



## Predictors of worsening insulin sensitivity in postmenopausal women

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### KEY WORDS

Insulin sensitivity  
Insulin resistance  
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Predictor

**Objective:** The purpose of this study was to determine predictors of worsening insulin sensitivity in postmenopausal women.

**Study design:** Seventy-one nonobese postmenopausal women were assigned randomly to receive hormone replacement therapy (conjugated estrogens, 0.625 mg, plus medroxyprogesterone acetate, 2.5 mg) or placebo daily for 1 year (34 women received hormone replacement therapy, and 37 women received placebo). At baseline and 12 months, the women received a computed tomography scan at the L4-L5 vertebral disk space, a dual x-ray absorptiometry scan, a euglycemic hyperinsulinemic clamp to measure insulin sensitivity, and a lipid profile. Declining insulin sensitivity was defined as the largest quartile change in insulin sensitivity in the women who received the placebo (−1.42 mg/min/kg lean body mass).

**Results:** By univariate analysis, we found that significant predictors of worsening insulin sensitivity were the use of hormone replacement therapy, baseline insulin sensitivity, a younger age, and <10 years since menopause. By logistic regression, we determined that hormone replacement therapy use and higher baseline insulin sensitivity were independent predictors of worsening insulin sensitivity.

**Conclusion:** The use of hormone replacement therapy and baseline insulin sensitivity are significant independent predictors of the development of worsening insulin sensitivity in postmenopausal women.

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Menopause is associated with an increased risk of cardiovascular disease. Some of this risk may be related to changes in body composition, body fat distribution, and insulin sensitivity.<sup>1-3</sup> With menopause, women gain body fat preferentially in the abdominal region,<sup>3,4</sup> which increases their risk of type 2 diabetes mellitus<sup>5</sup> and cardiovascular disease.<sup>6</sup>

If the loss of ovarian function reduces insulin sensitivity, it is plausible that hormone replacement therapy (HRT) would improve insulin sensitivity in postmenopausal women. Contrary to this hypothesis, in a randomized placebo-controlled trial, we found that oral combined conjugated estrogens and medroxyprogesterone acetate decreased insulin sensitivity in postmenopausal women without affecting body composition or body fat distribution.<sup>7</sup> In this study, some women had a more pronounced decrease in insulin sensitivity than others. The historic, biochemical, and metabolic factors that predict the greatest decrease in insulin sensitivity after menopause are unknown. These factors are important in counseling women about HRT use. We hypothesized that HRT use, body composition, baseline insulin sensitivity, age, time since menopause, and family history of diabetes mellitus may predict which women may have the greatest decrease in insulin sensitivity.

## Material and methods

### Participants

Postmenopausal women were recruited from the Burlington, Vermont, area by newspaper advertisement for 2 similar randomized, double-blinded, placebo-controlled studies that were designed to investigate the effect of HRT on body composition, body fat distribution, and insulin sensitivity. One study involved older postmenopausal women ( $n = 23$ ; age, 62-73 years), and the other study involved younger postmenopausal women ( $n = 48$ ; age, 44-59 years). Because these 2 groups did not overlap in age, categorical data analysis was performed. Postmenopausal status was defined by the absence of menses for  $<5$  years for the younger group and  $>5$  years for the older group; with a follicle-stimulating hormone (FSH) level of  $>30$  mIU/mL for both groups. Inclusion criteria were a body mass index (BMI) of  $<30$  kg/m<sup>2</sup>, a fasting glucose level of  $<112$  mg/dL, and a waist circumference of  $<94$  cm. The volunteers included in the study were 69 white women, 1 Abenaki Indian woman, and 1 Asian woman.

The women were assigned randomly in a double-blinded block design fashion to HRT (conjugated estrogens 0.625 mg daily plus medroxyprogesterone acetate 2.5 mg daily;  $n = 34$ ) or placebo ( $n = 37$ ) for 1 year. The study was approved by the Institutional Review Board and the General Clinical Research Center at The University of Vermont, and all women signed statements giving informed consent.

### Investigations

We performed euglycemic hyperinsulinemic clamps according to the methods of DeFronzo et al,<sup>8</sup> with modifications as previously described by our group at baseline and at 1 year.<sup>9</sup> After 3 days of standardized

meals, (55% carbohydrate, 30% fat, and 15% protein), volunteers were tested after an overnight fast. An intravenous catheter was placed in an antecubital vein for the infusion of insulin, [6,6-<sup>2</sup>H<sub>2</sub>]-glucose, and 20% dextrose. A second catheter was placed in the volunteer's contralateral hand and kept in a hot box (60°C) for sampling of arterialized blood samples. A constant infusion of insulin at 40 mU/min/m<sup>2</sup> was given for 2 hours to approximate postprandial insulin levels, and a 20% dextrose solution was infused at a variable rate for 2 hours. Plasma glucose levels were measured every 5 minutes during the insulin infusion to adjust the dextrose infusion and maintain fasting glucose levels. The exogenous infusion rate (in milligrams per minute) during the last 30 minutes of the 120-minute clamp was averaged as an index of insulin-stimulated glucose disposal (reported as insulin sensitivity). With this level of hyperinsulinemia, we have shown that hepatic glucose production is completely suppressed.<sup>7,10</sup>

### Serum assays

Plasma glucose concentrations were measured by the glucose oxidase method with an automated glucose analyzer (YSI Instruments, Yellow Springs, OH). Serum insulin concentrations were determined with a double-antibody radioimmunoassay (Diagnostic Products Corp, Los Angeles, CA). Serum FSH was measured with a chemiluminescent assay (Bayer Diagnostics, Tarrytown, NY). Inter- and intra-assay coefficients of variation for FSH were 0.3% and 2.2%, respectively.

### Body composition

Fat mass, percent fat, and lean body mass (LBM) were measured at baseline and at 1 year by dual-photon x-ray absorptiometry with a densitometer (Lunar DPX-L; Lunar Corp, Madison, WI) as previously reported.<sup>9</sup> Scans were analyzed with the Lunar (version 1.3y) DPX-L extended analysis program for body composition. The coefficient of variation for repeated measurements in our laboratory was 1% for fat mass. Waist circumference in centimeters in the standing position was measured as the smallest distance around the abdomen.

### Computed tomography

Intra-abdominal fat (square centimeters), subcutaneous abdominal fat (square centimeters), and sagittal diameter (centimeters) were measured at the L4-L5 vertebral disk space at an attenuation range of  $-190$  to  $-30$  Hounsfield units by computed tomography with a scanner (GE High Speed Advantage; General Electric Medical Systems, Milwaukee, WI).<sup>9</sup> These measurements were performed at baseline and at 1 year. Sagittal diameter was measured as the anterior-posterior distance in millimeters at this disk level. The within-subject

variation for repeated analysis of fat measurements in our laboratory was <1%.

### Definition of Declining Insulin Sensitivity

All predictors that were investigated in this study were examined relative to a change in insulin sensitivity and expressed as a change in insulin sensitivity (milligrams per minute per kilogram LBM) at 12 months. The effect of worsening insulin sensitivity was examined by the dichotomization of these changes in insulin sensitivity at the lowest quartile of the untreated (placebo) women. The definition of worsening insulin sensitivity corresponded to the largest quartile of negative change ( $\geq -1.42$  mg/min/kg LBM). The analysis of results was then based on characteristics of those women who had insulin sensitivity in the lowest quartile versus all other quartiles.

### Statistical analysis

Potential predictors of a decline in insulin sensitivity that met the definition of worsening insulin sensitivity at 1 year of study were age (years), number of years since menopause (>10 years vs  $\leq 10$  years), baseline insulin sensitivity (milligrams per minute per kilogram LBM), weight (kilograms), BMI ( $\text{kg}/\text{m}^2$ ), waist circumference (centimeters), fasting glucose (milligrams per deciliter), fasting insulin (milligrams per deciliter), intra-abdominal fat (square centimeters), subcutaneous abdominal fat (square centimeters), total fat (square centimeters), high density lipoprotein (HDL; milligrams per deciliter), low density lipoprotein (LDL; milligrams per deciliter), HDL/LDL ratio, triglycerides (milligrams per deciliter), and family history of diabetes mellitus (type I and II) in first-degree relatives. These variables were determined at baseline.

For univariate analysis, baseline clinical variables were analyzed with Fisher's exact test for categorical variables and the Student *t* test for continuous variables.<sup>11</sup> Those variables that were found to be predictive of worsening insulin sensitivity at a probability value of <.05 were examined further with a stepwise logistic regression model to determine their independent influence. Odds ratios and the corresponding 95% CIs were obtained for each measure that was used in the logistic regression model along with the Hosmer-Lemeshow goodness of fit index. Probability values <5% were considered significant. Statistical analysis was conducted with BMDP statistical software (University of California, Berkeley, CA).<sup>12</sup>

### Results

Baseline characteristics of study volunteers are shown in Table I. Differences between the younger postmenopausal women and the older postmenopausal women included a significantly greater body weight, BMI, waist

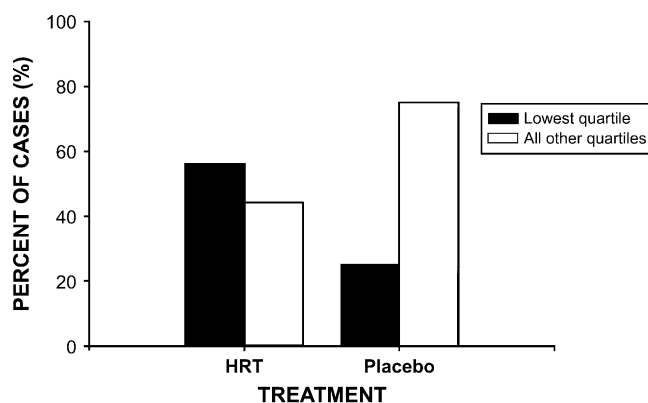
**Table I** Baseline characteristics of younger and older postmenopausal women

Variable	Younger women (n=48)*	Older women (n=23)*	P value
Age (y)	51.1 $\pm$ 3.7	66.0 $\pm$ 2.5	.0001
Years since menopause	1.6 $\pm$ 1.0	16.0 $\pm$ 7.4	.0001
Weight (kg)	65.6 $\pm$ 9.1	72.4 $\pm$ 12.0	.01
BMI ( $\text{kg}/\text{m}^2$ )	24.8 $\pm$ 3.3	27.1 $\pm$ 4.5	.02
Waist circumference (cm)	80.0 $\pm$ 7.6	88.0 $\pm$ 7.7	.0006
Fasting glucose (mg/dL)	80.7 $\pm$ 5.1	82.3 $\pm$ 5.0	.02
Fasting insulin ( $\mu\text{U}/\text{mL}$ )	10.6 $\pm$ 4.8	11.3 $\pm$ 4.8	.61
Insulin sensitivity/kg/LBM (mg/min/kg)	9.8 $\pm$ 3.1	8.0 $\pm$ 2.9	.024
LBM (kg)	39.9 $\pm$ 3.51	39.9 $\pm$ 5.49	.99
Total fat ( $\text{cm}^2$ )	23.0 $\pm$ 6.7	28.6 $\pm$ 8.5	.004
Intra-abdominal fat ( $\text{cm}^2$ )	88.4 $\pm$ 34.9	117.9 $\pm$ 52.9	.021
Subcutaneous fat ( $\text{cm}^2$ )	275.1 $\pm$ 83.8	331.0 $\pm$ 122.5	.057
HDL (mg/dL)	59.4 $\pm$ 16.2	62.4 $\pm$ 13.0	.456
LDL (mg/dL)	123.5 $\pm$ 30.6	133.2 $\pm$ 36.6	.27
HDL/LDL ratio	3.7 $\pm$ 1.1	3.7 $\pm$ 1.0	.99
Triglycerides (mg/dL)	121.4 $\pm$ 74.8	133.1 $\pm$ 58.8	.52

\* Data are given as mean  $\pm$  SD.

circumference, intra-abdominal fat, total fat, and number of years since menopause in the older women. The older women also had a lower insulin sensitivity/LBM at baseline than the younger postmenopausal women. LBM, HDL, LDL, HDL/LDL ratio, and triglycerides were not significantly different between groups at baseline. The 2 groups were combined for the analysis of change in insulin sensitivity because the Cochran-Mantel-Haenszel test for homogeneity, when analyzing the effect of treatment (HRT and placebo), indicated that the groups were homogeneous ( $P = .141$ ) and thus could be combined.

At baseline, absolute insulin sensitivity for the entire group  $\pm$  SD was  $394.9 \pm 125.2$  mg/min, with a change at 1 year of  $-25.1 \pm 134.6$  mg/min (range,  $-387$  to  $+338$  mg/min). Means  $\pm$  SD of serum glucose for at baseline during the last 30 minutes of the clamp (steady state) were  $79.2 \pm 3.5$  mg/dL for the HRT group and  $83.7 \pm 6.2$  mg/dL for the placebo group; at 1 year, serum glucose level during the last 30 minutes of the clamp was  $78.0 \pm 3.5$  mg/dL for the HRT group and  $79.8 \pm 4.5$  mg/dL for the placebo group. For insulin level at baseline, the mean  $\pm$  SD at steady state was  $86.4 \pm 24.1$   $\mu\text{U}/\text{mL}$  for the HRT group and  $80.6 \pm 26.2$   $\mu\text{U}/\text{mL}$  for the placebo group. At 1 year, means of serum insulin level during the last 30 minutes of the clamp were  $70.0 \pm 17.9$   $\mu\text{U}/\text{mL}$  for the HRT group and  $72.2 \pm 11.2$   $\mu\text{U}/\text{mL}$  for the placebo group.

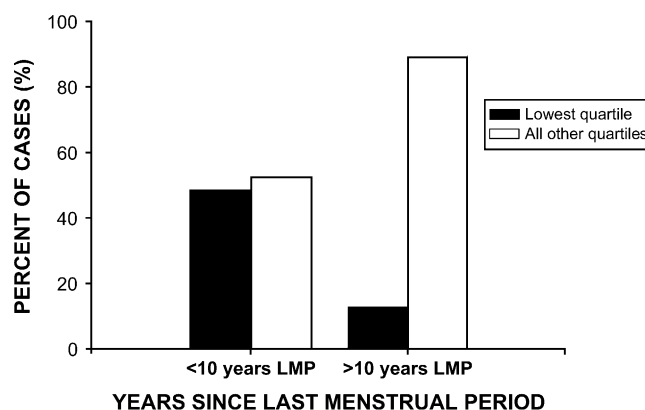


\* $P=.008$ ; Differences in effect of treatment on insulin sensitivity

**Figure 1** Decline in insulin sensitivity. Effect of HRT. Twenty-five percent of women ( $n = 9$ ) who received placebo showed a decline in insulin sensitivity into the lowest quartile, whereas 56% ( $n = 19$ ) of the women who received HRT did show a prominent decline. Seventy-five percent of women who received placebo ( $n = 28$ ) and 44% of the women who received HRT ( $n = 15$ ) did not demonstrate a prominent change in insulin sensitivity. Differences in the change in insulin sensitivity between treatment groups were significant ( $P = .008$ ).

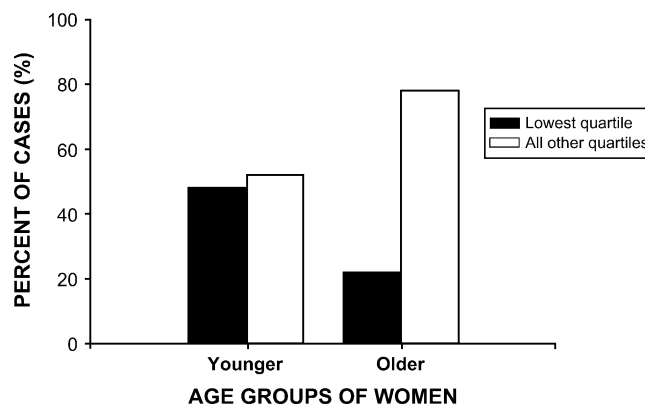
With univariate analysis with the Student  $t$  test for continuous variables and the Fisher Exact test for categorical variables, significant predictors of the development of poor insulin sensitivity were shown to be the use of HRT, fewer years since menopause, baseline insulin sensitivity/LBM, and younger age. Fifty-six percent of women who received HRT showed worsening insulin sensitivity, whereas only 25% of women who received placebo showed such a decline (Figure 1). Furthermore, 44% of women who received HRT did not show a worsening of insulin sensitivity compared with 75% of women who received placebo. These differences in the effect of HRT on insulin sensitivity were significantly different between groups ( $P = .008$ ).

Years since menopause also predicted a worsening in insulin sensitivity. More women who were  $<10$  years postmenopausal (48%) compared with those  $>10$  years since their last menstrual period (LMP) (12%) showed a worsening of insulin sensitivity (Figure 2). Eighty-eight percent of women who were  $>10$  years postmenopausal did not show a worsening in insulin sensitivity as compared with 52% of women who were  $<10$  years since their last menstrual period. The difference in effect of number of years since menopause on insulin sensitivity was statistically significant between the groups ( $P = .009$ ). Similarly, age affected the decrease in insulin sensitivity. More of the younger women experienced worsening insulin sensitivity (48%) compared with the older women (22%;  $P = .041$ ; Figure 3). Women who showed the greatest negative change in insulin sensitivity had a greater insulin sensitivity at baseline than those women who did not show such a prominent decline ( $P = .0001$ ; Table II).



\* $P=.009$ ; Differences in change in insulin sensitivity between groups

**Figure 2** Decline in insulin sensitivity. Years since last menstrual period: 48% of women ( $n = 26$ ) who were  $\leq 10$  years since the onset of menopause showed a decline in insulin sensitivity that met the definition of poor insulin sensitivity, whereas 12% of the women ( $n = 2$ ) who were  $> 10$  years since menopause did meet that definition. Fifty-two percent of the women ( $n = 28$ ) with  $\leq 10$  years since menopause and 88% of the women ( $n = 15$ ) who were  $> 10$  years after menopause did not show a prominent decline in insulin sensitivity. Differences in the change in insulin sensitivity between groups were significant ( $P = .009$ ).



\* $P=.041$ ; Differences between age groups of women

**Figure 3** Decline in insulin sensitivity. Age at baseline: 48% of the women ( $n = 23$ ) in the younger age group at baseline and 22% of the women ( $n = 11$ ) of the older age group showed a decline in insulin sensitivity that met the definition of poor insulin sensitivity. Fifty-two percent of the younger aged women ( $n = 25$ ) and 78% of the older aged women ( $n = 18$ ) did not show a prominent decline in insulin sensitivity. Differences in the change in insulin sensitivity were significant between groups ( $P = .041$ ).

BMI, waist circumference, weight, subcutaneous fat, total fat, intra-abdominal fat, fasting glucose, and components of the lipid profile (LDL, HDL, LDL/HDL ratio, triglycerides) did not predict a worsening in insulin sensitivity (Table II). Fasting insulin was not predictive of a worsening in insulin sensitivity (lowest quartile,

**Table II** Predictors of poor insulin sensitivity (mean  $\pm$  standard deviation)

Variable	Lowest quartile (n=28)	All other quartiles (n=43)	P value
Age (y)	52.8 $\pm$ 6.5	57.9 $\pm$ 7.9	.006
Insulin sensitivity/kg/LBM(mg/min/kg)	10.9 $\pm$ 3.2	8.1 $\pm$ 2.6	.0001
Weight (kg)	66.1 $\pm$ 9.6	68.3 $\pm$ 11.0	.26
BMI (kg/m <sup>2</sup> )	24.8 $\pm$ 3.7	26.0 $\pm$ 3.8	.18
Intra-abdominal fat (cm <sup>2</sup> )	95.4 $\pm$ 34.9	99.8 $\pm$ 48.8	.68
Waist circumference (cm)	81.2 $\pm$ 8.2	84.7 $\pm$ 8.1	.09
Fasting glucose (mg/dL)	80.1 $\pm$ 4.2	81.9 $\pm$ 8.1	.14
Fasting insulin ( $\mu$ U/mL)	11.0 $\pm$ 5.8	10.9 $\pm$ 4.3	.92
LDL (mg/dL)	129.1 $\pm$ 31.2	125.8 $\pm$ 34.3	.71
HDL (mg/dL)	58.8 $\pm$ 15.6	61.6 $\pm$ 14.8	.49
HDL/LDL ratio	4.0 $\pm$ 1.4	3.5 $\pm$ 0.9	.20

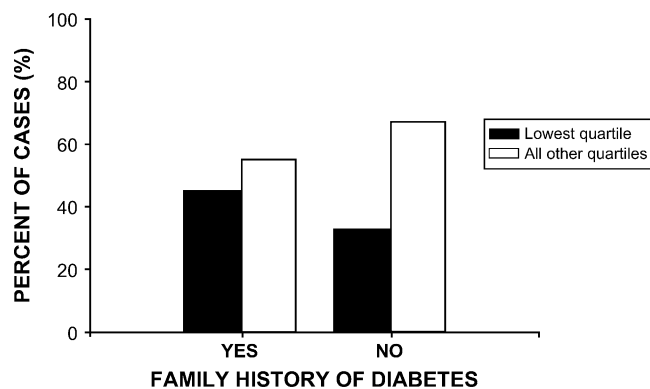
11.0  $\pm$  5.8 [n = 16]; all other quartiles, 10.0  $\pm$  4.3 [n = 32];  $P = .92$ ). Furthermore, a family history of diabetes mellitus (Figure 4) did not predict a worsening in insulin sensitivity. Only 1 study participant had a positive family history of both parents having type II diabetes mellitus.

Multivariate analysis showed that the use of HRT and baseline insulin sensitivity were significant independent predictors of a worsening in insulin sensitivity. The odds ratio for a significant decline in insulin sensitivity with the use of HRT was 4.65 (95% CI, 1.42-15.2;  $P = .022$ ) and for baseline insulin sensitivity was 1.43 (95% CI, 1.16-1.79;  $P = .004$ ).

## Comment

We report that predictors of a worsening in insulin sensitivity in postmenopausal women are the use of HRT, higher baseline insulin sensitivity, younger age, and being <10 years since menopause. Independent predictors of a significant decline in insulin sensitivity include higher baseline insulin sensitivity and the use of HRT. In a randomized trial, our laboratory previously reported that HRT decreased insulin sensitivity in non-obese postmenopausal women by 17% after 1 year.<sup>7</sup>

To our knowledge, the present study is the first to report the factors that predict a worsening in insulin sensitivity in postmenopausal women. Our use of criterion parameters to measure glucose metabolism, body composition, and body fat distribution (euglycemic clamp, computed tomography scan, dual-photon x-ray absorptiometry) strengthens our conclusions.



\* $P = .34$ ; Differences between groups were not significant

**Figure 4** Decline in insulin sensitivity. Family history of diabetes mellitus (type I and II): 45% of the women (n = 17) who had a family history of diabetes mellitus showed a decline of insulin sensitivity into the lowest quartile, and 33% of the women (n = 11) without a family history of diabetes mellitus did so. Fifty-five percent of the women (n = 21) with a family history of diabetes mellitus and 67% of those women (n = 22) without a family history of diabetes mellitus did not show a prominent change in insulin sensitivity. These differences in the change in insulin sensitivity between these groups were not significant ( $P = .34$ ).

Our finding that continuous combined conjugated estrogens plus medroxyprogesterone acetate was 4.65 times more likely to cause a worsening in insulin sensitivity compared with placebo is consistent with our randomized trial of the effect of HRT on body composition and insulin sensitivity in younger postmenopausal women<sup>7</sup> and with an 3-month randomized blinded trial in Europe of lean women aged 56  $\pm$  3 years.<sup>13</sup> In contrast, trials in which postmenopausal women were given estrogen alone without a progestin do not report a decrease in insulin sensitivity.<sup>14,15</sup> These findings suggest that healthy postmenopausal women who are considering initiating oral combined estrogen plus progestin HRT should consider that their insulin sensitivity may decline with treatment. However, no women became diabetic during the 1-year period receiving HRT in our study that was based on fasting glucose levels. A report from the Women's Health Initiative suggests that HRT reduces the incidence of diabetes mellitus by 21% in older postmenopausal women after 5.6 years of use, as determined by self-reporting of the diagnosis of diabetes mellitus.<sup>16</sup> However, only 8% of women in this study had fasting glucose and insulin levels to determine homeostasis model assessment of insulin resistance (HOMA-IR), which is an estimate of insulin resistance. The authors conclude that HRT reduces the incidence of diabetes mellitus, but the number of participants with fasting glucose and insulin measurements was too small to determine whether the reduction in diabetes mellitus occurs through a reduction in insulin resistance. Our study suggests that the reduction in the incidence in diabetes mellitus with HRT does not

occur through a reduction in insulin resistance, because HRT increased insulin resistance according to euglycemic clamp studies.

Higher insulin sensitivity at baseline was found to predict a worsening in insulin sensitivity (odds ratio, 1.43). It has been reported that the mechanism for a decrease in insulin sensitivity with HRT is likely due to a peripheral mechanism at the level of glucose uptake by muscle and fat.<sup>17</sup> It is possible that the maximal reduction in glucose uptake by skeletal muscle with a subsequent reduction in glycogen synthetase occurs when these processes are greater initially (such as in women with higher baseline insulin sensitivity). Further studies are needed to confirm this hypothesis.

The women who had a worsening insulin sensitivity were also younger ( $52.8 \pm 6.5$  years) compared with those who did not ( $57.0 \pm 7.9$  years) and were menopausal more recently. The reasons for our finding of a greater decrease in insulin sensitivity in younger women are not clear. Younger women had a greater baseline insulin sensitivity than did the older women (9.8 vs 8.0 mg/min/kg LBM) and thus may have had a greater decrease insulin sensitivity. Furthermore, older women in our study may have been particularly healthy, because they were required to have a BMI of  $<30$  kg/m<sup>2</sup> and be free of diabetes mellitus and cardiovascular disease to be included in the study. Animal studies suggest that insulin-mediated glucose disposal decreases into adulthood, but no further, as the animals aged.<sup>18</sup>

Family history of diabetes mellitus in the postmenopausal women in our study (first-degree relatives) was not predictive of worsening insulin sensitivity. This finding is consistent with a recent cross-sectional study by Mitchell et al,<sup>19</sup> who found no association between family history of type 2 diabetes mellitus and insulin resistance in a lean Hispanic population. However, in more overweight subjects in that study, family history of type 2 diabetes mellitus was related significantly to reduced insulin sensitivity and to increased subcutaneous and visceral fat.<sup>19</sup> They concluded that the expression of transmitted diabetes mellitus genes may be suppressed in leaner, more physically active populations. Furthermore, Goldfine et al<sup>20</sup> recently reported that low glucose disposal rates were associated strongly with the development of diabetes mellitus when individuals had 2 parents with diabetes mellitus but were not strongly predictive without such a strong family history of diabetes mellitus. Thus, in our study, we would expect to find no association between family history of diabetes mellitus and insulin sensitivity in our population of nonobese healthy postmenopausal women who had a very low incidence of 2 parents with diabetes mellitus (1/71 volunteers). Of 71 subjects total, one woman had 2 parents with diabetes mellitus; 25 women had 1 parent with diabetes mellitus, and 27 women had a first-degree relative (parent or sibling) with diabetes mellitus, based on history

that was given. Thus, 38% of the women had a first-degree relative with diabetes mellitus. This percentage is consistent with the National Health and Nutrition Examination survey that reported that 3172 adults had a family history of diabetes mellitus in a first-degree relative (parents and siblings) of 10,283 adults (31%).<sup>21</sup>

Body composition and body fat distribution are related significantly to insulin sensitivity in postmenopausal women.<sup>22</sup> Palaniappan et al<sup>23</sup> recently reported that a waist circumference  $>89$  cm gave a 1.7-fold increase in the development of the metabolic syndrome. We report that intra-abdominal fat, subcutaneous fat, total fat, waist circumference, and weight did not predict worsening insulin sensitivity. By definition, our study subjects were not obese, with a baseline waist circumference  $<94$  cm. Furthermore, factors such as exercise capacity ( $VO_{2\max}$ ) may be more important than are total and regional adiposity to the determination of insulin sensitivity in nonobese women.<sup>24</sup> Therefore, body composition and body fat distribution may be less predictive of the decline in insulin sensitivity in nonobese populations such as ours.

Lipid parameters (HDL, LDL, HDL/LDL ratio, triglycerides) were not found to be predictive of worsening insulin sensitivity in our nonobese postmenopausal women. Low HDL cholesterol was predictive of the metabolic syndrome in obese men and women,<sup>23</sup> which appears different from our volunteers.

Fasting glucose or fasting insulin was not predictive of a worsening of insulin sensitivity. This is expected because others have reported that fasting glucose and insulin and calculations that involve these values (HOMA-IR) do not correlate with insulin sensitivity as measured by the gold standard method, the euglycemic clamp.<sup>8,25</sup> Thus, for patient counseling purposes, fasting glucose and fasting insulin are not helpful in determining which menopausal women will have a prominent decrease in insulin sensitivity.

Our study is limited in that the subjects were nonobese and mostly white. Furthermore, our study measured only insulin sensitivity and not insulin secretion, which may also be altered in early diabetes mellitus. Older postmenopausal women who met the same inclusion criteria as younger postmenopausal women may be particularly healthy, thus reflecting inherent differences between these 2 groups.

In summary, we report that HRT is the greatest predictor of a worsening of insulin sensitivity in postmenopausal women over a 1-year follow-up period. A higher baseline insulin sensitivity is also predictive. Healthy older postmenopausal women may be at lower risk of experiencing a significant decline in insulin sensitivity than younger women. Healthy postmenopausal women who consider initiating HRT should be aware of the possibility of the development of insulin resistance.

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