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Carotid Artery Intima Thickness and Flow Velocity after Discontinuation of Hormone Replacement Therapy in Postmenopausal Women: Follow-up Study

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Aim. To investigate the effect of discontinuation of hormone replacement therapy on the intima thickness and blood flow velocity of the common carotid artery.

Methods. The thickness of the left common carotid artery intima and maximal systolic blood velocity were measured by real-time and Doppler ultrasonography in 75 healthy postmenopausal women starting sequential combined hormone replacement therapy. The measurements were performed at the start and after 6 and 12 months of the therapy. Thirty two women decided to discontinue the therapy after 6 months, whereas 43 continued.

Results. In the group that continued with the hormone replacement therapy, a significant decrease was recorded in the mean baseline values for carotid artery intima thickness and flow velocity at 6 months (0.35±0.11 vs 0.54±0.19 mm and 0.73±0.16 vs 0.87±0.19 m/s, respectively, p 0.001) and 12 months of follow-up (0.36±0.1 mm and 0.72±0.15 m/s vs baseline, respectively, p 0.001). In women who discontinued the therapy, there were significant deviations from the baseline values in the intima thickness (0.36±0.11 vs. 0.59±0.09 mm, p=0.010) and flow velocity (0.75±0.14 vs. 0.85±0.16 m/s, p 0.001) at 6 but not at 12 months of the follow-up (0.55±0.12 mm, and 0.85±0.17 m/s vs baseline; p=0.148 and p=0.965, respectively).

Conclusion. Decreased flow velocity and reduced intima thickness were directly related to blood vessel wall dilatation after estrogen component of hormone replacement therapy. Discontinuation of the hormone replacement therapy returned the flow velocity and intima thickness to their baseline values.

Key words: *blood flow velocity; carotid artery, common; hormone replacement therapy; postmenopause; tunica intima; ultrasonography, Doppler*

Initiation, duration, benefits, and risks of the postmenopausal hormone replacement therapy remain controversial issue (1). Although epidemiological data indicate a general decrease in the risk for cardiovascular disease in women using hormone replacement therapy, some studies showed that today estrogen users enjoy greater protection against heart disease than before (2-4). Vessel tortuosity, its narrowing, or wall stiffening, usually caused by atherosclerosis (5), can restrict blood flow. The hormone replacement therapy, on the other hand, increases blood flow to all organs (6). Furthermore, cardiovascular protection provided by hormone replacement therapy is achieved directly and through estrogen-mediated mechanisms involved in the development of atherosclerosis (7-10). Beside these favorable actions, studies on non-atherosclerotic subjects have shown that hormone replacement therapy improves some Doppler-derived parameters in the uterine (11) and internal carotid and middle cerebral (12) arteries. These effects of estrogen on the reactivity of arterial vessels may disappear rapidly after estrogen discontinuation (13). All this makes hormonal replacement therapy important in the cardiovascular protection.

The aim of this study was to determine whether changes in the blood flow velocity and intima thickness of the common carotid artery could be observed after the discontinuation of postmenopausal hormone replacement therapy.

Subjects and Methods

Subjects

A total of 100 Caucasian postmenopausal women from our gynecology outpatient service were asked to participate in a prospective

Table 1. Education in postmenopausal women grouped according to the compliance to hormone replacement therapy (HRT)

Level of education	Hormone replacement therapy (No. of women)		
	continued	p[a]	ceased
Two-year college or university	29	0.05	13
Secondary or lower	14		19
Total	43		32

[a]Chi-square=4.32.

study, which lasted from April 1998 to December 1999. The inclusion criterion was no hormone replacement therapy before the study. All women gave informed consent prior to the beginning of the study, and the Hospitals Ethics Committee approved the study protocol. The postmenopausal status was defined as at least one-year period since the last menstruation to the time of the study, and follicle stimulating hormone (FSH) and estradiol serum levels in the postmenopausal range (30 IU/L, 200 pmol/L, respectively).

Conditions known to affect the cardiovascular system were taken as exclusion criteria, such as diabetes mellitus, hypertension, hyperlipidemia, obesity, and smoking (14). Women with any gynecological disease, as well as those using medication with known cardiovascular and hormonal effects, were also ruled out. Upon the inclusion in the study, all women received sequential combined oral hormone therapy – 2 mg estradiol, and 1 mg noretisteron-acetate (*Trisequens*, Novo Nordisk, Bagsvaerd, Denmark) per day.

The final sample comprised 75 women: 43 who took hormone replacement therapy continuously for 12 months and 32 who decided on their own to discontinue the therapy after 6 months. Twenty five women who discontinued hormone replacement therapy either before or after a 6-month therapy period were excluded from the study. All women examined were of similar age and geographic area of residence, but differed in their educational level.

Measurements

The intima thickness of the left common carotid artery and its maximal systolic blood velocity were measured three times: before starting sequential combined hormone replacement therapy, and after 6 and 12 months of therapy. The measurements were performed with an ACUSON 128XP/10 device (Mountain View, CA, USA), using a 7 MHz for imaging and a 5 MHz for velocity measurements. Imaging scanner sensitivity was kept as low as feasible to optimize the accuracy of thickness measurements. During the measurements, the women were in supine position, with the head turned slightly contralaterally. The probe was angled at 45 degrees to the carotid wall. Angle-corrected velocity measurements were obtained from the distal part of the common carotid artery, just before the bifurcation. Maximal systolic velocity was defined as the highest velocity (m/s) recorded during an examination. The thickness of the intimal layer (mm) was measured with a standard procedure (15).

Blinding and Observer Variability

The ultrasound investigator was unaware of the therapy status of the patients. The coefficients of variation of the maximum systolic velocity and the intima thickness of the left common carotid artery were 2% and 3%, respectively. They were calculated from 10 ultrasound measurements done by the same observer in 2 women randomly selected from the study group. Ultrasound measurements were carried out within 2 days (5 measurements a day per each woman) with a 5-minutes interval in between.

Statistical Analysis

The data were analyzed by SAS/PC, version 6.12 (SAS Institute, Cary, NC, USA). The differences between 3 measurements of velocity and intima thickness in each group of women were tested by one-way analysis of variance (ANOVA). The criteria for ANOVA have been met. When ANOVA was significant, Tukey's test was performed and types I error level was set at 5% to isolate the differences between the groups.

Table 2. Maximal systolic velocity (m/s) in the left common carotid artery in relation to the compliance to hormone replacement therapy (HRT)

Group	Velocity (mean SD)		
	baseline	6 months	12 months
Continued HRT	0.87 0.19	0.73 0.16Ş	0.72 0.15Ş
Ceased HRT	0.85 0.16	0.75 0.14Ş	0.85 0.17

Şp 0.05 in comparison to baseline values (ANOVA, Tukey post hoc test).

Table 3. Intima thickness (mm) of the left common carotid artery in relation to the compliance to hormone replacement therapy (HRT)

Group	Intima thickness (mean SD)		
	baseline	6 months	12 months
Continued HRT	0.54 0.15	0.35 0.11Ş	0.36 0.10Ş
Ceased HRT	0.59 0.09	0.36 0.11Ş	0.55 0.12

Şp 0.05 in comparison to baseline values (ANOVA, Tukey post hoc test).

Results

The age of the women who continued with hormone replacement therapy was 52±3 years (mean±SD), and 53±3 years for those who ceased the therapy (p 0.05). The two groups differed only in the degree of their education. More women with higher education continued with the hormone replacement therapy (chi-square=4.32, p 0.05) (Table 1).

The difference between the baseline and 6- and 12-month measurements was statistically significant for the mean maximal systolic velocity in women who continued with the hormone replacement therapy (Table 2). In women who ceased the therapy after 6 months, significant difference was observed only at 6- (p 0.001), but not at 12-month (p=0.965) examination (Table 2). The same trend was observed for the intima thickness of the common carotid artery (Table 3). In the group of women who continued with the hormone replacement therapy, the mean thickness decreased significantly after 6 and 12 months of therapy compared to baseline values. However, in the group of women who discontinued the therapy, a significant decrease was noted between the baseline and 6-month (p 0.001) but not 12-month values (p=0.148).

Discussion

Relevant epidemiological data show that the mortality from cardiovascular diseases is significantly reduced only in current estrogen users (4). Our results clearly demonstrated that the discontinuation of hormone replacement therapy reversed the therapy-induced changes in the carotid circulation. The reduction in the velocity that we observed did not have to reflect for certain an improvement in the carotid blood flow during the therapy. However, the decrease in the intima thickness indicated the cardioprotective effect of estrogen (16).

To the best of our knowledge, there are no published studies investigating the internal layer thickness after the discontinuation of the replacement therapy. Although the intima-media thickness of the carotid artery has been ac-

cepted as an index of subclinical atherosclerosis (17), it is usually measured when the influence of menopause and hormone replacement therapy on preclinical atherosclerosis is assessed (18). We measured the intima layer because we hypothesized that the main changes were happening in the intimal area, as indicated by other studies (16).

Wagner et al (19) found a 70% reduction in LDL uptake after hormone replacement therapy in monkeys, suggesting that estrogen may reduce atherosclerosis. In some other animal and human studies (20,21), estrogen replacement led to a successful regression of plaques, contributing to the secondary prevention of cardiovascular disease. There are however, some opposite results, which question the link between the carotid intima-media thickness and the replacement therapy (22,23). Our results differ from previous findings perhaps because we measured the intima thickness at the upper margin of the thyroid cartilage. This area closely corresponds to the carotid bifurcation, where one would expect the effects of estrogen to be more profound than in other sites (24). Although other research (25) demonstrated no response to estrogen-induced vasodilatation in large peripheral arteries, we supposed that the observed hemodynamic changes directly caused the dilatation of the wall of the common carotid artery. Furthermore, it has been found that women on hormone replacement therapy are better educated and more health conscious (26). Due to their different lifestyles, health consciousness in our hormone replacement therapy group could have had a greater influence on the outcome than the therapy discontinuation. According to the anamnestic data at the beginning of this study, the women who continued the therapy were educated more than those who discontinued the hormone replacement therapy, indicating that a similar explanation may be valid for our study.

In conclusion, changes in blood flow velocity and intima thickness as a result of directly caused blood vessel network vasodilatation, with increasing the vessel lumen and thinning the blood vessel wall, is in agreement with the short-term beneficiary estrogen effects (23,27). The factors that caused women to stop or continue with the hormone replacement therapy also have to be included in the analysis of the observed differences in vascular hemodynamics. To estimate the real benefit of the hormone therapy in protecting women from cardiovascular disease, it would be important for future randomized clinical trials to focus on factors such as education, lifestyle, compliance, and diet.

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