Postmenopausal Hormone Therapy Is Associated With Atherosclerosis Progression in Women With Abnormal Glucose Tolerance

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Background—Abnormal glucose tolerance (AGT; diabetes or impaired glucose tolerance) is associated with increased risk of cardiovascular disease, especially in women. Cardiovascular disease rates in women increase after menopause. The Women’s Health Initiative found that postmenopausal hormone therapy (PHT) increased the risk of cardiovascular disease and that effects in diabetic women did not differ from those in women without diabetes. In this study, we hypothesized that PHT would have a worse effect on disease among women with AGT.

Methods and Results—We randomly assigned 423 postmenopausal women with angiographically defined atherosclerosis (321 women had exit angiograms) with or without AGT to receive estrogen, estrogen plus progestin, or a placebo for 2.8 ± 0.9 years. LDL was lower and HDL and triglycerides were higher after PHT in non-AGT and AGT women, but more adverse changes occurred in C-reactive protein and fibrinogen in women with AGT (P = 0.11 and P = 0.02 for interactions). PHT had no effect on fasting glucose or insulin concentrations in women without AGT, but in women with AGT, fasting glucose levels, insulin concentration, and insulin resistance as assessed by the HOMA (homeostasis model) calculation decreased slightly (P = 0.28, P = 0.25, P = 0.14 for interaction, respectively). Atherosclerotic progression was greater in women with AGT. Atherosclerotic progression in previously nondiseased segments was enhanced by PHT to a greater extent in women with AGT (P = 0.11 for interaction).

Conclusions—PHT is associated with a worsening of coronary atherosclerosis and exacerbation of the profile of inflammatory markers in women with AGT. Therefore, PHT is not warranted for use in diabetic women. Further study is needed to explore the improvement in insulin resistance and glycemia that appears to occur with PHT in women with AGT. (Circulation. 2004;110:201-206.)

Key Words: angiography ■ cardiovascular diseases ■ diabetes mellitus ■ hormones ■ women

Diabetes and abnormal glucose tolerance (AGT) are associated with increased risk of cardiovascular disease (CVD).1 The effect of diabetes on CVD appears to be worse in women than in men.2–8 Because CVD rates increase with age, especially after menopause, the influence of postmenopausal hormone use on CVD in postmenopausal women has been a subject of interest. In the Women’s Health Initiative (WHI) Hormone Trial, combined treatment with estrogen and progestin was found to increase the risk of heart disease, stroke, and thromboembolic events in postmenopausal women.9 No significant interaction between baseline diabetes and postmenopausal hormone therapy (PHT) was found in either the WHI9 or the Heart and Estrogen/Progestin Replacement Study (HERS).10,11 indicating that PHT has an adverse effect on CVD in women with diabetes, but no information has been presented on the effects of PHT on angiographically documented atherosclerosis in postmenopausal women with diabetes or impaired glucose tolerance.

Recent reports from the HERS12 and WHI13 randomized trials indicate that PHT reduces the incidence of diabetes. It is therefore important to consider the effects of PHT on both vascular disease and CVD risk factors in postmenopausal women with diabetes or insulin resistance. The Women’s Angiographic Vitamin and Estrogen (WAVE) Study14 was a prospective angiographic study that randomized women to receive either PHT or a placebo for a 3-year period. Because the women were recruited into WAVE on the basis of having coronary disease, many of these women had diabetes or glucose intolerance at baseline. In this article, the findings on CVD risk factors and CVD assessed by angiography in postmenopausal women with AGT (diabetes or impaired fasting glucose) after 3 years of PHT are presented.
Methods

Participants
Postmenopausal women were recruited into WAVE between July 1997 and August 1999 at 7 clinical sites in the United States and Canada. The institutional review board at each site approved the study. The study design and methods have been reported previously. Postmenopausal status was defined as having had a bilateral oophorectomy at any age, being <55 years of age with a follicle-stimulating hormone level of ≥40 mIU/mL, or being >55 years of age.

A coronary angiogram, performed within 4 months of study entry, was required to show one or more 15% to 75% coronary stenoses in at least 1 major coronary artery or primary branch that had no catheter intervention. Major exclusion criteria were PHT use within 3 months; evidence of potential breast, uterine, or cervical cancer; uncontrolled diabetes or hypertension; myocardial infarction within 4 weeks; prior or planned coronary bypass surgery; fasting levels of triglycerides >400 mg/dL; creatinine level >2.0 mg/dL; symptomatic gallstones; NYHA class IV heart failure or left ventricular ejection fraction known to be <25%; history of hemorrhagic stroke, bleeding diathesis, pulmonary embolus, or idiopathic deep vein thrombosis; or untreated osteoporosis.

After enrollment, the 423 women were randomly assigned to 4 treatment groups of equal size stratified by clinical center and previous hysterectomy status (14 strata). Women who had undergone hysterectomy took conjugated equine estrogens (0.625 mg Premarin, Wyeth-Ayerst) or a placebo, and women with an intact uterus took 1 tablet of conjugated equine estrogens and medroxyprogesterone acetate (0.625 mg/2.5 mg Premparo, Wyeth-Ayerst) or a placebo.

Follow-Up Procedures
Height, weight, blood pressure, and waist circumference were measured at baseline and every 6 months. Pelvic examination, Pap smear, mammography, and a physical examination were done at baseline and every 12 months. Blood was obtained from subjects after an overnight fast at baseline, at 18 months, and at the conclusion of the study. Glucose was measured by the glucose oxidase method with a Vitros analyzer (Johnson & Johnson, Inc). Insulin was measured by radioimmunnoassay (Linco Research, Inc). Fibrinogen was measured via the Clauss method with an MDA analyzer (Organon Teknika, Inc). A high-sensitivity C-reactive protein (CRP) assay was used.

At each visit, a nurse asked the women about any hospitalizations, and any clinical events were recorded. Appropriate documentation was obtained for all events reported. Per standard criteria, 4 members of the steering committee who were blinded to the treatment assignment classified all potential myocardial infarctions and deaths.

Study exit angiograms were obtained a mean of 2.8±0.9 years after initiation of the study. Exit angiograms were obtained on 321 women (76%). Follow-up data and blood measures were available on 313 women (74%). Clinically indicated angiograms performed during the study were reviewed to determine whether revascularization had been performed. These angiograms were used for end-point analysis in patients for whom an exit angiogram could not be obtained (n=41) or if they were performed within 9 months of the scheduled exit angiogram.

Angiographic Measures
Angiographic Core Laboratory staff were blinded to treatment assignment. Computer-assisted quantification of both visually abnormal (stenotic) segments and visually normal segments was performed on cine film or digital recordings. Angiographic images of individual stenoses were selected from the orthogonal view that provided optimal visualization and maximized the degree of stenosis for eccentric lesions.

For stenosis quantification, the operator identified the stenosis-containing segment, the proximal and distal extents of the lesion, and the location of an adjacent normal-appearing vessel for diameter references. Visually normal coronary segments were similarly quantified, with segment length generally matching the average length of diseased segments.

Dimensional calibration was based on the contrast-filled catheter diameter. The computer-determined artery lumen boundaries were based on first- and second-derivative edge-finding algorithms (Sanders Data Systems). For both stenosis-containing segments and visually normal control segments, the minimum lumen diameter, average segment diameter, and percent stenosis (based on available reference diameters) were computed. Measurement reproducibility of minimum lumen diameter was assessed by requantification of a random sample of 58 participants. The second measure differed from the first by -0.004±0.22 mm when both were obtained by the same technician and by 0.005±0.081 mm when different technicians obtained the measurements.

Diabetes (fasting glucose >126 mg/dL) and impaired fasting glucose (110 to 125 mg/dL) were determined by use of the American Diabetes Association criteria. Insulin resistance (HOMA-IR) was calculated according to the HOMA calculation: FI (μU/mL)×FG (mmol/L)/22.5, where FI is fasting insulin and FG is fasting glucose. Because both impaired glucose tolerance and diabetes are associated with increased risk of CVD, the 2 groups were analyzed together (AGT group).

Statistical Analyses
The primary study end point, identified at the beginning of the trial, was change in the mean minimum lesion diameter of all qualifying segments and the incidence of myocardial infarction and death. Angiographic progression and clinical events analyzed separately were identified as secondary end points. The minimum and average lumen diameter changes were calculated for all lesions and averaged for each patient. The primary study end points in the treatment and control groups were compared by use of a nonparametric rank test based on the Van der Waerden scores. Patients who died during the study or had a myocardial infarction were assigned the worst ranks. All analyses were based on intention to treat. Intergroup comparisons of baseline features and angiographic outcomes were done by use of t tests, χ² tests, or Fisher’s exact tests as appropriate. Age adjustment did not significantly alter the results of any of the analyses.

Results
Compared with normal glucose tolerance (NGT) women, AGT women were younger (P=0.006); were more likely to be black or of another minority ethnic group (P=0.001); were more obese (P=0.001); had greater waist circumferences (P=0.001); and had higher glucose values, A1C concentrations, and insulin resistance. These women also had lower HDL levels (P=0.001), higher triglyceride levels (P=0.002), higher fibrinogen concentrations (P=0.003), and higher levels of CRP (P=0.025) (Table 1).

The influence of PHT on CVD risk factors in women with and without AGT is shown in Table 2. AGT women showed the same effects of PHT as did NGT women; ie, LDL concentrations were lower, HDL and triglyceride concentrations were higher, and no significant differences were found between AGT and NGT women in the observed effects of PHT on lipoproteins. PHT had no effect on weight or waist circumference in either group. PHT increased fibrinogen levels in AGT but decreased fibrinogen levels in NGT. This interaction was almost statistically significant (P=0.11). In AGT women, increases in CRP occurred with PHT compared with placebo, whereas in NGT, a slight decrease occurred in CRP with PHT; the interaction was significant (P<0.02).

In comparisons of the effects of PHT on glucose and insulin concentrations and HOMA-IR estimations of insulin resistance (Table 2), PHT was found to have no effect in NGT
women on glucose, insulin levels, or HOMA-IR. On the other hand, in AGT women, PHT appeared to have more effect; decreases occurred in fasting glucose, insulin concentrations, and HOMA-IR, although none reached statistical significance and the interaction terms were not significant.

AGT women had more rapid progression of coronary atherosclerosis than did NGT women (Table 3). Changes in minimum and average lumen diameters in diseased segments of all AGT women, shown as decreases in lumen diameter, were worse than in those of NGT women ($P < 0.005$ and $P < 0.001$). Changes for nondiseased segments, expressed as increases or decreases in lumen diameter, also tended to be worse in AGT versus NGT women ($P < 0.26$ and $P < 0.14$).

The Figure shows the effects of PHT on disease measured by angiography in diseased or nondiseased segments as change per year in minimum and average lumen diameters. No differences were found in comparisons of the adverse effects of PHT on minimum and average lumen diameters in diseased segments in the AGT versus NGT women. On the other hand, there were differing effects on nondiseased segments. In AGT women, PHT was associated with a decrease in both minimum and average lumen diameters. In contrast, no effects were seen in the NGT women ($P = 0.11$ for interaction between glucose tolerance status and effect of PHT).

When the primary end point (a composite of minimum lumen diameter and coronary heart disease events, with coronary heart disease events imputed as worst rank) for the trial was assessed in AGT and NGT women, PHT had no significant effect in the NGT women ($P = 0.52$). However, PHT had an adverse effect, which almost reached statistical significance ($P = 0.07$), in the AGT women.

### Discussion

The WAVE cohort contained a large proportion of women with either diabetes or impaired fasting glucose, thus affording an opportunity to examine the effects of PHT on atherosclerosis in these women who are at higher risk for CVD. Hormone therapy accelerated disease progression, as indicated by decreases in mean and average lumen diameters in diseased segments of women with NGT and AGT. In addition, in AGT women, a tendency was found toward a greater adverse effect of hormone therapy on nondiseased segments: For both minimum and average lumen diameters, decreases occurred with PHT use among AGT women, whereas little effect was seen in the NGT women. Although the primary end point, a combination of angiographic change and clinical events, was not powered for subgroup analysis, it also showed a worse effect of PHT in the AGT women.

The present study is the first to examine the effect of hormone therapy on coronary atherosclerosis in AGT women. In both the WHI and HERS, although results for women with diabetes were not reported separately, global effects on CVD and breast cancer occurred in women with and without diabetes. The finding in the present study of an adverse effect of PHT on nondiseased segments: For both minimum and average lumen diameters, decreases occurred with PHT use among AGT women, whereas little effect was seen in the NGT women. Although the primary end point, a combination of angiographic change and clinical events, was not powered for subgroup analysis, it also showed a worse effect of PHT in the AGT women.
TABLE 3. Progression of Coronary Artery Disease by Glucose Tolerance Status

<table>
<thead>
<tr>
<th>Change From Baseline to Follow-Up</th>
<th>Women with AGT</th>
<th>Women with NGT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Placebo</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>63</td>
<td>−9.46 (41.63)</td>
</tr>
<tr>
<td>LDL cholesterol, mg/dL</td>
<td>59</td>
<td>−11.08 (36.82)</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dL</td>
<td>63</td>
<td>0.56 (9.17)</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>63</td>
<td>10.57 (89.77)</td>
</tr>
<tr>
<td>C-fibrinogen, mg/dL</td>
<td>42</td>
<td>20.0 (102.82)</td>
</tr>
<tr>
<td>CRP, mg/mL</td>
<td>51</td>
<td>−0.46 (1.66)</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>72</td>
<td>5.74 (21.25)</td>
</tr>
<tr>
<td>Waist circumference, cm</td>
<td>61</td>
<td>1.76 (5.97)</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>72</td>
<td>2.37 (4.94)</td>
</tr>
<tr>
<td>Fasting glucose, mg/dL</td>
<td>57</td>
<td>6.25 (73.33)</td>
</tr>
<tr>
<td>A1C, n</td>
<td>46</td>
<td>0.12 (1.81)</td>
</tr>
<tr>
<td>Insulin, μU/mL</td>
<td>56</td>
<td>7.46 (33.20)</td>
</tr>
<tr>
<td>HOMA, n</td>
<td>56</td>
<td>3.57 (17.51)</td>
</tr>
</tbody>
</table>

Probability values for test of interaction between AGT and PHT for change: fibrinogen, P=0.11; CRP, P=0.02; fasting glucose, P=0.28; A1C, P=0.51; insulin, P=0.23; HOMA, P=0.14.

Our data are the first to compare atherosclerosis progression in women with and without AGT. We observed more rapid progression of coronary atherosclerosis in both diseased and nondiseased segments in AGT compared with NGT women. The adverse effects of diabetes have been described previously,21–23 but in studies mainly of men. It is reasonable that the greater progression observed in AGT women could have been related to their greater baseline disease; however, the data show that women with diabetes who take PHT will increase their risk for exacerbation of coronary disease.

The effects of PHT on risk factors for CVD were examined to better understand the data obtained by angiography. Lipoprotein profiles exhibited similar changes in women with and without AGT (ie, a decrease in LDL and an increase in HDL and triglycerides). The worsening atherosclerosis, despite the favorable changes in these 2 lipoprotein risk factors, is consistent with findings in other studies.9,10 Increases in triglyceride levels were not worse in the AGT women, despite their propensity for diabetes-induced elevations in triglycerides. In contrast to the lipoprotein profiles, adverse effects for AGT women were found in CRP and fibrinogen. In NGT women, fibrinogen increases less in the PHT group compared with placebo, whereas in the AGT group, fibrinogen increases more with PHT. CRP changes occurring with PHT were worse in AGT women. Because diabetes has been associated with the inflammatory process, with reports of mediators, including interleukin-6 and CRP, being elevated in people with diabetes,24,25 this additional adverse profile may
partially explain the adverse effects of PHT on the coronary findings.

Although the differences did not reach statistical significance, decreases in glucose and insulin concentrations were observed in the AGT women who were taking PHT, and insulin resistance as measured by HOMA was improved. Some researchers have shown an improvement in glucose and insulin levels in women with diabetes after initiation of PHT.26–28 An analysis of observational data also suggested that glucose control in AGT women might be improved by PHT.29–31 In the Postmenopausal Estrogen/Progestin Interventions (PEPI) Study,32 nonsignificant decreases in glucose and insulin were found. Our findings are consistent with those from HERS. Among those randomized to estrogen/progestin, fasting serum glucose level did not change during the trial. In contrast, women assigned to placebo had a significant rise in fasting glucose level.11,12 Thus, the present data, taken as a whole, suggest that PHT may be associated with slight improvements in glycemia and insulin resistance in women with diabetes or impaired glucose tolerance. The effect may reflect fundamental metabolic changes in glucoregulation induced by the more estrogenic hormonal milieu.33–35 This finding warrants further investigation with the hope of developing selective estrogen-like analogs that might be useful in improving insulin resistance and possibly glucose control in diabetic women.

Despite the suggestion of improved insulin resistance in AGT women who are taking PHT, there was progression of coronary atherosclerotic disease in both diseased and nondiseased (by angiography) segments in these women. Therefore, PHT appears to worsen coronary atherosclerosis through mechanisms that are not counteracted by potential beneficial effects on lipoproteins or insulin resistance.

Limitations of this study include the relatively small sample size and the fact that women were followed up for only 3 years. Thus, we could not examine the effects of PHT on the incidence of diabetes. The sample size also did not allow us to control for use of concomitant medications or for separate analyses of estrogen alone versus estrogen plus progestin. Coronary lumen measurements from angiography cannot differentiate encroachment by atherosclerotic plaque from alterations in vascular tone. Changes in vascular tone could result from failure to adhere to the protocol requirement for preangiogram administration of nitroglycerine, an effect of concomitant medications with vasoactive properties, or possibly PHT itself.

In summary, the present data contribute to our understanding of the increased coronary event rate associated with PHT in women with AGT by describing measurable angiographic changes in nondiseased compared with diseased segments in these women and exacerbation in the profile of inflammatory markers. Thus, this regimen would not be warranted for use...
in diabetic women who already have increased risk for atherosclerotic vascular disease. More research is needed to identify the mechanism of the improvement in insulin resistance and glycaemia that appears to occur with estrogen therapy in women with abnormal glucose tolerance.

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References

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