show that older obese men are more insulin resistant than older obese women, despite lower total body fat and subcutaneous abdominal fat and higher fat-free mass, WHR, and VAT:SAT. In addition, the men remain more insulin resistant than women even after M is adjusted for sex-related differences in abdominal fat distribution. Thus, other mechanisms such as skeletal muscle metabolism and insulin signaling must contribute to the gender differences in insulin resistance in older individuals. These and other potential mechanisms will require further investigation to prescribe preventive lifestyle and pharmacological therapies to prevent diabetes and the CVD complications associated with insulin resistance.

The results of several previous investigations were inconclusive for sex-related differences in insulin sensitivity in older and middle-aged men compared with older and middle-aged women, with 2 studies observing a significant difference in insulin sensitivity (Cnop et al. 2003; Ryan et al. 2001a) and 1 study observing no difference in insulin sensitivity (Lee et al. 2005). The present study observed a significant difference in insulin sensitivity between older men compared with older women, similar to the results of Ryan et al. (2001a) and Cnop et al. (2003). Ryan et al. (2001a) examined the effects of resistance training on insulin action in insulin-resistant older men and women, and observed 26% lower baseline insulin action values in the men than in the women. Cnop et al. (2003) examined the relationships between adiponectin, body fat, insulin sensitivity, and plasma lipoproteins, and observed a 14% lower insulin action value in men than in women aged 32–75 years, a wider age range than the present study. The results of these studies are in contrast to those of Lee et al. (2005), who observed no difference in insulin sensitivity between older men and women in a study examining predictors of insulin sensitivity in older adults.

There are a few potential explanations for why the results of the present study differ from previously published studies. It is possible that the differences in technique and the assumptions used to determine insulin sensitivity (rapidly sampled intravenous glucose tolerance tests vs. euglycemic clamp) may have contributed to the differences in results of the present study and those of Lee et al. (2005). Differences in subject selection may also contribute to the conflicting results. The present study included Caucasian men and postmenopausal women not receiving hormone replacement therapy over an approximately 20 year age span over the age of 50 years, with a BMI in the overweight or obese range (25–40 kg·m⁻²). Postmenopausal status was confirmed by criteria including lack of menses for at least 1 year and elevated plasma follicle-stimulating hormone levels. In the study by Lee et al. (2005), subjects were of a similar age range to the present study (50–80 years), but the BMI ranged from 15 to 40 kg·m⁻². There were no efforts by Lee et al. (2005) to control for hormone replacement therapy in post-menopausal female subjects. In addition, subjects who were taking anti-hypertensive medications were tapered from their medications and studied after a minimum of 4 weeks without drug therapy. In the present study, subjects were allowed to continue taking anti-hypertensive medications during the study period, as long as the specific medication did not affect glucose metabolism.

Contrary to the findings in previous studies (Goodpaster et al. 2003; Ryan et al. 2001a; Ross et al. 2002; Kotani et al. 1994; Freedman et al. 1990; Lemieux et al. 1994), VAT was not significantly higher in the older men than in the older women, and there was only a significant relationship between M and VAT in the women, not in the men. SAT was

significantly higher in the women than in the men, but contrary to the findings of other investigators, there was not a significant relationship between SAT and insulin sensitivity (Goodpaster et al. 1997). Our selection of a homogenous population of obese, healthy subjects with a narrow range of body fatness and the small sample size may have limited the ability to detect significant sex differences in VAT deposition or a relationship between M and VAT, SAT, or the ratio of VAT:SAT in the men and women. In addition, few, if any, of the women in the present study could be classified as being upper-body obese, whereas few, if any, of the men could be classified as being lower-body obese. Thus, sex-related differences in body fat distribution limit the interpretation of the results primarily to older women with lower-body obesity and men with upper body obesity. The present study observed that sex-related differences in M persisted after controlling for differences in VAT:SAT, waist, or WHR. Previous studies by this and other laboratories have observed significant relationships between insulin sensitivity, subcutaneous, visceral or total abdominal adiposity (Abate et al. 1995; Coon et al. 1992; Fujioka et al. 1987; Kohrt et al. 1993; Lee et al. 2005; Ross et al. 2002; Ryan et al. 2001b). All of these studies suggest an important role for increased abdominal obesity in modulating insulin sensitivity and glucose tolerance in middle-aged and older individuals, in spite of the significant sex-related differences in body fat distribution. The contribution of subcutaneous and visceral abdominal fat and body fat distribution to sex-related differences in insulin sensitivity may be related to differences in abdominal fat cell metabolism, particularly the effects of estrogen, testosterone, catecholamines, and other hormones (Jensen et al. 1996; Lonnqvist et al. 1997), as well as differences in adipokine production and secretion. Production and secretion of adipokines or whether differences in adipose tissue, skeletal muscle, and hepatic fat metabolism contribute to sex-related differences in insulin sensitivity were not examined as part of this study. Future research will need to address these questions.

There are both strengths and limitations inherent to a cross-sectional study, wherein the conclusions are applicable only to Caucasian, sedentary, obese, older men and women with normal or impaired glucose tolerance. All of the men and women were sedentary and healthy, and had no major medical conditions. In addition, none of the women in this study ever used hormone-replacement therapy, thus eliminating its use as a confounding factor that could have influenced the results. Although 9 male and 7 female study participants were classified as having impaired glucose tolerance, which may be a limitation of the study, this is representative of the middle-aged and older population. In addition, prior to the glucose clamps, all subjects were weight stable on constant composition-calculated diets, eliminating the effects of body mass and dietary changes immediately prior to the clamp on M. One limitation of the study is that hepatic glucose output was not measured during the glucose clamps. Of note, the insulin concentrations achieved during the clamps were most likely sufficient to suppress hepatic glucose output in these non-diabetic men and women, as substantiated by other investigators (Hughes et al. 1993; Meneilly et al. 1987). This suggests that gender-related differences in hepatic glucose production do not likely explain the differences in M.

In conclusion, our findings suggest that healthy, sedentary, older men are more insulin resistant than healthy, sedentary, post-menopausal women, even after adjusting for differences in abdominal fat distribution. Other metabolic factors that may contribute to the greater insulin sensitivity in women compared with men of comparable age and BMI, such as differences in the metabolism of adipose tissue and skeletal muscle, are under investigation.

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Fig. 1. Relationship between glucose disposal (M , $\mu\text{mol}\cdot\text{L}^{-1}\cdot\text{kg}_{\text{FFM}}^{-1}\cdot\text{min}^{-1}$) and waist circumference in men and women.

Table 1

Physical characteristics of the subjects

Subjects (gender)	Height (cm)	Mass (kg)	BMI ($\text{kg}\cdot\text{m}^{-2}$)	Waist (cm)	Hip (cm)	WHR	% Fat	Fat mass (kg)	FFM (kg)	VAT (cm^2)	SAT (cm^2)	VAT:SAT
Women (n = 29)	162.6±1.4	84.4±2.3	32.0±0.9	93.9±2.0	115.4±1.8	0.81±0.01	46.3±1.0	39.1±1.7	44.5±1.1	164.6±12.6	449.5±20.8	0.39±0.04
Men (n = 28)	177.8±1.3*	98.1±2.2*	31.0±0.5	108.5±1.5*	110.5±1.3*	0.98±0.01*	31.4±0.8*	30.7±1.1*	66.5±1.3*	180.0±10.5	301.9±11.8*	0.61±0.04*

Note: Values are means ± SEM. VAT, visceral abdominal fat; SAT, subcutaneous abdominal fat.* Asterisk indicates $p < 0.05$ vs. women.

Metabolic characteristics of subjects

Table 2

Subject (gender)	Fasting glucose (mmol·L ⁻¹)	Fasting insulin (pmol·L ⁻¹)	M (μmol·L ⁻¹ ·kg _{FFM} ⁻¹ ·min ⁻¹)	Insulin at 90–120' (I, pmol·L ⁻¹)
Women	5.5±0.1	60±4	46.7±3.1	462±9
Men	5.7±0.1	84±9*	21.7±1.1*	562±21*

Note: FFM, fat-free mass; M, glucose disposal calculated from between the 90th and 120th min of 240 pmol·m⁻²·min⁻¹ euglycemic–hyperinsulinemic clamp. Insulin at 90–120' is the average insulin concentration during same 30 min period. Values are means ± SEM.

* Asterisk indicates $p < 0.05$ vs. women.

Table 3

Correlations between M and measures of body composition

Measure of BC	M ($\mu\text{mol}\cdot\text{L}^{-1}\cdot\text{kg}_{\text{FFM}}\cdot\text{min}^{-1}$)	
	Men	Women
Waist	-0.50 * ($p = 0.01$)	-0.41 * ($p = 0.03$)
WHR	-0.31 ($p = 0.31$)	-0.55 * ($p = 0.002$)
VAT	-0.27 ($p = 0.19$)	-0.44 * ($p = 0.02$)
SAT	-0.29 ($p = 0.14$)	-0.06 ($p = 0.78$)
VAT:SAT	-0.06 ($p = 0.79$)	-0.38 ($p = 0.05$)

Note: BC, body composition; FFM, fat free mass; M, glucose disposal calculated between 90th and 120th min of $240 \text{ pmol}\cdot\text{m}^{-2}\cdot\text{min}^{-1}$ euglycemic-hyperinsulinemic clamp. Values in parentheses indicate p value for each correlation.

* Asterisk indicates $p < 0.05$.