Effects of Conventional or Lower Doses of Hormone Replacement Therapy in Postmenopausal Women

Kwang Kon Koh, Mi-Seung Shin, Ichiro Sakuma, Jeong Yeal Ahn, Dong Kyu Jin, Hyung Sik Kim, Dae Sung Kim, Seung Hwan Han, Wook-Jin Chung, Eak Kyun Shin

Objective—The effects of hormone replacement therapy (HRT) can affect many aspects relevant to cardiovascular disease, including vasomotor function, inflammation, and hemostasis. Recent studies have demonstrated that current doses of HRT exert a mixture of both protective and adverse effects. In the current study, we compared the effects of lower doses of HRT (L-HRT) and conventional doses of HRT (C-HRT) on a variety of relevant cardiovascular parameters.

Methods and Results—This randomized, double-blind, crossover study included 57 women who received micronized progesterone 100 mg with either conjugated equine estrogen 0.625 mg (C-HRT) or 0.3 mg (L-HRT) daily for 2 months. L-HRT showed comparable effects to C-HRT on high-density lipoprotein cholesterol and triglyceride levels, but not on low-density lipoprotein cholesterol levels. C-HRT and L-HRT significantly improved the percent flow-mediated dilator response to hyperemia from baseline values (both $P<0.001$) by a similar degree ($P=0.719$). C-HRT significantly increased high-sensitivity C-reactive protein (hsCRP) levels from baseline values ($P<0.001$); however, L-HRT did not significantly change hsCRP ($P=0.874$). C-HRT and L-HRT significantly decreased antithrombin III from baseline values ($P<0.001$ and $P=0.042$, respectively). C-HRT significantly increased prothrombin fragment 1+2 (F1+2) from baseline values ($P<0.001$); however, L-HRT did not significantly change F1+2 ($P=0.558$). Of interest, the effects of C-HRT and L-HRT on hsCRP, antithrombin III, and F1+2 were significantly different (all $P<0.001$). C-HRT and L-HRT significantly reduced plasma PAI-1 antigen levels from baseline values ($P=0.002$ and $P=0.038$, respectively) to a similar degree ($P=0.184$).

Conclusions—Compared with C-HRT, L-HRT has comparable effects on lipoproteins, flow-mediated dilation, and PAI-1 antigen levels. However, L-HRT did not increase hsCRP or F1+2 levels, and it decreased antithrombin III less than C-HRT. **(*Arterioscler Thromb Vasc Biol*. 2004;24:1516-1521.)**

Key Words: hormone replacement therapy ■ lower doses ■ endothelial function ■ inflammation ■ hemostasis ■ menopause

Prospective cohort surveys suggest that hormone replacement therapy (HRT) 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 HRT did not reduce the risk of cardiovascular events and further demonstrated some trends toward an increased risk of cardiovascular events. The increased risk of coronary heart disease was surprising given that low-density lipoprotein (LDL) cholesterol levels decreased and that high-density lipoprotein (HDL) cholesterol levels increased. The reasons may result from the effects of HRT on 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]

Activation of coagulation pathways has been detected dose-dependently in postmenopausal women treated with conjugated equine estrogen (CEE) 0.625 and 1.25 mg.[7] In this regard, we reported that conventional dosages of CEE 0.625 mg increased tissue factor activity and F1+2, indicator of coagulation activation,[8,9] and observational studies demonstrated that the risk for thromboembolism increases dose-dependently in postmenopausal women.[2,10,11] The apparent protective effect of CEE in the Nurses' Health Study was noted only at the 0.3 mg and 0.625 mg doses; 1.25 mg and higher doses were not cardioprotective.[11]

It has been reported that ≈59% of women discontinue HRT within 2 years, and the use of lower doses of HRT has been proposed to improve long-term compliance with HRT.[12] Recently, lower doses (CEE 0.3 mg) of HRT (L-HRT) demonstrated comparable effects to conventional doses (CEE 0.625 mg) of HRT (C-HRT) on menopausal symptoms,[13,14] endometrial protection,[15] plasma lipoproteins, carbohydrate metabolism,[16] and bone mineral density.[17,18] The liver is a

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From the Departments of Cardiology (K.K.K., M.-S.S., D.K.J., S.H.H., W.-J.C., E.K.S.), Clinical Pathology (J.Y.A.), and Cardiovascular Medicine (I.S.), Hokkaido University Graduate School of Medicine, Sapporo, Japan; and the Departments of Radiology (H.S.K.) and Preventive Medicine (Biostatistics) (D.S.K.), Gachon Medical School, Incheon, Korea.

Correspondence to Dr Kwang Kon Koh, Professor of Medicine Director, Vascular Medicine and Atherosclerosis Unit Division of Cardiology, Gil Heart Center Gachon Medical School 1198 Kuwol-dong, Namdong-gu Incheon, Korea 405-760. E-mail kwangk@ghil.com

major source of coagulants and CRP;[19] therefore, oral administration of L-HRT may activate coagulation pathway and CRP less than C-HRT.

However, the effects of L-HRT on vasomotor function, inflammation marker CRP, and hemostasis markers in postmenopausal women have not been compared directly with C-HRT. Therefore, the purpose of this study was to determine the effects of C-HRT and L-HRT on vasomotor function, CRP, and hemostasis markers in postmenopausal women.

Methods

Study Population and Design

Sixty postmenopausal women participated in this study, all with plasma 17β-estradiol levels $<$50 pg/mL and cessation of menses for at least 1 year. No subjects had used any cholesterol-lowering agent, estrogen therapy, antioxidant vitamin supplements, or angiotensin-converting enzyme inhibitors during the preceding 2 months. None had diabetes, was a smoker, or had previous angina. This study used a randomized, double-blind, crossover design. We used the National Heart, Lung, and Blood Institute's definitions[20] for overweight as the cutoff points: body mass index $\geq$25.0 and $<$30.0 kg/m^2. We used World Health Organizations/International Society of Hypertension definitions[21] for hypertension defined as systolic and diastolic blood pressure $\geq$140 or $\geq$90 mm Hg, respectively. Severe and moderate hypertension was excluded to avoid drug effects. Thirty had hypertension and 13 women were overweight, and the other 17 women were normotensive and of normal weight. Sixty women received micronized progesterone (MP) 100 mg with either CEE 0.625 mg or 0.3 mg daily during 2 months, with a 2-month washout period because they did not undergo hysterectomy before. Two hypertensive and 1 overweight women in C-HRT withdrew because of severe vaginal bleeding. Thus, a total of 57 using C-HRT and L-HRT completed all phases of the study. The 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 approximately 8:00 AM after an overnight fast, at each baseline, and at the end of each treatment period, and were immediately coded so that investigators performing 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.[8,9,22–24] In all patients, plasma was collected for the measurement of high-sensitivity C-reactive protein (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 samples) were measured in blinded pairs on the same enzyme-linked immunosorbent assay kit to minimize run-to-run variability. The interassay and intra-assay coefficients of variation were $<$6%.

Vascular Studies

Imaging studies of the right brachial artery were performed using ATL HDI 3000 ultrasound machine equipped with a 10-MHz linear-array transducer, based on a previously published technique.[22,23,25] All images were transmitted to a personal computer via Ethernet with DICOM format (digital imaging and communication in medicine) and then saved on the hard disk of a personal computer as a BMP format. Arterial diameters were measured with Image Tool for Windows version 2.0 (University of Texas Health Science Center, San Antonio, Texas). 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 performed in 10 studies selected at random. The interobserver and intraobserver variability for repeated measurement of maximum diameter were 0.004$\pm$0.039 mm and 0.005$\pm$0.089 mm, respectively. The interobserver and intraobserver variability for repeated measurement of percent flow-mediated dilation were 0.07$\pm$1.27% and 0.15$\pm$1.24%, respectively.

Statistical Analysis

Data are expressed as mean$\pm$SEM or median (range: 25% to 75%). After testing data for normality, we used Student paired *t* test or Wilcoxon signed-rank test to compare values at each baseline and after each therapy and the relative changes in values in response to treatment, as reported in the Table. Pearson or Spearman correlation coefficient analysis was used to assess associations between measured parameters. We calculated that 50 subjects would provide 80% power for detecting difference of absolute increase, 1.5% or greater flow-mediated dilation of the brachial artery between baseline and L-HRT, with α=0.05 based on our previous studies.[22,23,25] The comparison of endothelium-dependent dilation among C-HRT and L-HRT treatment schemes was prospectively designated as the primary end point. All other comparisons were considered secondary end points. P $<$0.05 was deemed as statistically significant.

Results

Baseline values before C-HRT or L-HRT treatment period were compared. 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 found. After 2 months of C-HRT or L-HRT treatment, plasma levels of 17β-estradiol significantly increased from baseline values (Table).

Effects of Therapies on Lipids

The effects of therapies on lipids are shown in the Table. C-HRT and L-HRT significantly reduced total cholesterol levels by 6$\pm$2% and 2$\pm$2%, respectively, from baseline values ($P$$<$0.001 and P=0.038, respectively) and LDL cholesterol levels by 18$\pm$3% and 6$\pm$3%, respectively, from baseline values ($P$$<$0.001 and P=0.003, respectively). C-HRT and L-HRT significantly increased triglyceride levels by 35$\pm$7% and 34$\pm$11%, respectively, from baseline values (P=0.001 and P=0.047, respectively) and HDL cholesterol levels by 10$\pm$2% and 6$\pm$2%, respectively, from baseline values ($P$$<$0.001 and P=0.060, respectively). Compared with L-HRT, C-HRT significantly reduced LDL cholesterol levels (P=0.005); otherwise, there were no significant differences between both.

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). C-HRT and L-HRT significantly improved the percent flow-mediated dilator response to hyperemia by 47$\pm$8% and 44$\pm$5%, respectively, from baseline values (both $P$$<$0.001; Figure 1) by a similar degree (P=0.719). The brachial artery dilator response to nitroglycerin between each therapy was not significantly changed from baseline measurements (P=0.220 and P=0.159, respectively).

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	CEE 0.625 mg+MP (n=57)		CEE 0.3 mg+MP (n=57)		*P*		
	Baseline 1	C-HRT	Baseline 2	L-HRT	B1 vs CH	B2 vs LH	CH vs LH
Age	57±1		57±1				
Body mass index	24.8±0.5		24.8±0.5				
Estradiol (pg/mL)	27±2	79±6	24±2	55±7	<0.001	<0.001	0.123
Lipids (mg/dL)							
Total cholesterol	218±5	203±4	213±4	206±4	<0.001	0.038	0.093
Triglycerides	147±11	179±13	148±11	169±12	0.001	0.047	0.940
HDL cholesterol	53±1	57±2	53±2	55±2	<0.001	0.060	0.163
LDL cholesterol	135±4	110±4	131±4	119±3	<0.001	0.003	0.005
Vasomotor function							
Brachial artery diameter, mm							
Basal-1	3.81±0.11	3.77±0.11	3.77±0.10	3.70±0.16	0.777	0.536	
Hyperemia	4.02±0.12	4.06±0.11	3.99±0.11	3.98±0.16	0.706	0.912	
Basal-2	3.83±0.14	3.87±0.12	3.82±0.12	3.73±0.18	0.726	0.492	
Nitroglycerin	4.29±0.16	4.33±0.13	4.32±0.16	4.22±0.18	0.745	0.478	
Brachial artery flow, mL/min							
Basal-1	64±8	61±9	62±7	53±6	0.721	0.209	
Hyperemia	387±26	374±45	384±24	389±36	0.812	0.867	
Increase in flow, %	494±65	507±58	587±86	500±45	0.931	0.352	
Basal-2	58±4	52±5	56±4	57±5	0.313	0.927	
Nitroglycerin	62±4	77±6	61±5	64±7	0.108	0.677	
Flow-mediated dilation (%)	4.82±0.21	6.43±0.21	4.77±0.18	6.53±0.21	<0.001	<0.001	0.719
Nitroglycerin dilation (%)	13.65±0.51	14.16±0.49	13.99±0.45	14.54±0.41	0.220	0.159	0.963
C-reactive protein (mg/dL):	(0.04–0.17)	(0.06–0.34)	(0.05–0.25)	(0.05–0.18)	<0.001	0.874	<0.001
Median	0.083	0.150	0.077	0.076			
Antithrombin III (mg/dL)	30.1±0.6	26.6±0.5	29.7±0.5	28.5±0.5	<0.001	0.042	<0.001
F1+2 (nmol/L):	(1.36–1.92)	(1.51–4.13)	(1.28–2.00)	(1.36–2.05)	<0.001	0.558	<0.001
Median	1.57	2.13	1.55	1.66			
Fibrinogen (mg/dL)	292±8	278±7	286±8	279±7	0.114	0.345	0.700
PAI-1 (ng/mL)	36±3	27±2	36±2	31±2	0.002	0.038	0.184

Data are expressed as means±SEM or range (25%–75%).
CEE+MP=conjugated equine estrogen combined with micronized progesterone 100 mg (HRT).
B indicates baseline; H, hormone replacement therapy.

Effects of Therapies on hsCRP and Hemostasis

C-HRT significantly increased hsCRP by 149±27% from baseline values ($P<0.001$); however, L-HRT did not significantly change hsCRP ($P=0.874$). The effects of C-HRT and L-HRT on hsCRP were significantly different ($P<0.001$). There were significant inverse correlations between pretreatment CRP levels and the degree of change in CRP after C-HRT ($r=-0.434$, $P=0.001$) and after L-HRT ($r=-0.496$, $P<0.001$). C-HRT and L-HRT significantly decreased antithrombin III by 11±2% and 3±2%, respectively, from baseline values ($P<0.001$ and $P=0.042$, respectively). C-HRT significantly reduced antithrombin III more than L-HRT ($P<0.001$). C-HRT significantly increased F1+2 by 187±55% from baseline values ($P<0.001$); however, L-HRT did not significantly change F1+2 ($P=0.558$). The effects of C-HRT and L-HRT on F1+2 were significantly different ($P<0.001$; Figure 2). There was no significant correlation between pretreatment F1+2 levels and the degree of change in F1+2 after C-HRT ($r=0.151$, $P=0.260$) or L-HRT ($r=-0.264$, $P=0.054$). C-HRT and L-HRT significantly reduced plasma PAI-1 antigen levels by 12±6% and 2±6%, respectively, from baseline values ($P=0.002$ and $P=0.038$, respectively) to a similar degree ($P=0.184$). There were significant inverse correlations between pretreatment PAI-1 levels and the degree of changes in PAI-1 after C-HRT ($r=-0.418$, $P=0.002$) and after L-HRT ($r=-0.513$, $P<0.001$). Neither therapy significantly changed fibrinogen levels from baseline values.

There were significant correlations between body mass index and hsCRP levels before C-HRT and L-HRT ($r=0.360$, $P=0.008$ and $r=0.328$, $P=0.017$, respectively). However, there were no significant correlations between the degree of change in flow-mediated dilation and the degree of change in lipoprotein or CRP levels after C-HRT ($-0.198\leq r\leq 0.144$)

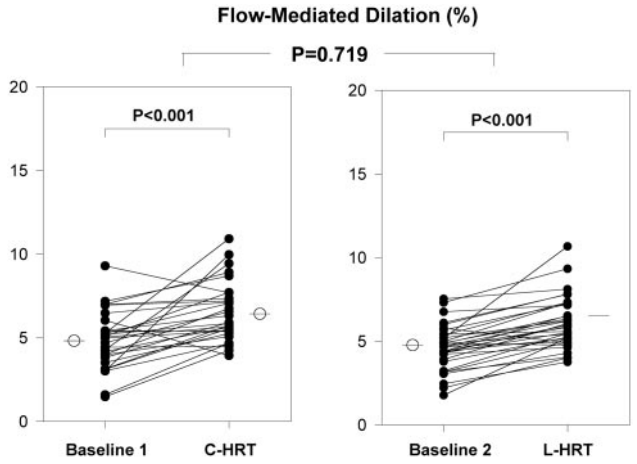

Figure 1. Flow-mediated dilation before treatment (baseline) and after micronized progesterone combined with conjugated equine estrogen 0.625 mg (C-HRT) or 0.3 mg (L-HRT) treatment. Both therapies significantly improved the percent flow-mediated dilator response to hyperemia relative to baseline measurements (both $P<0.001$) by a similar degree. Mean values are identified by white circles.

and after L-HRT ($-0.162 \leq r \leq 0.212$). There were no significant correlations between pretreatment triglyceride levels and pretreatment PAI-1 levels. However, there were significant correlations between body mass index and pretreatment PAI-1 levels ($r=0.303$, $P=0.027$). 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 C-HRT ($0.020 \leq r \leq 0.041$) and after L-HRT ($-0.048 \leq r \leq 0.009$).

Discussion

We have previously shown that C-HRT improved nitric oxide bioavailability, reduced circulating levels of markers of inflammation,[22,25] and improved fibrinolysis potential[24,26] in postmenopausal women. However, we and others have reported that C-HRT increased hsCRP levels[9,27,28] and thromboembolism risk through activating coagulation system. However, no studies have directly compared the effects of C-HRT and L-HRT on vascular function.

In the current study, we demonstrate comparable effects of L-HRT and C-HRT on both HDL cholesterol and triglycerides, although the effects were not comparable on LDL cholesterol levels, consistent with previous reports.[16,18] We also observed comparable effects of L-HRT and C-HRT on flow-mediated dilation, which also was consistent with a previous report.[29–31]

We observed hsCRP levels were significantly correlated with body mass index, which are consistent with another study.[32] We observed that in contrast to C-HRT, L-HRT did not significantly increase hsCRP levels. These different effects of C-HRT and L-HRT may be clinically very relevant. Epidemiologic studies have consistently shown that elevated CRP is a risk factor for coronary heart disease among women.[33] CRP increases the expression of tissue factor[34] and adhesion molecules,[35] promotes monocyte chemotaxis,[36] and decreases endothelial nitric oxide synthase expression and activity.[37] In addition, CRP may contribute to atherogenesis by facilitating uptake of LDL by macrophages, thus accelerating foam cell formation.[38] Tissue factor activates the extrinsic coagulation cascade, providing a link between inflammation and thrombosis. In this regard, we recently reported that C-HRT significantly increased CRP and tissue factor activity and increased thrombosis in postmenopausal women.[9] These observations have led many investigators to suggest that the disappointing results of the recent clinical trials may be caused in part by C-HRT–induced increases in hsCRP.[3,39,40] Of interest, we observed that the highest pretreatment CRP levels increased to the least extent after C-HRT.

We observed that C-HRT significantly reduced antithrombin III and increased F1+2 levels, consistent with others.[7] Of note, we observed that the effects of L-HRT on antithrombin III were significantly less than C-HRT; furthermore, like hsCRP, L-HRT did not significantly increase F1+2 levels. We also observed that L-HRT had comparable effects to C-HRT regarding PAI-1 antigen levels, suggesting an improvement of fibrinolysis potential.[6,26] Furthermore, the highest pretreatment PAI-1 antigen levels decreased to the greatest extent than the lowest pretreatment PAI-1 antigen levels after C-HRT and L-HRT. These observations are consistent with our previous reports[24,26] and that of others.[16] However, there were no significant correlations between the effects of HRT on coagulation and fibrinolysis markers, which are consistent with our previous reports[9,24] and others.[41,42] Scarabin et al[41] reported no correlation between fibrinolytic potential and coagulation activation using C-HRT regimens. Cushman et al[42] found that hemostasis markers and evidence of procoagulation were not associated and fibrinolytic potential increased. Taken together, L-HRT may increase fibrinolysis potential with little changes on coagulation, unlike C-HRT.

The liver is a major source of coagulants, CRP, and PAI-1.[19,43] Thus, the presence of estrogen in different concentrations in the portal circulation, after absorption from the

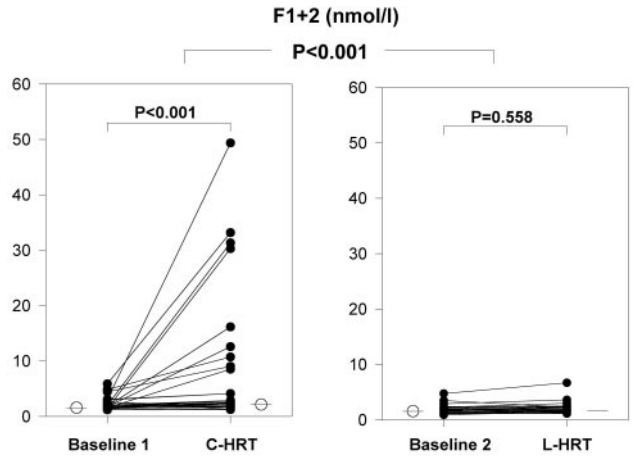

Figure 2. Plasma prothrombin fragment 1+2 (F1+2) levels before treatment (baseline) and after micronized progesterone combined with conjugated equine estrogen 0.625 mg (C-HRT) or 0.3 mg (L-HRT) treatment. C-HRT significantly increased F1+2 from baseline values ($P<0.001$); however, L-HRT did not significantly change F1+2 ($P=0.558$). Of interest, the effects of C-HRT and L-HRT on F1+2 were significantly different ($P<0.001$). Median values are identified by white circles.

gut, may show different synthesis of coagulants and CRP, although no mechanism of such an effect has been proposed. Accordingly, L-HRT might not demonstrate exactly the same effects as C-HRT.

In summary, we observed that L-HRT has comparable effects to C-HRT on lipoproteins, flow-mediated dilation, and PAI-1 antigen levels. However, L-HRT did not increase hsCRP or F1+2 levels, and it decreased antithrombin III less than C-HRT. Therefore, L-HRT may be considered as an alternative to C-HRT in postmenopausal women. However, clinical recommendations regarding the effects of L-HRT on cardiovascular outcomes must await the performance of additional studies with clinical end points.

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