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Estrogen replacement therapy decreases plasma adiponectin but not resistin in postmenopausal women

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Abstract

The effects of estrogen replacement therapy (ERT) to cardiovascular disease risk are still unclear. Low adiponectin and high resistin plasma concentrations are reported to be associated with atherosclerosis. However, it is not known how ERT affects plasma adiponectin and resistin concentrations. Seventy-three hysterectomized, nondiabetic, postmenopausal women were randomized in a double-blind, double-dummy study to receive either peroral estradiol valerate or transdermal 17β-estradiol gel for 6 months. Biochemical measurements were determined from samples taken before and after the therapy. Peroral estradiol valerate therapy decreased adiponectin concentrations from 13.6 to 11.6 mg/L (P = .008), whereas transdermal 17β-estradiol gel had no effect (12.7 vs 12.2 mg/L). Neither treatment changed the resistin concentrations significantly. Plasma concentrations of estradiol and estrone did not correlate with adiponectin or resistin concentrations before or after therapy. The change in adiponectin concentration correlated significantly with the changes in waist-hip ratio, very low-density lipoprotein triglycerides, and insulin-like growth factor 1 in the peroral estradiol valerate group. The changes in these variables and the change in estradiol concentration explained 43.1% (P = .001) of the variability in the change of plasma adiponectin, the change in very low-density lipoprotein triglycerides being the strongest determinant (β = −.407, P = .011). The results show that peroral ERT can decrease plasma adiponectin levels. However, ERT does not seem to influence plasma resistin concentrations.

1. Introduction

It is well established that women have a lower risk for cardiovascular diseases than men. However, this advantage vanishes after menopause in conjunction with a decline in estrogen production. Estrogen has therefore been suggested to be a cardiovascular protective agent in women, and hormone replacement therapy (HRT) has been proposed as 1 way to decrease the risk for cardiovascular disease after menopause. However, in large clinical trials, HRT has not been demonstrated to have positive effects on the risk of cardiovascular disease (reviewed by Collins [1]). For example, in the Woman's Health Initiative randomized controlled trial, 2 treatment strategies, that is, estrogen alone and estrogen combined with progestin, were prematurely terminated because the health risks exceeded the benefits. In these large trials, the risk of coronary heart disease (CHD) was observed to be elevated in the first years of treatment [2,3].

The large trials of HRT have been focused on orally administered estrogens, which have a strong positive impact on high-density lipoprotein (HDL) and low-density lipoprotein (LDL) levels. In contrast to oral treatments, transdermal estradiol has been reported to induce positive effects on other important cardiovascular risk markers such as triglycerides, LDL particle size, coagulation, and C-reactive protein. These differences between treatments are largely related to the effect of oral estrogen on liver metabolism, and these can be avoided by the nonoral route of administration (reviewed by Modena et al [4]). Despite these beneficial effects, the Papworth HRT atherosclerosis study failed to demonstrate any signs of CHD prevention

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with transdermal HRT in postmenopausal women with ischemic heart disease during a mean follow-up of 30.8 months [5]. However, it is possible that the small sample size (134 treated vs 121 controls) and high dropout rate in the HRT group (40%) diminished the power of that study; and thus, more studies are required to assess the clinical significance of transdermal estrogen replacement therapy (ERT) to CHD.

Two rather recently discovered hormones, adiponectin and resistin, have been linked with cardiovascular disease but in opposite ways. Adiponectin is expressed in adipocytes [6], whereas resistin is produced in peripheral blood mononuclear cells [7]. Low adiponectin (reviewed by Han et al [6]) and high resistin [8-14] concentrations have been associated with cardiovascular disease. A low level of adiponectin also seems to be linked with the metabolic syndrome (reviewed by Lara-Castro et al [15]). Interestingly, women have been reported to display higher concentrations of both adiponectin and resistin than men [6,16,17]. It has been speculated that female sex hormones could affect both adiponectin and resistin production.

There is some evidence that menopause may alter the adiponectin and resistin concentrations, although there is no consensus on this matter. Chu et al [18] reported that obese postmenopausal women with metabolic syndrome have higher plasma concentrations of resistin and lower adiponectin levels than obese and nonobese premenopausal controls. On the contrary, Gavrila et al [19] noted that postmenopausal women have a higher adiponectin concentration than premenopausal women.

The effect of the HRT on adiponectin and resistin has been the object of only a few studies. According to Sumino et al [20], 3 or 6 months of the HRT did not change the plasma concentration of adiponectin, whereas Chu et al [21] reported a significant increase after transdermal estrogen therapy in women with the metabolic syndrome. In the same study, only oral therapy had a significant lowering effect on plasma resistin levels [21]. In an observational study [22], it has been reported that adiponectin concentrations are lower in postmenopausal women using HRT than in those not using HRT.

Adiponectin and resistin have not been studied widely in postmenopausal women, and the effect of estrogen on these hormones is also rather poorly understood. Therefore, we wanted to explore the effect of unopposed ERT delivered by 2 different routes of administration on the plasma concentrations of adiponectin and resistin in hysterectomized postmenopausal women.

2. Study subjects and methods

Hysterectomized postmenopausal women were recruited for the investigation of the effects of peroral and transdermal ERT. Written informed consent was obtained from all subjects. The study was approved by the Ethical Committee of the University of Oulu and was compatible with the Declaration of Helsinki. The study took place in 1993-1994. Its design and the subjects have been described in detail previously [23,24]. Briefly, 79 postmenopausal women were randomly chosen to receive either estradiol valerate 2 mg/d (Orion Pharma, Espoo, Finland) orally with placebo gel (PE group) or estradiol gel 1 g/d containing 1 mg 17β-estradiol (Divigel, Orion Pharma) transdermally with placebo tablets (TE group) for 6 months. The criteria for inclusion were as follows: age of 45 to 65 years, previous hysterectomy with at least 1 remaining ovary, postmenopausal status confirmed by serum follicle-stimulating hormone (FSH) greater than 30 IU/L, body mass index (BMI) less than 30 kg/m^2, and fasting blood glucose less than 6.7 mmol/L. Heavy smokers (>20 cigarettes per day) and subjects with endocrine disease or uncontrolled blood pressure (systolic blood pressure >160 mm Hg or diastolic blood pressure >95 mm Hg) were excluded. For subjects who had used HRT, a washout period of at least 2 months was required before enrolment into the study. Plasma and serum samples were obtained in the morning after an overnight fast at baseline and after 6 months of therapy. Plasma samples were stored at −20°C after collection, and 73 samples were available for the adiponectin and resistin measurements.

2.1. Measurements of adiponectin and resistin

Plasma adiponectin and resistin concentrations were measured in duplicate according to the manufacturer's instructions using commercially available enzyme-linked immunoassay kits (Linco Research, St. Charles, MO). The samples obtained from 1 subject at baseline and after therapy were measured in the same assay. In the adiponectin and resistin measurements, the interassay variations were 12.5% and 3.6%, respectively.

2.2. Other measurements

Estradiol, estrone, and free testosterone were measured from serum with the routine radioimmunoassays used in Oulu University Hospital. In addition, FSH, luteinizing hormone (LH), and sex hormone-binding globulin (SHBG) were measured from serum, whereas total insulin-like growth factor 1 (IGF-1) and IGF binding protein 1 were measured from plasma. Standard 75-g oral glucose tolerance test was performed; and fasting and postchallenge blood glucose and serum insulin were determined at 30, 60, and 120 minutes. The measurements described above and the calculations for insulin sensitivity index have been described previously in detail [23]. In addition, total cholesterol, HDL, LDL, very low-density lipoprotein (VLDL) cholesterol, total triglycerides, VLDL triglycerides, and apolipoproteins (apo B and A-1) were measured from plasma; and the clearance rate (fractional catabolic rate) and production rate of LDL apo B were determined as described previously [24].

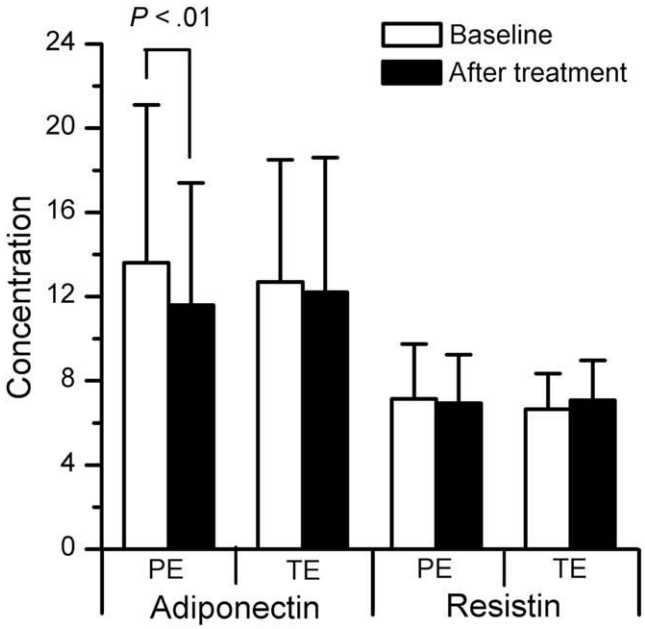

Fig. 1. Adiponectin (in milligrams per liter) and resistin (in nanograms per milliliter) concentrations (mean ± SD) before and after PE or TE ERT.

2.3. Statistical analysis

Data analyses were done with the SPSS 14.0 software package (SPSS 2005, Chicago, IL). Distribution of smokers and previous HRT users in the treatment groups was compared with χ^2 test. To compare the values before and after 6 months of therapy, paired-sample t test or Wilcoxon signed rank test was performed based on the normality of the distribution. Differences between the therapies were analyzed with independent-sample t test. Correlations were tested either with Pearson correlation coefficient in the case of normally distributed variables or Spearman rank correlation when the criteria for normal distribution were not met. Linear regression analysis was performed to study the determinants of the adiponectin change in the PE group. A logarithm transformation was applied when necessary to normalize the distribution. A P value of .05 was used as the limit of statistical significance. Results are presented as mean ± standard deviation (SD).

3. Results

3.1. The effects of ERTs

The 2 treatment groups were similar in their baseline adiponectin and resistin concentrations as well as in BMI. In addition, the number of smokers and previous HRT users did not differ between the treatment groups.

The effects of the ERT therapies to plasma adiponectin and resistin concentrations are illustrated in Fig. 1. In the PE group, the plasma adiponectin concentration decreased

Table 1
The mean values of clinical variables before and after 6 months of ERT

	PE group (n = 35)		TE group (n = 38)	
	Baseline	After therapy	Baseline	After therapy
BMI (kg/m^2)	26.4 ± 2.8	26.4 ± 2.6	25.9 ± 2.28	26.1 ± 2.5
WH ratio	0.81 ± 0.06	0.81 ± 0.05	0.8 ± 0.05	0.80 ± 0.05
Estrone (pmol/L)	176.1 ± 91.9	2176 ± 1156***	224.5 ± 139	418.2 ± 196***
Estradiol (pmol/L)	0.09 ± 0.13	0.35 ± 0.21***	0.11 ± 0.18	0.26 ± 0.16***
FSH (IU/mL)	68.2 ± 24.3	35.0 ± 19.6***	61.3 ± 19.6	37.1 ± 17.4***
LH (IU/L)	35.0 ± 12.9	22.6 ± 10.7***	30.5 ± 10.5	19.5 ± 9.12***
SHBG (nmol/L)	47.5 ± 24.3	96.0 ± 50.7***	45.4 ± 15.9	51.6 ± 25.1*
Free testosterone (pmol/L)	3.50 ± 1.7	2.33 ± 0.8***	3.42 ± 1.5	2.83 ± 1.2
Total cholesterol (mmol/L)	6.36 ± 0.94	5.82 ± 0.80***	6.31 ± 0.92	5.9 ± 0.86***
LDL cholesterol (mmol/L)	4.19 ± 0.83	3.40 ± 0.78***	4.11 ± 0.86	3.72 ± 0.78***
HDL cholesterol (mmol/L)	1.60 ± 0.35	1.80 ± 0.36***	1.58 ± 0.38	1.59 ± 0.34
VLDL cholesterol (mmol/L)	0.38 ± 0.26	0.37 ± 0.21	0.46 ± 0.28	0.38 ± 0.25*
Total triglycerides (mmol/L)	1.26 ± 0.51	1.4 ± 0.52***	1.38 ± 0.59	1.37 ± 0.6
Triglycerides in VLDL (mmol/L)	0.55 ± 0.3	0.59 ± 0.34	0.62 ± 0.38	0.58 ± 0.38*
Apo B (g/L)	1.10 ± 0.29	0.97 ± 0.23***	1.11 ± 0.31	1.07 ± 0.30
FCR of LDL apo B (pools/d)	0.29 ± 0.04	0.35 ± 0.04***	0.31 ± 0.05	0.31 ± 0.04
LDL apo B production (mg/[kg d])	12.37 ± 3.1	13.26 ± 2.7*	12.8 ± 2.23	12.75 ± 2.39
Apo A-1	1.97 ± 0.35	2.0 ± 0.46	1.92 ± 0.41	1.82 ± 0.34
Fasting glucose (mmol/L)	4.4 ± 0.45	4.35 ± 0.53	4.48 ± 0.44	4.42 ± 0.53
Fasting insulin (mU/L)	10.4 ± 4.1	10.5 ± 5.5	9.85 ± 5.5	9.68 ± 5.6
Total IGF-I (nmol/L)	6.56 ± 2.8	5.73 ± 2.2*	6.20 ± 2.0	6.36 ± 1.7
IGFBP-I (nmol/L)	4.52 ± 4.3	9.22 ± 7.8***	5.69 ± 3.6	6.94 ± 4.2

Data presented are means ± SD. Effects of treatment were tested with paired-sample t test or with nonparametric Wilcoxon signed rank test. FCR indicates fractional catabolic rate; IGFBP-I, IGF binding protein 1.

* $P < .05$.

*** $P \leq .001$.

significantly from a mean value of 13.6 ± 7.5 to 11.6 ± 5.8 mg/L ($P < .01$). The mean change in the PE group was −1.95 ± 6.8 mg/L. In the TE group, the change from 12.7 ± 5.8 to 12.2 ± 6.4 mg/L did not reach statistical significance (mean change, −0.48 ± 5.4 mg/L). Changes in plasma resistin concentrations from 7.15 ± 2.6 to 6.94 ± 2.3 ng/mL in the PE and from 6.65 ± 1.7 to 7.07 ± 1.9 ng/mL in the TE group were not significant. The effects of the ERT therapies on the other clinical variables have been presented in previous studies [23,24]; but for clarity, some of the changes are listed in Table 1.

3.2. Baseline correlations

Plasma adiponectin or resistin concentrations were not related to the serum estradiol or estrone concentrations during the baseline or after the ERTs. The various correlations of adiponectin at the baseline are presented in Table 2. At the baseline, the plasma resistin concentration correlated significantly only with SHBG ($r = 0.248$, $P < .05$), HDL cholesterol ($r = -0.282$, $P < .05$), and apo A-1 ($r = -0.264$, $P < .05$).

3.3. What explains the change in plasma adiponectin occurring after PE therapy?

Because ERT significantly changed the concentration of adiponectin only in the PE group, we tested correlations between changes in this group. There was a significant correlation between the change in adiponectin levels and the change in waist-hip (WH) ratio ($r = -0.386$, $P = .029$), although the baseline and posttherapy measurements did not correlate significantly. Plasma adiponectin level correlated significantly with several lipids (Table 2) at baseline, but the change in the adiponectin concentration correlated only with the change in VLDL triglycerides ($r = -0.454$, $P = .009$). A similar correlation trend was observed also with changes in triglycerides and VLDL cholesterol. The change in adiponectin correlated also with the change in IGF-1 ($r = -0.39$, $P = .025$). These

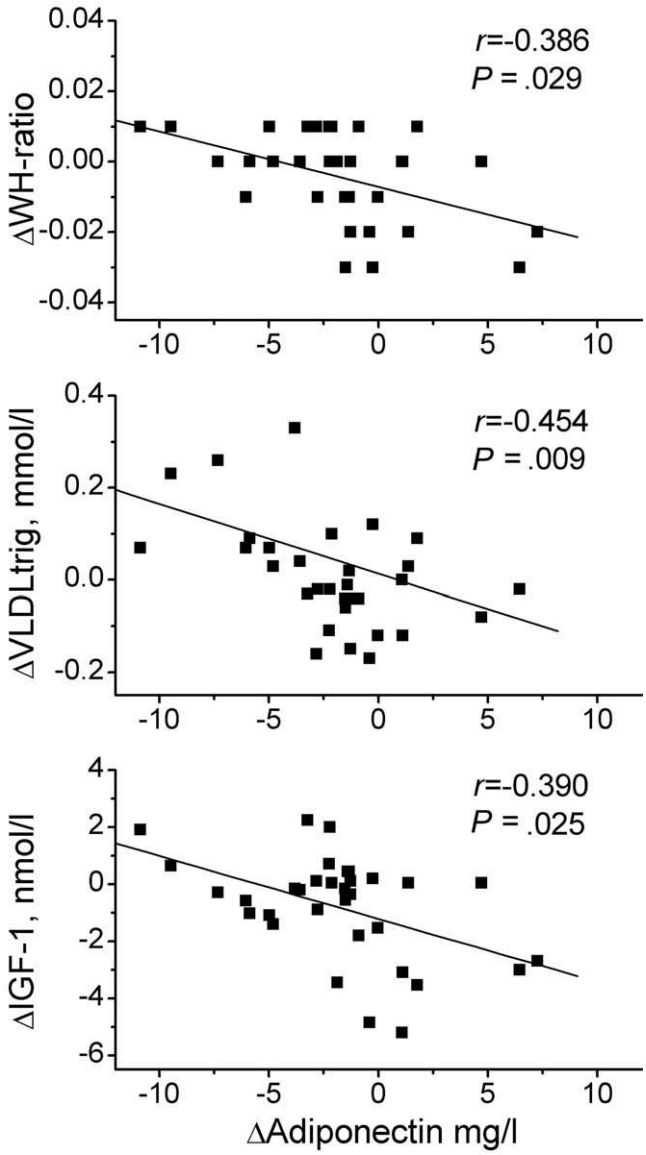

Fig. 2. Correlations between the change (Δ) in adiponectin and the changes in WH ratio, triglycerides in VLDL (VLDLtrig), and IGF-1 in the peroral treatment group.

Table 2
Correlation coefficients for associations with the plasma adiponectin concentration at the baseline

Variable	r
BMI	−0.259*
WH ratio	−0.185
Estradiol	0.025
LH	0.243*
Free testosterone	−0.022
HDL cholesterol	0.283*
LDL cholesterol	−0.120
VLDL cholesterol	−0.351**
Mean triglycerides	−0.385***
VLDL triglycerides	−0.404 ***
Fasting glucose	−0.136
Fasting insulin	−0.210
Insulin sensitivity index	0.286*
IGF-1	−0.043

* $P < .05$.
** $P < .01$.
*** $P \leq .001$.

Table 3
Linear regression model explaining the change in the plasma adiponectin level in the PE treatment group

Change in the independent variable	Standardized β	95% Confidence interval for B	Significance
WH ratio	−.288	−180 to 4.41	.061
Estradiol	.202	−1.35 to 6.83	.179
Triglycerides in VLDL	−.407	−24.9 to (−3.6)	.011
IGF-1	.211	−1.1 to 0.19	.169
Model R^2 (adjusted) = 0.431			.001

parameters correlating significantly with the change in plasma adiponectin are presented in Fig. 2.

The variables correlating with the change in adiponectin and also the change in estradiol were included into a linear regression model (Table 3). The regression model was able to explain 43.1% (adjusted R^2 = 0.431, P = .001) of the variation in the change of adiponectin concentration in the PE group. With respect to the variables in the model, only the change in VLDL triglycerides explained significantly the variation in the change in adiponectin.

4. Discussion

In the present study, the effects of both the PE and the TE ERT on plasma adiponectin and resistin concentrations were studied in postmenopausal hysterectomized women. After a treatment period of 6 months, only the plasma adiponectin concentration was changed in the PE group. Only a few studies have addressed this topic earlier [21,25], although elevated plasma adiponectin [6] and resistin concentrations have been reported in women [16,17]. This sexual dimorphism has been suggested to be attributable to female sex hormones [16,26].

In the present study, the PE treatment decreased adiponectin concentration significantly, whereas TE had no effect. Our results are contradictory to the findings of Chu and coworkers [21]. They reported no change in plasma adiponectin after PE but a significant increase after TE. Chu et al [21] used smaller doses of estrogen over a shorter period (3 months) with both treatments, which could explain the difference in the results. The increase in adiponectin after TE reported by Chu et al could be attributable to the slight decrease detected in BMI (32.1 vs 30.8 kg/m^2), this also being speculated by the authors [21]. In the present study, neither treatment affected the BMI (Table 1). In other studies, PE treatment has been combined with progesterone, resulting in either no change [20,27] or decrease [28] in plasma adiponectin concentrations; but the use of progesterone prevents a reliable comparison with our results.

In our study, no correlations were seen between estradiol, estrone, and adiponectin. In other studies, an insignificant [25,29,30] or negative association [16,19,20,22] between adiponectin and estrogen has been reported. The regression analysis revealed that the change in VLDL triglycerides but not in estradiol was the strongest variable explaining the variation in the change in adiponectin after PE treatment. Based on these results, it can be speculated that the change in adiponectin levels seen after the PE treatment is not attributable to the increased estrogen but rather to the change in lipids. This could also explain the difference between the PE and TE treatments because PE has also unfavorable effects on the lipid profile (reviewed by Modena et al [4]). On the other hand, adiponectin has been reported to associate with VLDL, intermediate-density lipoprotein, and LDL catabolism [31-33] and to regulate activity of lipoprotein lipase and hepatic lipase, which are responsible for the catabolism of triglyceride-rich lipoproteins (reviewed by Lara-Castro et al [15]). However, the exact mechanism of the decrease in adiponectin after PE remains unknown.

In this study, we reported that adiponectin was correlated with several lipoprotein values before the ERTs and that the change in adiponectin after the PE was explained by VLDL triglycerides. The association between adiponectin and lipids is supported by the interesting component study of metabolic syndrome in which adiponectin was connected to the lipid cluster and not to the body fat cluster [34]. The association of adiponectin to positive lipid profile may partly explain its atheroprotective effects (reviewed by Han et al [6]). The reduction seen in plasma adiponectin levels after the PE treatment may be 1 contributor to the increased risk of CHD observed in the first years of peroral treatment in the Woman's Health Initiative randomized controlled trial [2].

The change in adiponectin evoked by the PE correlated also with the changes in WH ratio and IGF-1. The association with the change in WH ratio is somewhat unexpected because BMI or WH ratio did not change significantly after the PE. It is possible that even a minor, nonsignificant change in WH ratio is sufficient to affect the plasma adiponectin concentration. The negative correlation between changes in adiponectin and IGF-1 is supported by studies in rodents and 3T3-L1 adipocytes in which treatment with IGF-1 has been reported to decrease adiponectin concentrations [35,36]. The association between the changes in adiponectin and IGF-1 was not due to insulin because neither of these variables was related to changes in glucose metabolism. It is unlikely that the changes in IGF-1 and WH ratio are important modulators of plasma adiponectin during the PE because they did not remain as significant explanatory factors of the change in adiponectin levels when the change in VLDL triglycerides was taken into account.

One possible limitation of the present study was that we measured only the total adiponectin concentration. Adiponectin circulates in 3 different oligomeric forms as has been reviewed recently by Wang et al [37]. It has been demonstrated that the lower plasma concentration of adiponectin in men could be due to a smaller amount of the high–molecular weight form of adiponectin. Secretion of high–molecular weight adiponectin has been reported to decline in response to testosterone (reviewed by Wang et al [37]). However, the effect of estrogen on the relative amounts of the different forms of adiponectin has not been evaluated. New studies are required to assess the possibly differential effects of PE and TE on the different forms of adiponectin.

Resistin, which was also measured in the present study, is considered to be involved in inflammatory processes (reviewed by Pang and Le [38]). Other inflammatory factors, such as C-reactive protein, cell adhesion molecules, monocyte chemoattractant protein 1, and tumor necrosis factor α,

have been reported to be influenced by different HRTs (reviewed by Koh and Sakuma [39]). In a cross-sectional study, postmenopausal women have been reported to have higher resistin concentrations compared with premenopausal women [18]. Chu et al [21] have previously studied the effects of ERT on plasma resistin levels. They reported that oral estradiol increased the resistin concentration after 3 months of therapy, whereas transdermal therapy had no effect [21]. However, in the present study, neither treatment affected significantly the plasma resistin concentrations, although the estrogen doses administered here were higher than those in the study of Chu and coworkers. In addition, no relationships between resistin and estradiol or estrone were observed. As far as we are aware, the correlations between resistin and estrogen have not been evaluated in postmenopausal women. However, in adult women with polycystic ovary syndrome, serum levels of resistin and estradiol did not correlate significantly [40,41]. The sexual dimorphism in plasma resistin concentrations is probably caused by factors other than estrogens.

In conclusion, in the present study, we had an opportunity to examine the effect of unopposed ERT delivered by different routes of administration on the plasma adiponectin and resistin concentrations. Because high adiponectin is usually associated with a positive metabolic profile, the decrease in the plasma adiponectin concentration, especially that detected with the PE treatment, suggests that at least short-term ERT seems to be unfavorable. This change in adiponectin could be part of the "early harm" profile of the PEs detected in clinical trials. The plasma resistin concentration was not significantly changed by either ERT treatment. We also conclude that estrogen does not seem to be an important modulator of the plasma resistin concentration.

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