Significant Differential Effects of Hormone Therapy or Tibolone on Markers of Cardiovascular Disease in Postmenopausal Women

A Randomized, Double-Blind, Placebo-Controlled, Crossover Study

Kwang Kon Koh, Jeong Yeal Ahn, Dong Kyu Jin, Byung-Koo Yoon, Hyung Sik Kim, Dae Sung Kim, Woong Chol Kang, Seung Hwan Han, In Suk Choi, Eak Kyun Shin

Objective—The objective was to compare the effects of tibolone and hormone therapy (HT) on lipid profile, vasodilation, and factors associated with inflammation and hemostasis.

Methods and Results—Fifty-three women received micronized progesterone (MP, 100 mg) with conjugated equine estrogen (CEE, 0.625 mg) or tibolone (2.5 mg) daily for 2 months, with a 2-month washout period. Compared with HT, tibolone significantly reduced total cholesterol (P<0.001), triglyceride (P<0.001), and HDL cholesterol (P<0.001) levels as well as triglyceride/HDL cholesterol ratios (P<0.001) but not LDL cholesterol levels. Tibolone significantly improved flow-mediated brachial artery dilator response to hyperemia from baseline values (P<0.001) by a magnitude similar to that found with HT (P=0.628). Compared with tibolone, which showed no changes, HT significantly increased high-sensitivity C-reactive protein (hsCRP, P=0.030) and reduced antithrombin III (P<0.001). HT and tibolone significantly increased prothrombin fragment 1+2 (F1+2) from baseline values (P<0.001 and P=0.004, respectively). The effects of HT and tibolone on hsCRP, antithrombin III, and F1+2 were significantly different. HT and tibolone significantly reduced plasma levels of plasminogen activator inhibitor type 1 antigen from baseline levels (P=0.006 and P=0.005, respectively) to a similar degree (P=0.988).

Conclusions—Tibolone significantly improved flow-mediated brachial artery dilator response by a magnitude similar to that found with CEE+MP; however, tibolone did not significantly change hsCRP and antithrombin III, and tibolone increased F1+2 less than did CEE+MP. (Arterioscler Thromb Vasc Biol. 2003;23:1889-1894.)

Key Words: hormone therapy • tibolone • endothelial function • inflammation • hemostasis

Prospective cohort surveys suggest that hormone therapy (HT) decreases the risk of coronary artery disease in relatively young and healthy postmenopausal women.1,2 In contrast, 2 recent randomized studies, the Heart and Estrogen/Progestin Replacement Study (HERS)3 and the Women’s Health Initiative (WHI),4 reported that HT did not reduce the risk of cardiovascular events and, furthermore, demonstrated some trends toward an increased risk of cardiovascular events. The increased risk of coronary heart disease (CHD) was surprising, given that LDL cholesterol levels decreased and that HDL cholesterol levels increased. The reasons may result from the effects of HT on an increase in triglyceride and C-reactive protein (CRP) levels and thromboembolism risk through activating coagulation pathways, evidenced by decreased antithrombin III and increased prothrombin fragment 1+2 (F1+2).5,6

Tibolone, a synthetic steroid with estrogenic, androgenic, and progestogenic properties, relieves climacteric symptoms and prevents postmenopausal bone loss. Furthermore, compared with HT, tibolone has no effect on breast cancer incidence and does not promote endometrial hyperplasia or rare vaginal bleeding.7 Tibolone has some beneficial effects, such as reduction of triglyceride, total cholesterol, LDL cholesterol, and lipoprotein(a) levels, reducing the risk of CHD.7 Nonetheless, its antiatherosclerotic effects have been questioned because of consistent reductions in the levels of HDL cholesterol, which has antiatherosclerotic properties. However, recent animal studies have demonstrated that the use of tibolone results in significantly less atherosclerosis than does use of placebo8 or, at least, that use of tibolone compared with control results in no increase in coronary atherosclerosis,9 despite a marked reduction of HDL chole-

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Effects of Placebo, Hormone Therapy, or Tibolone in Postmenopausal Women

<table>
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<tr>
<th></th>
<th>Placebo (n=26)</th>
<th>CEE+MP (n=53)</th>
<th>Tibolone (n=53)</th>
<th>P Values</th>
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<tr>
<td></td>
<td>Baseline</td>
<td>Baseline 1</td>
<td>HT (H)</td>
<td>Baseline 2</td>
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<tr>
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<td><strong>Body mass index</strong></td>
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<td><strong>Estradiol, pg/mL</strong></td>
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<td><strong>Lipids, mg/dL</strong></td>
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<td>Triglycerides</td>
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<td>Triglycerides/HDL cholesterol</td>
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<td><strong>Vasomotor, %</strong></td>
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<td>FMD</td>
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<td>(0.04–0.21)</td>
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<td>Antithrombin III</td>
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<td>279±11</td>
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<td>39±4</td>
<td>37±3</td>
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</table>

Data are expressed as mean±SEM or median (range, 25% to 75%). CEE+MP indicates conjugated equine estrogen 0.625 mg combined with micronized progesterone 100 mg (HT); B, baseline; H, hormone therapy; T, tibolone; FMD, flow-mediated dilation; NTG, nitroglycerin dilation.

terol levels. Overall, tibolone has complex effects on lipids, some that might be expected to improve vasomotor function and others that might worsen vasomotor function.

Recent findings from HERS and WHI have indicated a slightly increased risk of venous thromboembolism in HT users, which has been attributed to estrogen-dependent disturbances of hemostasis. However, it is not clear whether the effects of HT on risk factors of venous thromboembolism similarly apply to compounds with tissue-specific hormonal activity, which have an androgenic effect. In theory, a tendency toward fibrinolytic activity of the hemostatic system can be expected from preparations with some androgenic activity.

Therefore, we hypothesize that compared with HT, tibolone has different effects on the markers of cardiovascular disease in postmenopausal women. The objective of the present study was to compare the effects of tibolone and HT on lipid profile, vasodilation, and factors associated with inflammation and hemostasis.

Methods

Study Population and Design

Eight-two healthy postmenopausal women participated in the present study; all had plasma 17β-estradiol levels <50 pg/mL and reported cessation of menses for at least 1 year. No subject had taken any cholesterol-lowering agent, estrogen therapy, antioxidant vitamin supplements, or ACE inhibitors during the preceding 2 months. Baseline 17β-estradiol and lipoprotein levels are shown in the Table. No subject had diabetes, was a smoker, or had previous angina.

Twenty-seven women received placebo, and 55 women received micronized progesterone (MP, 100 mg) with conjugated equine estrogen (CEE, 0.625 mg) or tibolone (2.5 mg) daily for 2 months, with a 2-month washout period. One woman in the placebo group and 2 women in the conventional HT group withdrew because of a change in employment and severe vaginal bleeding, respectively. Thus, a total of 26 women in the placebo group and 53 women in the HT and tibolone group completed all phases of the study. We used the definitions of the National Heart, Lung, and Blood Institute for overweight as the cutoff points: body mass index ≥25.0 and weight ≥30.0 kg/m². We used WHO/ISH definitions for hypertension: systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg. Severe and moderate hypertension was excluded to avoid drug effects. Seven and 5 women in the placebo group and 15 and 10 women in the HT or tibolone group were hypertensive and overweight, respectively, and 14 women in the placebo group and 28 women in the HT or tibolone group were normotensive with normal weight. The average age past menopause was 7 years for the placebo group and for the HT or tibolone group. The present study was approved by the Gil Hospital Institute Review Board, and all participants gave written, informed consent.

Laboratory Assays

Blood samples for laboratory assays and vascular studies were obtained at ~8:00 AM after an overnight fast, at each baseline, and at the end of each treatment period, and were immediately coded so that the investigators performing the laboratory assays were blinded to subject identity or study sequence. Assays for lipids, fibrinogen, antithrombin III, F1+2, and plasminogen activator inhibitor type 1 (PAI-1) antigens were measured as previously described. In all patients, plasma was collected for the measurement of high-sensitivity CRP (hsCRP) levels by commercially available kits (Immundiagnostik CRP ELISA test). The lower limit of detection was 0.0001 mg/dL. All samples from the same patient (batch
Vascular Studies
Imaging studies of the right brachial artery were performed with an ATL HDI 3000 ultrasound machine equipped with a 10-MHz linear-array transducer with the use of a previously published technique. Measurements were performed by 2 independent investigators (D.K.J. and H.S.K.) blinded to the subject’s identity and medication status. Measurements of maximum diameter and percent flow-mediated dilation were made in 10 studies selected at random. The interobserver and intraobserver variabilities for repeated measurement of maximum diameter were 0.004±0.039 and 0.005±0.089 mm, respectively. The interobserver and intraobserver variabilities for repeated measurement of percent flow-mediated dilation were 0.07±1.27% and 0.15±1.24%, respectively.

Statistical Analysis
Data are expressed as mean±SEM or median (range 25% to 75%).

Results
In 26 postmenopausal women, placebo did not significantly change any parameter from the respective baseline value. Baseline values before the HT or tibolone treatment period were compared, and no significant differences were noted (Table). To assess the possibility of a carryover effect from the initial treatment phase to the next treatment phase, we compared the baseline values before the first treatment phase with those before the second treatment phase. No significant differences were noted. After 2 months of CEE combined with MP, plasma levels of 17β-estradiol significantly increased from baseline levels; however, there were no changes after tibolone therapy (Table).

Effects of Therapies on Lipids
The effects of therapies on lipids are shown in the Table. HT and tibolone significantly reduced total cholesterol levels by 6±2% and 16±2%, respectively, from baseline values; HT significantly increased triglyceride levels by 34±7% and tibolone reduced triglyceride levels by 35±4% from baseline values; HT significantly increased HDL cholesterol levels by 9±2% and tibolone reduced HDL cholesterol levels by 27±2% from baseline values; and HT significantly increased triglyceride/HDL cholesterol ratios by 40±8% and tibolone reduced triglyceride/HDL cholesterol ratios by 3±8% from baseline values. As a result, compared with HT, tibolone significantly reduced LDL cholesterol levels and triglyceride/HDL cholesterol ratios (Figure 1). HT and tibolone significantly reduced LDL cholesterol levels by 17±3% and 4±3%, respectively, from baseline values; however, HT significantly reduced LDL cholesterol to a greater extent.

Effects of Therapies on Vasomotor Function
Basal brachial artery diameter and forearm blood flows were similar during the 2 treatment periods, as were the peak brachial artery diameters and forearm blood flows during reactive hyperemia and the percent increase in flow during hyperemia (data not shown). HT and tibolone significantly improved the percent flow-mediated dilator response to hyperemia by 48±8% and 53±7%, respectively, from baseline values (Figure 2) to a similar degree. The brachial artery dilator response to nitroglycerin between each therapy was not significantly changed from baseline measurements.

Effects of Therapies on hsCRP and Hemostasis
HT significantly increased hsCRP by 148±28% from baseline values; in contrast, tibolone produced no changes (Figure 1). HT (CEE+MP) and tibolone significantly increased triglyceride levels by 34±7% and −35±4%, respectively, from baseline values (P<0.002 and P<0.001, respectively) and triglyceride/HDL cholesterol ratios by 40±8% and −3±8%, respectively, from baseline values (P=0.004 and P=0.008, respectively). Compared with HT, tibolone significantly reduced triglyceride (P<0.001) and triglyceride/HDL cholesterol ratios (P<0.001). Bars indicate SEM.
was younger than the mean age (66.7 years) in HERS and considered healthy. The mean age (59 years) of our subjects was 1892 Arterioscler Thromb Vasc Biol. October 2003

3). HT significantly decreased antithrombin III by 10±2% from baseline values; in contrast, tibolone produced no changes. The effects of HT and tibolone on hsCRP and antithrombin III were significantly different. HT and tibolone significantly increased F1+2 by 198±59% and 14±4%, respectively, from baseline values. However, compared with tibolone, HT more significantly increased F1+2. There were no significant positive correlations between pretreatment F1+2 levels and the degree of change in F1+2 after HT (r=0.178, P=0.198) and after tibolone (r=−0.333, P=0.015). HT and tibolone significantly reduced plasma PAI-1 antigen levels to a similar degree, by 11±7% and 11±8%, respectively, from baseline values. There were significant inverse correlations between pretreatment PAI-1 antigen levels and the degree of changes in PAI-1 after HT (r=−0.402, P=0.003) and after tibolone (r=−0.535, P<0.001). Neither therapy significantly changed fibrinogen levels from baseline values.

There were significant correlations between body mass index and hsCRP levels before HT and tibolone (r=0.331, P=0.027 and r=0.324, P=0.030, respectively). However, there were no significant correlations between the degree of change in flow-mediated dilation and the degree of change in lipoprotein or hsCRP levels after HT (−0.170≤r≤0.048) and after tibolone (−0.014≤r≤0.042). There were no significant correlations between pretreatment triglyceride levels and pretreatment PAI-1 levels. However, there were weak correlations between body mass index and pretreatment PAI-1 levels (r=0.257, P=0.063). There were no significant correlations between the degree of change in antithrombin III or F1+2 and the degree of change in PAI-1 antigen levels after HT (−0.005≤r≤0.057) and after tibolone (−0.213≤r≤0.061).

**Discussion**

Compared with patients in HERS and WHI, our subjects were considered healthy. The mean age (59 years) of our subjects was younger than the mean age (66.7 years) in HERS and the mean age (63.3 years) in WHI. The mean body mass index (24.5) was much lower than that (28.5) in WHI. Our subjects did not have a history of smoking; however, 50.4% of the subjects in WHI had a history of smoking. Overall, our subjects had characteristics similar to those in the Nurses’ Health Study.2

In the present study, we observed that compared with HT, tibolone significantly reduced total cholesterol, triglyceride, and HDL cholesterol levels and triglyceride/HDL cholesterol ratios but not LDL cholesterol levels. Tibolone did not significantly change hsCRP, and antithrombin III and tibolone increased F1+2 less than did HT. Tibolone significantly improved flow-mediated brachial artery dilator response to a magnitude similar to that found with HT. It may be argued that further protection by HDL may not be required; therefore, the reduction in HDL level seen with tibolone may have no adverse consequences. In support of this speculation, we observed that tibolone significantly reduced the triglyceride/HDL cholesterol ratio, which is a powerful predictor of insulin resistance and CHD risk.19–21

The changes of lipoprotein levels, such as 16% reduction of total cholesterol, 27% reduction of HDL cholesterol, and 4% reduction of LDL cholesterol, and 35% reduction of triglyceride levels, after tibolone were consistent with those reported by others.7,22 Elevated blood triglyceride levels are an important risk factor for CHD, especially among women. Elevated triglycerides are associated with higher levels of dense LDL cholesterol.23 In this regard, oral CEE significantly increased plasma triglyceride and decreased LDL particle size, which counteracted the antioxidant effect of estrogen, in contrast to tibolone, which has an antioxidant effect.24–25

Tibolone significantly improved flow-mediated brachial artery dilator response. Clarkson et al26 observed no exacerbation of coronary artery atherosclerosis with oral contraceptive treatment despite reductions in HDL cholesterol levels. The plasma lipid–independent effects of ethinyl estradiol protected the coronary arteries from the deleterious effects of HDL cholesterol reductions. Indeed, we observed no correlations between the degree of change in flow-mediated dilation and the degree of change in lipoprotein levels after HT or tibolone. In a recent study, Clarkson et al20 demonstrated that tibolone neither increased coronary artery atherosclerosis nor reduced coronary artery atherosclerosis in cynomolgus monkeys; in contrast, HT reduced coronary artery atherosclerosis. In that study, the potential of tibolone for inhibiting coronary artery atherosclerosis might be underestimated because tibolone increased total cholesterol, LDL cholesterol, and triglyceride levels and decreased HDL cholesterol levels to a greater extent, which cannot be observed in women. A recent study27 demonstrated that the lowering of HDL cholesterol in postmenopausal women by tibolone was not associated with changes in cholesterol efflux capacity or paraoxonase activity. In that study, tibolone significantly decreased HDL cholesterol levels (from −22% to −32%) and apolipoprotein A-I (from −14% to −22%); however, these changes were not associated with changes in the activity of plasma to release [3H]cholesterol from radiolabeled fibroblasts or in the serum activity of the antioxidative enzyme paraoxonase/arylesterase. In other words, antiatherogenic activities of HDL remained unchanged despite decreased HDL
cholesterol. Indeed, tibolone prevented cholesterol accumulation and fatty streak formation in the aorta and the impairment of endothelial-dependent smooth muscle relaxation of the aorta, and these beneficial effects were plasma lipid independent. Also, there is no clinical evidence indicating that tibolone increases CHD rates. Tibolone has effects similar to those of progesterol regarding the antioxidant effect and the HDL cholesterol–lowering effect. Despite the reduction of HDL cholesterol, progesterol reduced the rate of restenosis and complications after percutaneous intervention in patients with coronary artery disease.

However, 1 study compared the effect of CEE combined with medroxyprogesterone acetate and tibolone for 3 months on flow-mediated dilation in healthy postmenopausal women. That study observed that HT improved flow-mediated dilation but that tibolone did not. We speculate that some differences of study design and of patient characteristics may have resulted in different observations compared with our present study. First of all, despite being randomized, some factors, such as smoking, lipoprotein levels, and baseline flow-mediated dilation, were different between the HT and tibolone groups. The differences of these factors clearly affect flow-mediated dilation. To avoid these kinds of issues and unmeasured bias, we decided to perform a crossover design in the present study. Furthermore, the aforementioned study did not provide the effects of HT and tibolone on lipoprotein levels. Although they calculated 30 subjects and presumed an absolute difference of 4% between HT and placebo, they observed only a 2% difference (unadjusted) between HT and placebo, which was not significant. Koh and colleagues and others have observed that CEE combined with medroxyprogesterone acetate or natural progesterone improves flow-mediated dilation. Also, their measurement of nitroglycerin dilation from 7.5% to 9.6% is much less than that found by our group and others, which may result from different techniques. In the present study, we recruited >50 subjects under the power calculation and observed that tibolone improved flow-mediated dilation >1.5% compared with baseline levels.

We observed that oral HT significantly increased hsCRP levels and that hsCRP levels were significantly correlated with body mass index; these findings are consistent with those of another study. We observed that in contrast to HT, tibolone did not significantly increase hsCRP levels. These different effects of HT and tibolone may be clinically very relevant; although the absolute value difference of CRP between baseline and HT or tibolone was small, it was highly significant in the present study. In our previous study, CEE significantly increased median CRP levels from 0.27 to 0.46 mg/dL in postmenopausal women. Epidemiological studies have consistently shown that elevated CRP is a risk factor for CHD even in apparently healthy women. Although a recent study observed that increased CRP levels after 3 years of HT treatment in the WHI trial did not cause cardiovascular events, the finding that CRP has several important atherogenic properties and is also an inflammation marker indicates that an HT-induced CRP increase may result in the progression of atherogenesis. CRP induces the expression of tissue factor, adhesion molecules, and angiotensin II type I receptor, promotes monocyte chemotaxis, decreases endothelial NO synthase expression and activity, and facilitates the uptake of LDL by macrophages. These observations have led many investigators to suggest that the disappointing results of the recent clinical trials may be due in part to HT-induced increases in hsCRP. We do not know why tibolone did not change hsCRP, but it may be due to its androgenic property. In support of this speculation, Wakatsuki et al observed that medroxyprogesterone acetate, which has an androgenic effect, attenuated the increase of CRP with oral CEE in women and that, as a consequence, its effect on CRP was not different from control.

It is also consistent that HT significantly reduced antithrombin III and increased F1 + 2, which is an explanation for the increased risk of thrombosis after HT. The effects of tibolone on antithrombin III were either an increase or no change. In the present study, we observed that tibolone did not change antithrombin III and that tibolone increased F1 + 2 less than did HT. We also observed that tibolone had effects comparable to those of HT regarding PAI-1 antigen levels, suggesting an improvement of fibrinolytic potential. However, there were no significant correlations between the effects of HT on coagulation and fibrinolytic markers; these findings are consistent with our previous findings. Tibolone lowered PAI activity and antigen levels and increased plasminogen and fibrinolytic activity. Taken together, unlike HT, tibolone may increase fibrinolytic potential, with little change in coagulation. In support of this fact, there have been no clinical studies reporting a risk of thrombosis with tibolone.

Our data suggest that tibolone may be considered an alternative to CEE+MP in postmenopausal women. However, clinical recommendations regarding the effects of tibolone on cardiovascular outcome must await the performance of additional studies with clinical end points.

Acknowledgments
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References
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