Vascular Impedance of Uterine, Inferior Vesicle, and Ophthalmic Arteries in Postmenopausal Women Receiving Hormonal Replacement Therapy: Comparative Doppler Study

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Aim. To investigate the effects of combined hormone replacement therapy (HRT) on the vascular impedance of the uterine, inferior vesicle, and ophthalmic artery.

Methods. Thirty-five postmenopausal patients were divided in two groups: 21 patients with 1-5 years of menopause and 14 patients with 6 years of menopause. Each group was examined in basal condition and after 1, 3, and 6 months of HRT. The blood flow impedances of the uterine, inferior vesicle, and ophthalmic arteries were analyzed by color Doppler. Estradiol plasma concentrations were assayed on the day of Doppler examination.

Results. The analysis of uterine and inferior vesicle artery flow velocities showed a significant positive correlation between the resistance index (RI) and years of menopause. Higher impedance values were found in patients with longer interval from last menstrual bleeding (p<0.05). In patients with ≥6 years of menopause, the impedances of uterine and inferior vesicle arteries were 0.94±0.03 and 0.91±0.04, respectively, whereas in patients with 1-5 years of menopause the impedances were 0.89±0.04 and 0.98±0.02, respectively. We noticed no significant correlation between baseline RI and duration of menopause at the level of ophthalmic artery in either group (0.72 vs. 0.73, respectively; p<0.05). After six months of HRT, plasma estradiol concentrations inversely correlated with RI of uterine (r=0.2556; p=0.021), inferior vesicle (r=0.2653; p=0.023) and ophthalmic (r=-0.2211; p=0.017) arteries.

Conclusion. Doppler studies of uterine, inferior vesicle, and ophthalmic arteries can provide specific and precise pathophysiological information to assess blood flow variations in correlation with combined HRT.

Key words: blood flow velocity; Doppler ultrasonography, color; estrogen replacement therapy; hormone replacement therapy, postmenopausal; ophthalmic artery; uterus, blood supply; postmenopause

Estrogen loss in menopause induces vasomotor symptoms and genital atrophy in postmenopausal women (1). Lower urinary tract symptoms are also widely considered to accompany menopause. Since steroid receptors have been located in the structures involved in micturition (2), it is assumed that these urinary symptoms depend on concentrations of sex hormones. Specifically, estrogen and progesterone receptors have been detected in the female pelvic floor muscles, urogenital ligaments, bladder, trigone, and urethra (3).

Furthermore, a long-term postmenopausal estrogen deprivation was proved to be a risk factor for cardiovascular and/or cerebrovascular disease (4). Observational clinical studies have repeatedly shown favorable associations between hormonal replacement therapy (HRT) and menopausal symptoms. Two meta-analyses indicated a 50% reduction in vascular disease risk in postmenopausal women on hormonal replacement therapy (4,5). There are several mechanisms whereby hormonal replacement therapy can affect the vascular system and all of them have both the metabolic and direct effects on arteries. The aim of this study was to investigate direct influence of hormonal replacement therapy on the vascular system. Uterine artery and inferior vesicle artery were used to assess the changes in urogenital system, whereas ophthalmic artery was a representative of cerebral circulation.
Subjects and Methods

Subjects

Between January 1999 and January 2000, 35 women of postmenopausal age attending Gynecological Endocrinological Clinic voluntarily participated in our study. The ultrasonographer performing the examination selected all the participants at random.

All women were in good health without any history of gynecological problems (uterine or adnexal masses), hyper-tension, diabetes, thyroid or renal disease, cerebro- and/or cardiovascular disease, glaucoma, or eye surgery. Non had previously taken any hormonal replacement therapy and all had had their last menstural bleeding at least 12 months before entering our study (median duration of menopause was 35 months, range 12-144). Their age ranged from 47-59 year (mean 53.4), and serum FSH concentrations were at least 30 IU/L (mean 47±16 IU/L).

The mean body mass index of the participants was 25.1±3.7 (kg/m²), the systolic blood pressure was 119±13 mmHg, and diastolic 77±10 mmHg.

The Hospital Ethics Review Committee approved the study protocol, and all the patients gave informed consent.

After a baseline check-up, including transvaginal ultrasound and color Doppler scan, patients were divided into two groups according to the duration of menopause, and were administered hormonal replacement therapy orally. Twenty-one patients, whose last menstrual bleeding was 1-5 years ago, were prescribed Trisequens (Novo Nordisk, Bagsvaerd, Denmark), whereas 14 patients in menopause longer than 6 years were prescribed Kliogest (Novo Nordisk). Trisequens is administered orally and contains human estrogens (2 mg E2, 1 mg estril) combined with only 10 days of progesterone (1 mg norethisterone acetate) per month. Kliogest is an estrogen-progesterone combination (2 mg E2, 1 mg norethisterone acetate).

The patients were studied in basal condition and after 1, 3, and 6 months of hormonal replacement therapy.

Color Doppler Analysis

All patients underwent transvaginal ultrasound examination of the pelvic organs. Doppler flow measurements of the uterine and inferior vesicle artery were performed.

We used Aloka Color Doppler SSD 2000 (Aloka, Tokyo, Japan) with a 5-MHz transvaginal probe for imaging and 6 MHz pulsed Doppler system for color visualization of blood flow. Pulsed repetition frequencies ranged from 2 to 42 kHz. The spatial peak temporal average range intensity was approximately 60 mW/cm². Wall filters (50 Hz) were used to eliminate low frequency signals of noise. After voiding, the patient assumed the lithotomy position and the probe was inserted into the posterior fornix of the vagina. Morphology of the adenexa was explored by B-mode sonography. The color signal from the main uterine arteries could be seen laterally to the cervix in a longitudinal plane. Inferior vesicle artery was studied when the residual bladder volume was under 30 mL. After visualizing the urethra and bladder neck in the midline, the probe was directed laterally and rotated for 15 until the base of bladder appeared. The vessel running from the pelvis side along the bladder base towards the bladder neck was the inferior vesical artery.

To analyze the ophthalmic artery, linear transducer (7.5 MHz) was placed on the closed eyelids of a patient after applying coupling gel. The patient was instructed to turn the eyes to the contralateral side due to the refractivity of the eye lenses. The probe was applied without pressure in the anterior-posterior direction. The ophthalmic artery was identified as larger-caliber pulsatile vessel typically adjacent to the optic nerve (superiorly and medially). When we received good signals, we recorded the resistance indices by placing the sample volume across the vessel and entering the pulsed mode.

To ensure standardized conditions, all patients rested for at least 15 minutes before scanning, and to avoid circadian variations in artery blood flow, all patients were examined between 8:00 and 11:00 a.m. A recording was regarded satisfactory when there were at least five consecutive waveforms, each showing a maximum Doppler shift. Resistance index, RI [peak systolic velocities – peak diastolic velocities/peak systolic velocities], was calculated from three consecutive uniform heartbeats. Since no significant differences between Doppler parameters of the left and right side were observed, we used the average value of both arteries. The reproducibility of Doppler measurements was tested in 10 patients, whose resistance index was measured three times at 10 minutes intervals by the same operator and analyzed by the analysis of variance. The coefficient of variation was 6.5% and the average duration of the procedure was 30 minutes.

Hormone Assay

Peripheral blood was obtained from the patients between 8:00 and 11:00 a.m. on the day of imaging and Doppler examinations.

Estradiol concentrations were determined with a microparticle enzyme immunoassay (MEIA) (Abbott Diagnostics, Chicago, IL, USA).

Statistical Analysis

We used Student’s t-test and analysis of variance for the statistical analyses. The relationship between the parameters was assessed with the linear regression method. Probability of 0.05 was considered statistically significant.

Results

We noticed a significant correlation between the baseline resistance index of the uterine arteries and the duration of menopause. Higher impedance values were obtained in patients who were in menopause ≥26 years, than in patients 1-5 years in menopause (0.94±0.03 vs. 0.89±0.04; p<0.05). The visualization rate of the uterine arteries in both groups was 100%.

Absent diastolic flow in uterine arteries was found in 3 (15.0%) patients with 1-5 years duration of menopause, and in 5 (35.7%) patients with ≥26 years menopause period. Introduction of hormonal replacement therapy significantly lowered the uterine artery resistance index (p<0.05) in both groups of patients. After the first month treatment, the uterine artery resistance index showed having stable values, and no differences in the effectiveness of hormonal replacement therapy were observed in women who began with hormonal replacement 6 or more years after menopause (p<0.05) (Fig. 1).

Figure 1. Uterine artery blood flow, expressed as resistance index (RI) in postmenopausal patients in basal condition and after 1, 3, and 6 months of hormonal replacement therapy. Triangles, 6 years of postmenopause; bars, 1-5 years of postmenopause. The RI significantly decreased in both groups after the first month of therapy (p<0.05, analysis of variance) and remained stable until the end of the treatment.
Visualization rate of clear Doppler signals of the inferior vesical arteries was 71.4% in postmenopausal patients in whom last menstrual bleeding occurred 1-5 years before the study. In the group of postmenopausal patients, in whom the last menstrual bleeding occurred ≥6 years ago, the visualization rate of inferior vesicle artery was only 50% (p < 0.05). Furthermore, this group of patients showed significantly higher inferior vesical artery resistance then postmenopausal patients in whom menopause occurred before 1-5 years (0.91 ± 0.04 vs. 0.98 ± 0.02; p < 0.05). Higher visualization rates for inferior vesical arteries in both groups were demonstrated after the first month of hormonal replacement therapy. In addition, in both groups blood flow velocity waveforms were characterized with decreased resistance index values after the first month of treatment when compared with the baseline values (p < 0.05), and remained unchanged in the following measurements (Fig. 2).

In the ophthalmic arteries, no significant correlation between baseline resistance index and the duration of menopause was noticed in either group (p < 0.05). Visualization of clear Doppler signals was possible in all 35 patients, showing no interruption of diastolic blood flow in ophthalmic arteries. Furthermore, blood flow in the ophthalmic artery increased during the hormonal replacement therapy, but a significant decrease in resistance index was observed not sooner than after 6 months of therapy (p < 0.001). There were no differences in the effectiveness of hormonal replacement therapy between the two patient groups (p > 0.05).

The estradiol values changed as indicated in Fig 4.

Plasma estradiol concentrations correlated inversely with RI of uterine (r = 0.2556; p = 0.021), inferior vesical (r = 0.2653; p = 0.023), and ophthalmic (r = -0.2211; p = 0.017) arteries.

Discussion

Apart from hormonal replacement therapy-induced changes in the lipids profile, carbohydrate and homocysteine metabolism, and fibrinolysis, much attention has been given to the alterations in arterial tone and blood flow in the context of hormonalreplacement therapy. Arterial vasodilatation is the most typical reaction to acute estrogen administration (5).

Our study showed that increasing age reduces uterine blood flow and blood flow to the bladder neck. Blood flow resistance indices in both uterine and inferior vesical arteries were age- and estrogen-dependent.

Uterine and inferior vesical artery flow velocity analyses revealed significant positive correlations between the resistance and duration of menopause. Furthermore, plasma estrogen concentrations correlated inversely to resistance indices after the onset of hormonal replacement therapy. We showed that uterine and bladder neck environment could be easily manipulated during the menopausal years by a proper hormonal stimulation, since a rapid and profound uterine vascular blood flow response to hormonal replacement therapy was observed. Changes in the Doppler signal pattern of uterine and inferior vesical artery flow, observed in our study as a response to hormonal replacement therapy, indicated a profound decrease in vascular resistance. Knowing the effect of circadian variations in uterine artery blood
flow in postmenopausal women (6), we performed all the measurements between 8:00 and 11:00 a.m.

Findings in our study are in accordance with some other studies (7-9). The possibility to manipulate the uterine environment by hormonal treatment and to assess its effects by color Doppler presents a challenge in the field of infertility because of the increased trend of later reproduction (10). Of course, not all Doppler studies showed the benefit of hormonal replacement therapy on uterine blood flow in postmenopausal women. For example, Žalud et al (11) showed that continuous hormonal replacement therapy significantly influenced the thickness of the postmenopausal endometrium but not the myometrium or the uterine artery blood flow.

The lower urinary tract is known to be estrogen sensitive, but a direct causal influence of aging (menopause) is not easy to demonstrate.

In our study, we showed a significant decrease in the visualization rates of inferior vesical artery with the duration of menopause. After the first month of hormonal replacement therapy, these findings significantly improved. No differences were observed in women who began hormonal replacement therapy several years after the onset of menopause. Therefore, the hormonal replacement therapy effect on lower urinary tract may be considered effective even when started after the beginning of menopause. In spite of its estrogen sensitivity and six months of therapy, the visualization rates of inferior vesical artery did not reach 100%.

In our opinion, severely damaged bladder neck vessels may not be able to respond to hormone replacement therapy in the same way as nor- mal vasculature, which might be important in treating postmenopausal urinary symptoms by hormones. Estrogen replacement therapy, as part of the pharmacological management in treating urinary symptoms, is still a matter of controversy. One of the recent studies (12) showed a significant increase in bladder wall thickness, which correlated positively with circulating plasma estradiol concentrations. Furthermore, significant improvements in subjective urinary symptomatology were observed in 90% of the patients. On the other hand, some other studies (14,15), like the majority of randomized controlled trials on estrogen in treatment of urinary incontinence, have not shown significant improvements in the prevalence of the subjective symptoms (16).

We also analyzed vessel wall function of the ophthalmic artery, a representative of the cerebral circulation. Doppler examination of ophthalmic artery was a technique easy to perform and our data showed that hormonal replacement therapy was effective in ameliorating the cerebral flow in healthy postmenopausal patients. We found no differences between baseline resistance index and the duration of menopause, which showed the ophthalmic artery less estrogen sensitive than uterine or vesical inferior artery. Statistical significance of the estrogen-mediated changes in ophthalmic artery was reached, but later than in inferior vesical and uterine arteries. Another study reported similar findings (17), whereas other authors, who observed the changes in the cerebral microcirculation in the central retinal artery, did not find such changes in the ophthalmic artery of postmenopausal patients on estradiol therapy (18,19). In our opinion, the ophthalmic artery is useful in monitoring hormonal replacement therapy effects on cerebral perfusion, since it is easily accessible brain artery.

In conclusion, transvaginal color Doppler can be used as an easily applicable, non-invasive tool for monitoring the efficacy of hormonal replacement therapy in postmenopausal women by quantification of blood flow through the uterine, vesical inferior, and ophthalmic arteries.

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