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Different effects of oral conjugated estrogen and transdermal estradiol on arterial stiffness and vascular inflammatory markers in postmenopausal women

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Abstract

Aims: We compared the effects of oral conjugated equine estrogen (CEE) therapy and transdermal estradiol therapy on pulse wave velocity (PWV) and circulating levels of vascular inflammatory markers in postmenopausal women and we also explored the interrelationship between the change in PWV and the changes in vascular inflammatory markers.

Methods and results: In a randomized 12-month trial, 28 postmenopausal women received a continuous oral CEE plus cyclic medroxyprogesterone acetate (MPA), 28 received a continuous transdermal estradiol patch plus cyclic MPA, and 27 did not receive either therapy. In each subject, we measured the brachial-ankle PWV (baPWV) using an automated device, the blood pressure, and the circulating levels of vascular inflammatory markers (C-reactive protein [CRP], cell adhesion molecules [CAMs], monocyte chemoattractant protein-1 [MCP-1], and matrix metalloproteinase [MMP-9]) before and 12 months after the start of the study. Oral CEE therapy did not change the baPWV but significantly increased the CRP and MMP-9 levels ($P < 0.05$, each) and significantly decreased the CAMs and MCP-1 levels ($P < 0.05$, each). Transdermal estradiol therapy significantly decreased the baPWV, and the CAMs and MCP-1 levels ($P < 0.05$, each) but had no effect on the CRP or MMP-9 levels. No significant changes were seen in the control group. The blood pressures of the subjects remained unchanged. In the transdermal estradiol group, the change in baPWV was not significantly correlated with the changes in vascular inflammatory markers.

Conclusion: Transdermal estradiol, but not oral CEE therapy, may have antiatherosclerotic effects by improving arterial stiffness. The reduction in baPWV may contribute to the direct effect of estrogen, but not to the decrease in estrogen-induced vascular inflammatory markers.

Keywords: Atherosclerosis; Estrogen; Inflammation; Lipids

1. Introduction

The Heart and Estrogen/Progestin Replacement Study (HERS) in women with coronary heart disease indicated that oral conjugated equine estrogen (CEE) therapy may not confer any benefits [1]. The Women's Health Initiative (WHI) in women without coronary heart disease reported that oral CEE therapy increases the risk of a heart attack or stroke [2,3]. Oral CEE therapy in postmenopausal women increases the circulating concentrations of C-reactive protein (CRP) [4], a marker of inflammation [5]; triglycerides [6], an independent risk factor for cardiovascular disease [7];

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and matrix metalloproteinase (MMP-9) [8], which is elevated in patients with unstable angina or acute myocardial infarction [9]. Therefore, the CEE-induced unfavorable changes in CRP, triglyceride, and MMP-9 levels may in part participate in the increased incidence of cardiovascular events observed in the clinical trials. On the other hand, transdermal estrogens reach the vessels directly, without passing through the liver although after oral administration, most estrogens reach the liver via the portal circulation and are metabolized through a process called the first-pass effect. Transdermal estradiol therapy in postmenopausal women does not increase circulating CRP [10], triglyceride [11], or MMP-9 [12] concentrations.

PWV is a known indicator of arterial stiffness [13,14] and arterial compliance [15] and has been regarded as a marker reflecting vascular damage [16]. PWV values measured using noninvasive automatic devices can be used not only as a marker of vascular damage [16], but as a predictor of the patient's prognosis [17]. In addition, cell adhesion molecules, like intercellular adhesion molecule (ICAM-1), vascular cell adhesion molecule (VCAM-1), and E-selectin, appear to be particularly important in the recruitment of monocytes from the blood into the intima of arteries, where they subsequently become lipid-filled foam cells, increasing the size of atherosclerotic plaques. Monocyte chemoattractant protein (MCP-1) predominantly mediates the recruitment of macrophages to the arterial lesion [18]. Hence, increased levels of cell adhesion molecules and MCP-1 contribute to the formation of vascular atherosclerosis [18]. Oral CEE therapy and transdermal estradiol therapy in postmenopausal women are known to affect the PWV [19–22] and the levels of vascular inflammatory markers [4,8,10,12,23,24]. Considering the results of the HERS and WHI trials and the CEE-induced elevations in triglyceride, CRP, and MMP-9 levels, transdermal estradiol therapy may have a different effect on aortic stiffness and vascular inflammation compared with oral CEE therapy. Furthermore, the circulating levels of vascular inflammatory markers are associated with the degree of PWV in various populations [25–27]. Therefore, we hypothesized that oral CEE or transdermal estradiol in postmenopausal women would alter PWV in combination with the changes in vascular inflammatory markers. However, the simultaneous measurements of PWV and circulating vascular inflammatory markers concentrations during oral CEE and transdermal estradiol therapy have not been reported.

Recently, the development of a new device has made it much easier to estimate the carotid-femoral PWV by measuring the brachial-ankle PWV (baPWV), which is well correlated with the carotid-femoral PWV [28]. Here, we compared the effects of oral CEE therapy and transdermal estradiol therapy on the baPWV and the circulating levels of vascular inflammatory markers and lipids in postmenopausal women and we also explored the interrelationship between the change in baPWV and the changes in vascular inflammatory markers after these therapies.

2. Materials and methods

2.1. Subjects

Ninety consecutive Japanese postmenopausal women participated in this study. Each subject had experienced natural menopause more than one year before the start of the study. The menopausal status was confirmed by a serum estradiol concentration of less than 20 pg/mL and a serum follicle-stimulating hormone (FSH) concentration of greater than 40 IU/L. None of the subjects smoked or had a history of thyroid disease, liver disease, diabetes mellitus, cardiovascular disease, hormone-dependent malignancy, or breast cancer; also, none of the subjects were currently taking any medication known to influence lipoprotein metabolism, and none had received hormone replacement therapy (HRT), other steroid hormones, or any medication that might affect the metabolism of sex steroids prior to enrollment in the present study. Untreated hypertensive subjects (blood pressure $\geq$ 140/90 mmHg) were included. All subjects had a normal ankle/brachial pressure index (ABI), as determined by Form/ABI (ABI > 0.9; Colin Co. Ltd., Komaki, Japan). Written informed consent was obtained from each participant before enrollment, and the Ethics Committee of the Cardiovascular Hospital of Central Japan approved the study.

2.2. Study protocol

Subjects were randomly assigned to one of three groups by the registration number of hospital for the duration of the 12-month study: a continuous oral CEE (0.625 mg/day) plus cyclic oral medroxyprogesterone acetate (MPA) (2.5 mg/day, for 12 days/month) ($n = 28$; mean age $\pm$ S.D., 54.8 $\pm$ 3.6 years; range, 48–66 years; mean body mass index [BMI] $\pm$ S.D., 22.7 $\pm$ 1.8 kg/m^2; oral CEE group), a continuous 17-β estradiol patch (absorption rate, 36 μg/day) plus cyclic oral MPA (2.5 mg/day, for 12 days/month) ($n = 28$; mean age, 55.2 $\pm$ 5.1 years; range, 48–66 years; mean BMI, 22.4 $\pm$ 3.3 kg/m^2; transdermal estradiol group), and a control group that did not receive HRT ($n = 27$; mean age, 55.9 $\pm$ 5.7 years; range, 49–65 years; mean BMI, 23.4 $\pm$ 2.0 kg/m^2; control group). Two subjects in the CEE group, two subjects in the transdermal estradiol group, and three subjects in the control group withdrew from the study because they did not complete the 12-month trial. Eight untreated hypertensive subjects in the CEE group, seven subjects in the transdermal estradiol group, and seven subjects in the control group were included. Each subject attended the HRT clinic at the Cardiovascular Hospital of Central Japan once a month for a physical checkup that included blood pressure and heart rate measurements. In each subject, the collection of a blood specimen and anthropometric, blood pressure, and baPWV measurements were performed between 9 a.m. and 10 a.m. after a 14-h overnight fast before and 12 months after the start of the study. The same investigator measured the blood pressure in the right arm of each subject using a mercury