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Carotid Artery Distensibility and Hormone Therapy and Menopause: The Los Angeles Atherosclerosis Study (LAAS)

Chrisandra Shufelt, MD, MS^{1,*}, Omeed Elboudwarej, MD^{1,*}, B. Delia Johnson, PhD², Puja Mehta, MD¹, Vera Bittner, MD, MSPH³, Glenn Braunstein, MD¹, Sarah Berga, MD⁴, Frank Stanczyk, PhD⁵, Kathleen Dwyer, PhD⁶, and C. Noel Bairey Merz, MD¹

¹Barbra Streisand Women's Heart Center, Cedars-Sinai Heart Institute, and Department of Medicine, Cedars-Sinai Medical Center, Los Angeles, CA

²University of Pittsburgh, Pittsburgh, PA

³Division of Cardiovascular Disease, University of Alabama at Birmingham, Birmingham, AL

⁴Department of Obstetrics and Gynecology, Wake Forest School of Medicine

⁵Departments of Obstetrics and Gynecology and Preventive Medicine, Keck School of Medicine, University of Southern California, Los Angeles, CA

⁶Department of Preventive Medicine, Institute for Prevention Research, Keck School of Medicine, University of Southern California, Los Angeles, CA

Abstract

Objective—Observational studies suggest that arterial distensibility decreases during menopause; however, the relation to hormone therapy use is controversial. We prospectively studied distensibility and hormone therapy use during different menopause stages.

Methods—161 women between 42–61 years of age without cardiovascular disease had carotid artery measurements by ultrasound to calculate the distensibility index at baseline and 3 years

Address for correspondence: Chrisandra Shufelt, MD, 8631 W. Third Street, Suite 740 East, Los Angeles, California 90048, Phone: (310) 423-9660, Fax: (310) 423-9668, shufeltc@cshs.org.

*Both contributed equally

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later. Menopause stage was classified at each visit as premenopausal, perimenopausal, and postmenopausal. Over 3 years of prospective observation, women were classified as remaining premenopausal, remaining postmenopausal, or transitioning, defined as change from premenopausal-to-perimenopausal, premenopausal-to-postmenopausal, perimenopausal-to-perimenopausal, or perimenopausal-to-postmenopausal.

Results—Distensibility declined over time in all menopause stages ($p<0.0001$). Compared to postmenopausal women, premenopausal and transitioning/no hormone therapy women had over twice the decline in distensibility index ($p=0.06$ and $p=0.016$, respectively), whereas transitioning/hormone therapy did not differ in distensibility decline ($p=0.28$). In a multivariate model, change in systolic blood pressure ($p<0.0001$) and change in pulse pressure ($p=0.004$) were independent predictors of distensibility index change and served as effect modulators. In the adjusted model, women in the premenopausal and transitioning/no hormone therapy groups had a significantly faster distensibility index decline ($p=0.002$ and 0.001 , respectively) than postmenopausal women, while the transitioning/hormone therapy group did not ($p=0.21$).

Conclusions—These findings confirm that menopause transition is associated with reduced vascular compliance. Hormone therapy is associated with better arterial distensibility only during menopause transition. Additional prospective studies are needed to confirm these findings and to determine if hormone therapy use beyond menopause transition is related to distensibility.

Keywords

arterial distensibility; menopause; hormone therapy; estrogen; progesterone

Introduction

Arterial distensibility has emerged as a useful prognostic indicator for cardiovascular disease (CVD) beyond standard risk factors, such as hypertension, hyperlipidemia, and diabetes.¹ Distensibility is a measure of an artery's ability to expand in response to changes in pulse pressure and an inverse measure of arterial stiffness. Loss of distensibility has been associated with the development of CVD, hypertension, and stroke in healthy individuals.²⁻⁴ In addition, markers of arterial distensibility, such as pulse pressure, have helped clarify the results of trials showing different clinical outcomes with differing antihypertensive therapy regimens despite similar reductions in blood pressure.⁵

With aging, CVD risk factors shift unfavorably for women and coincide temporally with a decline in estrogen levels and menopause. Cross-sectional data examining the influence of menopause transition on arterial distensibility have primarily shown an acceleration of age-related increase in stiffness,⁶⁻⁹ however, cross-sectional data cannot test independent relations between distensibility and age versus menopausal hormonal changes.^{10,11} Additionally, the impact of hormone therapy (HT) on arterial distensibility still remains controversial as some observational studies suggest a benefit while others have not found HT to have a substantive impact.¹²⁻¹⁴ Randomized controlled trials measuring distensibility in postmenopausal women on HT have not shown a benefit to date, potentially because of later HT initiation after vascular changes have already occurred.^{15,16}

The present study prospectively examines relations between menopause stage and changes in carotid artery distensibility over a 3-year period. It also examines the relationship of initiation of HT and distensibility. In addition, we sought to determine a relationship between arterial distensibility, hormonal change and CVD risk factors. We hypothesized that arterial distensibility would decline over time with concomitant reduction in estrogen levels, with the greatest decline occurring during menopause transition. Furthermore, we hypothesized that HT through estrogen replacement would be beneficially associated with these changes.

Materials and Methods

Study Population

The Los Angeles Atherosclerosis Study is a community-based cohort study of employees of a major utility company in southern California. All study subjects were recruited from the same company, from 4 different job categories: union, management, administrative, and other. Exclusion criteria were applied only at baseline and included a self-reported history of CVD (angina, myocardial infarction, revascularization, or stroke) and current treatment for cancer. Participants aged 40–60 years were randomly sampled from all employees within strata of sex, age, ethnicity, and smoking status. Hispanics and smokers were oversampled. The participation rate was 85% at study entry for a total cohort of 573 male and female participants, of which 280 were women. The population for the present analysis comprised 161 women aged 45–60 years at study entry who had sufficient information to determine menopausal status and distensibility index at baseline and 3-year follow up. The baseline examination was conducted between 1995 to 1996, and follow-up occurred 3 years later (mean SD: 3.0 ± 0.24 years). At baseline and 3-year visit, the women underwent evaluation of carotid intima-media thickness (cIMT). The study protocol was approved by the institutional review committee at Cedars-Sinai Medical Center and the University of Southern California, and all women provided written informed consent.

Determination of menopause status

We used the menopause status algorithm developed by the Women's Ischemia Syndrome Evaluation study to determine menopause stage at each study visit. This algorithm, which uses a combination of self-reported reproductive history and menstrual cycle pattern and dates with serum reproductive hormone levels, has been published elsewhere.¹⁷ Reproductive hormone levels were assessed by the Los Angeles Atherosclerosis Study reproductive hormone core laboratory using validated steroid and protein assay methods for total estradiol, bioavailable estradiol, estrone, progesterone, FSH, and LH.^{18–20} In addition to using the menopause status algorithm, the Los Angeles Atherosclerosis Study Hormone Committee led by reproductive endocrinologists and scientists (S.L.B., G.D.B., and F.S.) reviewed and adjudicated menopause stage at baseline and at 3 years based on all reproductive and relevant biometric information. Menopause stage at baseline was categorized as premenopausal (Pre), perimenopausal (Peri), and postmenopausal (Post). At the 3-year visit, study participants were categorized as remaining Pre, remaining Post, or transitioning (Tran), defined as a change from Pre-to-Peri, Pre-to-Post, Peri-to-Peri, or Peri-to-Post.

Measurement of risk factors

Study participants completed a nurse-administered questionnaire at each visit to determine demographic variables. A study nurse performed physical examinations and obtained height and weight measurements in light clothing. The seated blood pressure was determined using a standard sphygmomanometer with two separate readings after a minimum 10-minute rest. Serum and plasma samples were obtained after an overnight fast of at least 8 hours. HT use and name of hormone preparation were also attained at baseline and follow-up visit.

Distensibility Index

The distensibility index (DI) was calculated using the following formula²¹:

$$(2/\text{diastolic diameter of common carotid artery [CCA]}) \times ((\text{diastolic systolic diameter of CCA})/\text{pulse pressure})$$

Diastolic and systolic internal diameter of the CCA was measured as part of the cIMT protocol previously published.²² While cIMT was measured at each of the four visits, the systolic and diastolic internal diameters needed to calculate the DI were only measured at baseline and at the 3-year follow-up visit.

Statistical methods

Continuous variables are summarized as means $\pm$ standard deviation (SD) and dichotomous variables are reported as percentages. Highly skewed variables are reported as medians (interquartile range). Change in variables over time () was obtained by subtracting baseline values from those obtained at 3-year follow-up such that a positive value indicates an increase in the variable over time and a negative value a decrease. Differences across menopausal stages (Tables 1-3) were assessed by analysis of variance or non-parametric Kruskal-Wallis test, where appropriate.

All modeling used the generalized linear model (GLM) with menopausal status groups entered as a class variable. Differences in the mean baseline DI and mean change in DI among the menopausal status groups (Figure 1) used the CONTRASTS option. Prior to multivariate modeling, the distributions of all potential predictors were evaluated for deviations from normality and for clinically implausible outliers. Variables highly skewed to the right were log-transformed and those skewed to the left underwent power transformations. The DI was normally distributed and had no major outliers. To derive the final predictive model, all possible clinical and laboratory parameters from Table 1, with the exception of age, were first added, one at a time in separate models, to the menopausal stages in order to assess whether they were independent predictors of DI change and/or whether they affected the relationship in question. Variables with a $p < 0.20$ or whose introduction in the model changed the relationship between menopausal stages and DI change were then entered into forward stepwise regression. This was followed by individually adding other possible covariates until the final model contained only significant covariates. Using the SOLUTION option in PROC GLM, the final model displays the p -value across all menopausal groups as well as the parameters of each menopause stage compared to the reference group in addition to the independent covariates. Only 3 potential

predictors had missing values (glucose, LDLc, and FSH), none of which entered the models. All tests were 2-sided and $p = 0.05$ was considered statistically significant. All analyses were performed with SAS software version 9.3 (SAS Institute).

Results

The women's mean age was 51.5 ± 4.6 , 85 (53%) were white and 45 (28%) Hispanic. The majority (90%) were working in management or administrative positions, and there was no statistical difference between job position within each menopause group ($p=0.38$). The mean DI was 50.7 ± 18.5 at baseline and 38.9 ± 12.8 at 3 year follow-up. Among the 161 women, 17 (11%) were Pre for the duration of the study and not using HT, including birth control pills. There were 52 women who were Tran (32%), of whom 29 (56%) were on HT (14 estrogen only, 1 progesterone only, 10 estrogen/progesterone, and 4 with unknown HT formulation). The remaining 92 women were Post (57%) with 69 (75%) of them on HT (38 estrogen only, 26 dual estrogen/progesterone, and 5 with unknown HT formulation).

The baseline characteristics for the study participants are shown in Table 1. As expected, there was a statistically significant difference in FSH as well as age between Pre, Tran, and Post ($p<0.0001$). Additionally, use of anti-hypertensive medications and serum triglyceride levels were different with both anti-hypertensive use and triglycerides higher in the Tran/HT group ($p=0.047$ and $p=0.037$, respectively). There were no significant differences among the remaining variables across the menopause stages.

The baseline hemodynamic variables across the menopause stages are shown in Table 2. The mean baseline systolic blood pressure (SBP) was significantly different and lowest in Tran/No HT women ($p=0.024$). Similarly, pulse pressure varied among all the groups ($p=0.033$). Among the variables used to calculate the baseline DI, the internal diameter of the CCA measured during diastole was relatively larger in Post women ($p=0.037$). The baseline DI was significantly different by menopause stage with the higher baseline DI in Pre and Tran/No HT as compared to Tran/HT and Post ($p<0.0001$).

The change over the 3-year period () in hemodynamic variables by menopause stage is shown in Table 3. With the exception of FSH and DI ($p<0.0001$ and $p=0.046$, respectively), there were no statistical differences in other variables. The baseline DI and DI by menopause stage is illustrated in Figure 1. The difference in DI between the Post women on HT versus not on HT was not statistically significant ($p=0.38$); therefore both subgroups were combined to form the reference group. Without covariates in the model, women in the Pre and Tran/No HT had over twice the decline in DI compared to Post women [beta (standard error) Pre: -7.09 (3.80), $p=0.06$; Tran/No HT: -8.18 (3.36), $p=0.016$]. The DI decline in Tran/HT women did not differ statistically from that of the Post women (-3.35 [3.07], $p=0.28$).

We further evaluated change over time in risk factors as potential covariates. When adjusting for each covariate separately, two significant ($p<0.0001$) covariates (change in SBP and change in pulse pressure) enhanced the statistical relationship between menopause stage and DI ($p=0.019$ and 0.0003 , respectively). There was a strong correlation ($r=-0.71$ at

baseline and $r=-0.63$ at follow-up) between DI and pulse pressure. The only other significant covariate, change in heart rate, did not substantially modify the relationship between menopause stage and DI.

Table 4 presents the final multivariate model with Post used as the menopause stage reference and the independent covariates. The model R^2 was 0.55. Among the covariates, only change in heart rate ($p=0.003$) and change in pulse pressure ($p<0.0001$) remained independent predictors of change in DI. In comparison to the reference group Post, women in the Pre and Tran/No HT groups had a significantly faster DI decline ($p=0.002$ and 0.001 , respectively). In contrast, although the Tran/HT women did experience a somewhat faster DI decline compared to Post women, this difference was not statistically significant ($p=0.21$).

Because of strong collinearity with menopausal stage, age was not included in the final model. Adding baseline BMI ($p=0.51$) or change in BMI ($p=0.16$), a potential confounder, to the model did not alter the significant relationship between DI decline and menopause status or the other covariates.

Discussion

Our prospective study demonstrates that DI significantly differs by menopause stage. At baseline, DI was higher in Pre and Tran/No HT women and lower DI in Tran/HT and Post women. Over a 3-year period, the largest decline in DI occurred in Tran/No HT group, while the lowest DI decline was found in the Tran/HT group as compared to Post. These findings suggest that prior to postmenopause, HT use during transition is beneficially associated with arterial distensibility decline. Furthermore, postmenopausal HT appears to have no beneficial relation to distensibility. Finally, our results suggest that a higher SBP and higher pulse pressure modifies the observation of menopause status and DI decline.

Our findings are consistent with a previous study of 93 premenopausal age-matched and 93 postmenopausal women not on HT.⁸ A significantly lower arterial distensibility was observed in postmenopausal women further suggesting that after controlling for age, estrogen status plays an important role in vascular function. Additionally, a lower distensibility was found to correlate with the number of years a woman was postmenopausal suggesting that distensibility is negatively associated with cumulative years of estrogen loss. Prior studies have also shown that menopause may augment the age-related increase in arterial stiffness.^{9,23} Staessen et al. evaluated distensibility and pulse wave velocity in 315 women as they transitioned through menopause over 5.2 years matched to 315 men.²³ The findings were that arterial distensibility declined with age and after controlling for age, cardiovascular variables, and hormone use, Post women had a greater pulse wave velocity compared to Pre women. Additionally, these results could not be reproduced in the age-matched male controls suggesting menopause and estrogen loss may contribute to arterial stiffness above the effects of age. Similarly, our study found the greatest decline in arterial distensibility occurred in Pre and Tran women not on HT and that this difference was statistically significant compared to Post women.

Unlike most published studies examining arterial function and women on HT, our study is unique in that it further differentiates by menopause stages to assess the relationship between distensibility and HT use. Our results indicate that because there was a slower decline in DI in Tran women on HT compared to Post, HT use during menopause transition may potentially slow the observed changes in arterial function. Prior studies show evidence that vascular changes may begin in the earliest stages of menopause and that menopause transition accelerates the age-related decline in endothelial function and stiffness.^{24,25} A number of studies have also shown that arterial distensibility declines more rapidly in women than men beginning around 45 years of age, coinciding with the stage of early menopause transition where estrogen fluctuations may begin.^{26,27} The change in distensibility is not related to gender difference such as arterial size or baseline compliance.²² This greater reduction in distensibility may contribute to the increased prevalence of systolic hypertension in older women and higher CVD risk.²⁸

Observational studies investigating the impact of HT on vascular function in postmenopausal women have had mixed results, with some showing improvement in arterial elasticity^{12,13,29-32} and others indicating no benefit.^{14,21} Kawecka-Jaszcz et al. examined 76 postmenopausal women and found that there was significant improvement in pulse wave velocity, a surrogate for arterial compliance, after 3 months of HT.¹² While not as robust, a retrospective study of 56 postmenopausal women also found that HT improved pulse wave velocity as early as 4 weeks.³¹ Interestingly, one study showed that after 1-month of withdrawing HT in 11 postmenopausal women resulted in significantly worse arterial compliance.¹³ To date however, randomized control trials have not demonstrated that HT in postmenopausal women results in vascular improvement.^{21,33} Additionally, recent results from the Kronos Early Estrogen Prevention study in early postmenopausal women did not find a difference in cIMT on HT, both transdermal and oral, compared to placebo.³⁴ These data support our finding that HT use in Post women was not related to a significant change in DI decline compared to non-HT users.

While we did not observe a difference in change in DI when directly comparing Tran women on and Tran women off HT, our findings are consistent with a prior randomized trial of Tran women that found no difference in arterial distensibility or compliance at 6- and 24-months after HT use compared to the placebo.¹⁶ It is possible that differences in arterial function between women on or off HT may not readily be apparent in Tran women since estrogen levels are still fluctuating. Other studies have shown that structural arterial changes, such as cIMT and adventitial diameter, may worsen as early as three months after the final menstrual cycle.^{24,35} Furthermore, while the effects of progesterone on vascular reactivity are not entirely clear, there is evidence to suggest that progesterone may counteract some of the vasodilatory effects of estrogen.^{36,37} Therefore, use of combination estrogen and progesterone HT in 34% of Tran women in our study may have attenuated the estrogen-mediated changes in distensibility that would otherwise have been identified in the Tran period. Finally, it is possible that the spectrum of patients included as part of the Tran group, which included women from Pre-to-Peri to Pre-to-Post, was too broad to capture a significant change in vascular function over the 3-year study period.

In addition to aging, the decline in arterial distensibility during menopause transition may be related to lower serum estrogen levels. In addition to a direct atheroprotective effect,³⁸ estrogen has been shown to reduce endothelial dysfunction and improve vascular reactivity over a short period of time.³⁹⁻⁴¹ On a biochemical level, estrogen enhances endothelium-dependent vasodilatation via reduced endothelin release, stimulation of nitric oxide levels, and increased production of nitric oxide synthase, prostacyclin, and endothelium-derived hyperpolarizing factor.³⁷ These estrogen-mediated effects may mitigate the effect of low-grade inflammation, oxidative stress, and associated biomarkers of endothelial dysfunction that have been implicated in arterial stiffening.^{42,43}

With respect to CVD risk factors, our study found that adding systolic blood pressure and pulse pressure to our final model affected the relationship between menopause and DI decline. Other studies have identified additional risk factors associated with reduced arterial distensibility, including obesity,⁴⁴ daily insulin intake,⁴⁵ smoking,⁴⁶ oxidized LDL,⁴² African-American race,⁴⁷ increased HDL,⁴⁷ and HIV.⁴⁸ While we assessed similar patient characteristics at baseline and follow-up, statistical significance was not reached. One reason why our study may not have found that these variables were statistically significant is that we assessed change in covariates over time as opposed to absolute values at baseline or follow-up.

Our results show that pulse pressure, which can serve as a marker of underlying arterial stiffness, increased across menopause stages. This has been demonstrated in a prior prospective study showing younger age at onset of menopause was associated with higher pulse pressure than women who underwent menopause at an older age.⁴⁹ Higher pulse pressure has also been shown to be an independent predictor of adverse cardiovascular events.⁵⁰ Post women with a higher baseline pulse pressure have more rapid progression in atherosclerosis.⁵¹ With regard to blood pressure, prior studies have shown a significant association between higher blood pressure and carotid stiffness.^{52,53} Similar to pulse pressure, arterial stiffness is an independent predictor of increased coronary events in patients with hypertension.⁵⁴ The increase in arterial stiffness may increase blood pressure by creating a high pulse wave velocity that augments pressure.⁵⁵ Advancing age in women is marked by predominance of sympathetic tone and decreased vagal tonic modulation of heart rate.⁵⁶ Furthermore, there is a decrease in nitric oxide activity with aging and a diminished blood flow response to endothelium dependent and independent stimuli.⁵⁷ There is evidence of hormonal involvement given the variation in radial artery distensibility seen during the menopause cycle.⁵⁸ The rapid decline in distensibility during menopause transition may potentiate the increase in pulse pressure and SBP seen with aging, or vice versa.

Potential study limitations

Given the observational nature of this study, our findings indicate only an association between arterial distensibility and changes with menopause and HT use, not impact or causality. The transition through menopause is a gradual process that may not be accurately reflected by individual data points. However, the input of three reproductive endocrinologists in conjunction with the menopause status algorithm provides assurance

about the classification of each study participant. In addition, the results of Table 2 provide construct validity demonstrating consistency with markers known to change over the menopause transition. It should be noted that while a comprehensive approach was taken to assess all hemodynamic variables and measures of DI, the results of the study could not be adjusted for unmeasured variables, such as physical activity. Therefore, we cannot definitely exclude that aging and use of HT may be surrogates for other factors not included in the study. Another potential limitation is that use of HT in this study was not randomized and that the conclusion that HT may impact arterial distensibility should be interpreted with caution. The variability in dose, type, and route of administration of HT could have led to differential effects on arterial distensibility. The generalizability of the results may also be limited by the fact that the participants in this study had no known CVD, and therefore the effects of HT on arterial distensibility during menopause transition in the setting of significant atherosclerosis cannot be deduced. Finally, the small number of participants in the menopause groups may have underpowered the study and masked other significant findings, such as other covariates that may be independent predictors of change in DI or a significant difference in DI decline comparing Tran and/or Post women on and off HT.

Conclusion

Pre and Tran women not using HT have the largest decline in arterial distensibility compared to Post women. These findings indicate that menopause transition is associated with reduced vascular compliance. HT appears to have an impact on arterial distensibility only if taken during the transitional period of menopause, indicating that the perimenopausal window presents a critical time during which changes to arterial function may occur that increase the risk of CVD. Additional prospective studies are needed to confirm these findings and to assess whether the impact of HT on arterial distensibility is sustained long-term.

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Figure 1. The baseline distensibility index (DI) and change in DI over 3-year period

There is a decline in DI over time as women transition through menopause. The rate of the decline is greatest in transitioning (Tran) women not taking hormone therapy (HT). The decline in DI is statistically significant ($p=0.016$) when comparing Tran/No HT women to postmenopausal women (Post). Abbreviations: HT, hormone therapy; Pre, premenopausal; Tran, transitioning; Post, postmenopausal.

Table 1

Baseline characteristics

Baseline Variable	Menopause Stage over 3-Year Period				P-value
	Pre n=17	Tran/No HT n=23	Tran/HT n=29	Post n=92	
Age	47.4 ± 3.0	48.0 ± 3.1	49.3 ± 2.5	53.9 ± 4.3	<0.0001
BMI	25.9 ± 4.9	25.8 ± 5.6	27.9 ± 7.2	26.8 ± 5.3	0.52
Ever Smoker (%)	41	43	59	46	0.58
Diabetes (%)	6	4	3	1	0.23
HTN Medications (%)	18	0	28	17	0.037
Glucose (mg/dl) (total N=144)	98 ± 29	77 ± 31	92 ± 28	89 ± 28	0.19
LDL (mg/dl) (total N=149)	119 ± 29	122 ± 27	122 ± 32	130 ± 37	0.49
HDL (mg/dl)	60 ± 11	60 ± 17	64 ± 12	66 ± 15	0.25
TG (mg/dl)	100 ± 45	112 ± 79	164 ± 125	141 ± 78	0.047
FSH (mIU/ml) (Total N=152)	5.1 ± 2.8	15.8 ± 14.0	18.5 ± 16.6	59.3 ± 38.1	<0.0001

Abbreviations: BMI, body mass index; HDL, high-density lipoprotein; HTN, hypertension; FSH, follicle stimulating hormone; LDL, low-density lipoprotein; Pre, premenopausal; Post, postmenopausal; TG, triglycerides

Table 2

Baseline hemodynamic variables and components of distensibility index (DI)

Baseline Variable	Menopause Stage over 3-Year Period				P-value
	Pre n=17	Tran/No HT n=23	Tran/HT n=29	Post n=92	
SBP (mmHg)	123 ± 11	118 ± 15	129 ± 16	128 ± 16	0.024
DBP (mmHg)	89 ± 9	85 ± 9	89 ± 8	88 ± 9	0.31
Pulse Pressure (mmHg)	34 ± 8	34 ± 12	40 ± 14	40 ± 12	0.033
Heart Rate (beats/minute)	79 ± 9	78 ± 10	76 ± 13	80 ± 11	0.26
cIMT at SBP (mm)	0.64 ± 0.09	0.66 ± 0.04	0.69 ± 0.18	0.68 ± 0.07	0.27
cIMT at DBP (mm)	0.67 ± 0.09	0.68 ± 0.04	0.73 ± 0.20	0.71 ± 0.08	0.25
CCA Internal Diameter at SBP (mm)	5.5 ± 0.4	5.4 ± 0.4	5.6 ± 0.5	5.7 ± 0.7	0.10
CCA Internal Diameter at DBP (mm)	5.0 ± 0.4	5.0 ± 0.4	5.1 ± 0.4	5.3 ± 0.6	0.037
Internal Diameter SBP – Internal Diameter DBP	0.50 ± 0.09	0.46 ± 0.11	0.51 ± 0.13	0.45 ± 0.11	0.034
DI	61.7 ± 16.5	61.4 ± 23.7	51.9 ± 13.0	45.6 ± 17.0	<0.0001

Abbreviations: CCA, common carotid artery; DBP, diastolic blood pressure; DI, distensibility index; HT, hormone therapy; IMT, carotid intima-media thickness; Pre, premenopausal; Post, postmenopausal; SBP, systolic blood pressure

Table 3

Change in baseline and hemodynamic variables over 3-year period

Variable	Menopause Stage over 3-Year Period				P-value
	Pre n=17	Tran/No HT n=23	Tran/HT n=29	Post n=92	
Hemodynamic Variables and Distensibility Index (DI) Components					
SBP (seated)	3.2 ± 11.2	3.9 ± 13.5	3.6 ± 12.2	3.2 ± 13.3	0.99
DBP (seated)	-4.8 ± 6.8	-4.8 ± 7.8	-5.3 ± 8.3	-6.0 ± 9.2	0.89
Pulse Pressure	7.9 ± 9.6	8.7 ± 13.2	8.8 ± 11.0	9.3 ± 10.7	0.97
Pulse	-5.9 ± 8.8	-3.0 ± 8.5	-2.1 ± 12.5	-6.5 ± 10.2	0.16
cIMT at SBP	0.03 ± 0.05	0.01 ± 0.04	0.03 ± 0.05	0.02 ± 0.06	0.52
cIMT at DBP	0.03 ± 0.04	0.01 ± 0.04	0.02 ± 0.06	0.03 ± 0.06	0.54
CCA Internal Diameter at SBP	-0.06 ± 0.29	-0.02 ± 0.24	0.01 ± 0.24	-0.00 ± 0.23	0.82
CCA Internal Diameter at DBP	-0.02 ± 0.28	-0.00 ± 0.21	0.05 ± 0.24	-0.01 ± 0.20	0.68
Internal Diameter SBP – Internal Diameter DBP	-0.04 ± 0.07	-0.02 ± 0.06	-0.04 ± 0.13	0.01 ± 0.09	0.054
Distensibility Index	-16.4 ± 13.3	-17.5 ± 21.4	-12.7 ± 9.3	-9.3 ± 13.8	0.046
Other Baseline Variables					
BMI	1.1 ± 1.6	1.6 ± 2.3	0.4 ± 1.5	0.6 ± 1.7	0.07
Glucose (Total N=136)	1 ± 30	21 ± 25	18 ± 23	7 ± 34	0.11
LDL (Total N=142)	14 ± 23	24 ± 30	12 ± 22	10 ± 26	0.15
HDL	-12 ± 10	-12 ± 13	-8 ± 14	-11 ± 10	0.63
TG	25 ± 56	-1 ± 40	-11 ± 99	1 ± 60	0.36
FSH (Total N=145)	1 ± 3	20 ± 28	10 ± 12	-10 ± 36	<0.0001

Abbreviations: BMI, body mass index; CCA, common carotid artery; DBP, diastolic blood pressure; DI, distensibility index; FSH, follicle stimulating hormone; HDL, high-density lipoprotein; HT, hormone therapy; cIMT, carotid intima-media thickness; LDL, low-density lipoprotein; Pre, premenopausal; Post, postmenopausal; SBP, systolic blood pressure; TG, triglycerides

Table 4

Multivariate model of menopause stage and covariates on change in DI over 3-year period.

Variable	Beta (standard error)	P-value
Menopause group	*	0.0008
Pre	-8.2 (2.6)	0.002
Tran/No HT	-7.9 (2.3)	0.001
Tran/HT	-2.7 (2.2)	0.21
Post	Reference	-
Pulse Pressure	-0.90 (0.07)	<0.0001
Heart Rate	-0.23 (0.08)	0.003

Abbreviations: HT, hormone therapy; Pre, premenopausal; Tran, transitioning; Post, postmenopausal.

* Since menopause group as a single variable is categorical, no beta (standard error) can be calculated