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Vascular dysfunction across the stages of the menopause transition is associated with menopausal symptoms and quality of life

Kerry L. Hildreth, M.D.¹, Cemal Ozemek, Ph.D.², Wendy M. Kohrt, Ph.D.^{1,3}, Patrick J. Blatchford, Ph.D.⁴, and Kerrie L. Moreau, Ph.D.^{1,3}

¹Department of Medicine, Division of Geriatric Medicine, University of Colorado School of Medicine

²Department of Physical Therapy and the Integrative Physiology Laboratory, College of Applied Health Sciences, University of Illinois at Chicago

³Eastern Colorado VA Geriatric Research, Education and Clinical Center

⁴Colorado Biostatistical Consortium, Colorado School of Public Health, University of Colorado Denver

Abstract

Objective—The menopause transition is associated with somatic symptoms and increased rates of depression, which can impair quality of life (QOL) and increase cardiovascular disease (CVD) risk. This period is also associated with accelerated vascular aging (arterial stiffening and endothelial dysfunction), an antecedent to CVD. This secondary analysis sought to explore associations between depression, menopausal symptoms and QOL, and vascular aging across menopause stages.

Methods—Arterial stiffness (carotid artery compliance), endothelial function (brachial artery flow-mediated dilation-FMD), menopausal symptoms (Menopausal Symptom List), depression (Center for Epidemiologic Studies Depression Scale–CES-D), and QOL (Utian QOL Scale) were measured in 138 women (19–70y) classified as premenopausal (N=41, 34±8y; mean±SD), early- (N=25, 49±3y) or late-perimenopausal (N=26, 50±4y), or early- (N=22, 55±4y) or late-postmenopausal (N=24, 61±5y). Differences across menopause stages were determined using one-way ANOVA; associations between vascular measures and MSL, CES-D and UQOL were tested using Pearson correlation analyses.

Results—Menopausal symptoms, depression and QOL worsened across menopause stages, particularly in late-perimenopausal women. Vasosomatic symptom frequency, and general somatic symptom frequency and severity were inversely correlated with carotid artery compliance and FMD ($r = -0.27$ to -0.18 ; all $P < 0.05$). Only correlations with general somatic symptoms were

Correspondence and requests for reprints: Kerrie L. Moreau, PhD, 12631 East 17th Avenue, Mail Stop B-179, Aurora, CO 80045, Phone: (303) 724-1914 Fax: (303) 724-1918 kerrie.moreau@ucdenver.edu.

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significant after adjusting for multiple comparisons. Total QOL was positively correlated with carotid artery compliance ($r=0.23$, $P=0.01$). CES-D scores were not correlated with carotid artery compliance or FMD ($r=-0.08$, -0.03 , $P=0.35$).

Conclusions—Vascular dysfunction across the stages of menopause was associated with greater frequency and severity of menopausal symptoms, and lower QOL, but not depression. Mechanisms underlying these associations (e.g. inflammation, oxidative stress) should be explored.

Keywords

vascular aging; menopause; depression; quality of life; menopause symptoms

Introduction

Despite advances in treatment and prevention, cardiovascular disease (CVD) continues to be the leading cause of death among women in developed countries. Depression has been identified as a risk factor for CVD with several large epidemiologic studies reporting an association between depression or depressive symptoms and new fatal and non-fatal CVD events (1–3). Women have higher rates of depression than men (4, 5), and the prevalence appears to increase significantly as women transition through menopause (6–8). A number of common menopausal symptoms can potentiate depressive symptoms and contribute to a reduced quality of life for many women. Vasomotor symptoms in particular are closely related to depressive symptoms and negative mood (9, 10), and have also been linked to increased CVD risk (11–13).

Along with an increase in somatic and psychological symptoms, the menopause transition is associated with an acceleration in vascular aging. Markers of vascular aging, including large elastic artery stiffening and endothelial dysfunction, precede the development of clinical CVD and independently predict future CV events (14, 15). We previously reported that arterial stiffness is elevated and endothelial function is reduced across the stages of the menopause transition in healthy women who had not used any type of hormone therapy in the six months prior to enrollment (16, 17).

The association of menopausal symptoms, depression and quality of life with markers of preclinical atherosclerotic disease has not been well studied; to our knowledge, no previous studies have examined these associations across the stages of menopause. Accordingly, we sought to determine whether menopausal symptoms, depression, and quality of life are related to arterial stiffness, measured by carotid artery compliance, and endothelial function, measured by brachial artery flow-mediated dilation (FMD), in a well-characterized population of healthy premenopausal, perimenopausal and postmenopausal women.

Methods

Study population

One hundred thirty-eight healthy, community-dwelling women recruited from the Denver metropolitan area were enrolled in the study. Participant characteristics have been previously

described (17). Premenopausal women were aged 19–49 years with regular menstrual cycles (21–35 days) and no change in cycle length, confirmed with menstrual cycle calendars and ovulation prediction kits. Perimenopausal women were aged 43–56 years with irregular cycles, and postmenopausal women were aged 50–70 years with 12 months of amenorrhea. Perimenopausal women were further classified as early perimenopausal if they had 2 cycles with cycle length changes of 7 days, or late perimenopausal if they had 2 months of amenorrhea as defined by the Stages of Reproductive Aging Workshop (STRAW) (18). Postmenopausal women were classified as either early (<6 years) or late (≥6 years) postmenopause. Women with a history of hysterectomy or oophorectomy were excluded. Inclusion criteria included: sedentary or recreationally active (<3 days/week of vigorous exercise), no use of oral contraceptives or hormone therapy for 6 months prior to enrollment, non-smoking for 12 months, normotensive (resting blood pressure <140/90 mmHg), non-diabetic and fasted plasma glucose <110mg/dL, no use of medications that influence cardiovascular function (i.e. antihypertensive, lipid-lowering medications), and healthy as determined by medical history, physical examination and standard blood chemistries. Participants taking vitamin supplements or non-steroidal anti-inflammatory medications were asked to refrain from use for 4 weeks prior to vascular testing. The study was approved by the Colorado Multiple Institutional Review Board, and all participants provided written informed consent.

Measurements

Participants were studied in the supine position following an overnight fast (10 hours) with proper hydration (water only), and no caffeine. Participants maintained their normal dietary patterns, including sodium intake, for 2 days prior to testing. Premenopausal and, when possible, perimenopausal women were tested in the mid-follicular phase (7–10 days after the onset of menses) so that comparisons between these groups would be representative across the menstrual cycle. Late perimenopausal women were tested regardless of menstrual cycle phase after 2 months of amenorrhea. The study took place at the University of Colorado Clinical and Translational Sciences Institute (CCTSI) Clinical and Translational Research Center (CTRC).

Carotid Artery Imaging

Determination of carotid artery compliance was performed using high-resolution ultrasound imaging and measures of arterial pressure as previously described (19). Briefly, a longitudinal image of the cephalic portion of the carotid artery was acquired ~1–2 cm distal to the carotid bulb. Carotid images were analyzed for systolic and diastolic diameters using computerized semiautomated edge-detection software which allows accurate identification and measurements of carotid artery lumen diameter over a length of the artery (Vascular Analysis Tools v. 5.5, MIA, LLC, Coralville, Iowa). Peripheral artery blood pressures were measured with a semi-automated device over the brachial artery. All images were coded by number, blinded to menopause group, and analyzed by the same individual (K.L.M.).

Vascular endothelial-dependent vasodilation

Ultrasound measurements of brachial artery FMD were performed according to standard methods with duplex ultrasonography (GE Vivid I) using a multi-frequency linear-array

transducer as previously described (3, 9). Briefly, a pediatric cuff was placed on the upper forearm, and brachial artery images were acquired ~3–6 cm above the antecubital fossa. The ultrasound probe was clamped to ensure the location of the same arterial segment for serial measurements and to prevent involuntary movement. After obtaining concurrent measures of baseline brachial artery diameter and blood flow velocity, reactive hyperemia was produced by inflating the cuff to 250mmHg for 5 minutes, followed by rapid deflation. After the release of the arterial occlusion, Doppler blood flow velocity was acquired, and B-mode ultrasound brachial artery diameter images were measured continuously for 2 minutes. Brachial artery diameter and blood flow velocity were analyzed using a commercially available software package (Vascular Analysis Tools 5.5.1; Medical Imaging Applications, Iowa City, Iowa). All images were coded by number, blinded to menopause group, and analyzed by the same individual (K.L.M.). All procedures conformed strictly with recently published guidelines for assessing FMD in humans (5).

Seated Blood Pressure and Body Composition

Seated brachial arterial blood pressure was measured in triplicate with a semi-automated device in the morning following an overnight fast, as previously described (19). Total (percent of total mass) and central (percent of mass in trunk region) body fat were determined using dual-energy x-ray absorptiometry (Hologic Discovery, version 12.6, Bedford, Massachusetts). Minimal waist and hip circumferences were measured according to guidelines and waist-to-hip ratio (WHR) was calculated (20).

Blood Sampling

Fasted plasma concentrations of glucose, insulin, total (Roche Diagnostic Systems, Indianapolis, Indiana) and high-density lipoprotein (HDL, Diagnostic Chemicals Ltd, Oxford, CT) cholesterol were determined using enzymatic/colorimetric methods. Low-density lipoprotein (LDL) cholesterol was calculated using the Friedewald equation (21). Serum concentrations of follicle stimulating hormone (FSH), estradiol, and progesterone were measured using chemiluminescence. Estrone was measured using radioimmunoassay. Total testosterone was measured using 1-step competitive assay. All blood sampling occurred on the day of vascular testing. All assays were performed by the CCTSI CTRC core laboratory.

Menopausal Symptoms

Menopausal symptoms were assessed using the Menopausal Symptom List (MSL) (22). The MSL is a widely used, validated questionnaire that assesses the frequency and severity of eight psychological, nine vasosomatic and ten general somatic symptoms in the past three months. Frequency scores range from 0 (never) to 5 (almost always). Severity scores also range from 0 (not applicable) to 5 (extreme). Total frequency and severity scores for psychological, vasosomatic and general somatic symptoms are determined by multiplying each individual item score by the assigned weight (1 or 2) and summing all the items in that factor. Frequency and severity scores each range from 0–70 for psychological symptoms, 0–60 for vasosomatic symptoms, and 0–55 for general somatic symptoms, with higher scores indicating greater symptom frequency and/or severity.

Depression

Depressive symptoms were assessed using the 20-item Center for Epidemiologic Studies Depression (CES-D) scale (23). The CES-D is a widely used, validated questionnaire to measure depressive symptomatology in the general population with emphasis on depressed mood. Participants are asked to rate the frequency of depressive symptoms over the past week with options ranging from 0–3 (0 = rarely or none of the time; 1 = some or a little of the time; 2 = occasionally or a moderate amount of time; 3 = most or all of the time). Scores range from 0–60 with higher scores indicating more depressive symptoms. Scores of 16 have traditionally been used to indicate significant depressive symptomatology (24, 25).

Quality of Life

QOL was assessed using the Utian QOL Scale (UQOL), a validated questionnaire that measures menopause-related QOL in the past month on four sub-scales: occupational, health, emotional and sexual (26). The UQOL consists of 23 statements about which participants are asked to rate the degree to which they agree on a 5-point scale (1 = not true of me; 5 = very true of me). Sub-scale and total scores are determined by summing the responses, with higher scores indicating better quality of life. Scores range from 7–35 for occupational and health-related sub-scales, 6–30 for the emotional sub-scale, 3–15 for the sexual sub-scale, and 23–115 for total QOL.

Statistical analysis

Descriptive statistics were used to examine all data elements. Parameters with skewed distributions were log-transformed and are presented as median and interquartile range. A one-way analysis of variance (ANOVA) was used to assess differences in participant characteristics, and to compare vascular and hemodynamic parameters, and MSL, CESD, and UQOL scores across menopausal stages. Pearson correlation analyses were used to test for bivariate associations of MSL, CESD, and UQOL with carotid artery compliance and brachial artery FMD. P-values were adjusted for multiple comparisons using the Adaptive Holm method (27). Data analysis was performed with IBM SPSS Statistics, version 21.0.

Results

Participant characteristics

Among postmenopausal women, the reported age of and time since menopause were 51 ± 4 years and 7 ± 5 years, respectively. Forty-three percent of postmenopausal women had used estrogen-based hormone therapy for an average of 5.4 ± 4.5 years. Total body and trunk fat, systolic blood pressure, total cholesterol, LDL cholesterol and triglycerides were elevated across the stages of the menopause transition (Table 1, all $P < 0.05$). Levels of sex hormones followed expected patterns with FSH higher, and estradiol, progesterone, estrone and testosterone lower across the stages of menopause (all $P < 0.01$).

Vascular and Hemodynamic Parameters

Supine measures of systolic and diastolic blood pressure, mean arterial pressure and pulse pressure were elevated across the stages of menopause (Table 2). Arterial stiffness was

elevated (arterial compliance reduced), and endothelial function (brachial artery FMD) was reduced across menopause stages (Table 2).

Menopausal Symptoms, QOL, and Depression

Psychological, vasomotor and general somatic menopausal symptoms were different across menopause stages (all $P < 0.05$), with both frequency and severity of symptoms highest in late perimenopausal women (Table 3). Occupational and emotional quality of life were not different among menopause groups ($P = 0.40$ and 0.22 , respectively). Health-related, sexual and total QOL were lower in the late perimenopausal and early postmenopausal groups with significant differences between menopause stages in sexual and total quality of life (both $P < 0.05$). Depressive symptoms also differed by menopause group ($P = 0.03$); scores were highest in late perimenopausal women whereas early postmenopausal women were more likely to have scores consistent with significant depression. A total of 25 (18.1%) of participants were taking antidepressant medications. Seventy-two percent were using SSRIs, 12% were using SNRIs, and 16% were using other antidepressants (bupropion=3, valproate=1). CES-D scores were higher in women using antidepressants compared to non-users (8.2 ± 6.0 vs. 11.4 ± 8.3 , $p = 0.03$).

Correlations between Vascular Function and Mood, Quality of Life and Menopause Symptoms

In unadjusted analyses, there were no significant correlations of depressive symptoms with carotid artery compliance or brachial artery FMD (Table 4; all $P > 0.05$). Carotid artery compliance was correlated with total quality of life ($P = 0.01$), and tended to be associated with both health-related and sexual quality of life ($P = 0.06$ and $P = 0.07$, respectively). Brachial artery FMD was not associated with any quality of life measure (all $P > 0.05$). Both carotid artery compliance and FMD were correlated with vasomotor symptom frequency (both $P = 0.04$), and with general somatic symptom frequency and severity (all $P < 0.01$). After adjusting for multiple comparisons, only correlations between vascular measures and general somatic symptom frequency and severity remained significant ($P < 0.05$). Results excluding participants on antidepressant medication were similar, with the exception of additional correlations between carotid artery compliance and both health-related QOL and vasomotor symptom severity ($r = 0.20$; $p = 0.04$, and $r = -0.21$; $p = 0.03$, respectively).

Discussion

In this study of healthy women across the stages of menopause, arterial stiffening and endothelial dysfunction across the stages of the menopause transition were associated with more frequent and severe menopausal symptoms, and with poorer quality of life, but not with depression. To our knowledge, this was the first study to examine the association of mood, symptoms and quality of life measures with these key markers of vascular aging in a well-characterized population of women spanning the stages of the menopause transition.

Menopause and Vascular Aging

Vascular aging, characterized by endothelial dysfunction and large elastic artery stiffening, is a major risk factor for the development of CVD (28). In women, profound changes in the

hormonal environment during the menopause transition coincide with adverse changes in CVD risk factors (e.g. blood pressure, lipids, central adiposity, insulin resistance) (29–31). This confluence of factors may help to explain the acceleration of vascular aging during the late perimenopausal to postmenopausal period (32). We have previously shown a progressive reduction in endothelial function (17) and elevation in arterial stiffness (16) across the stages of the menopause transition, beginning in early perimenopause and becoming more pronounced in the late perimenopause to early postmenopausal period. These notable observations in vascular function have been attributed to declines in ovarian function and estrogen levels. In estrogen-deficient post-menopausal women, short-term estrogen treatment was associated with a significant improvement in brachial artery FMD (33–35). Likewise, we have shown that arterial stiffening is reduced in postmenopausal women with both acute and chronic hormone therapy (33, 35, 36).

Depression, Menopausal Symptoms and Quality of Life

Although the majority of women do not experience depression during the menopause transition, several studies suggested that, when compared to the premenopausal period, the risk of mood disorders is 2- to 3-times higher during the menopause transition (37). It has been hypothesized that the fluctuation in estrogen levels during perimenopause, rather than the decline, per se, increases the risk of depressive symptoms (37). Because estrogen is a potent neurosteroid that influences multiple neurotransmitter systems, the female brain must respond to regularly changing levels of estrogen across the menstrual cycle during the reproductive years. As cycles become irregular with the transition to menopause, increased flexibility is required to maintain homeostasis, and failure to rapidly adapt may predispose women to mood disturbances (37). This hypothesis is supported by data showing the variability of estradiol levels was the strongest risk factor for a diagnosis of depression in a longitudinal study of women across the menopause transition (38), and that a longer perimenopausal interval (i.e. a longer period of hormonal unpredictability) was also associated with an increased risk of depression (39). Results from the present study support those of the Study of Women's Health Across the Nation (SWAN), in which both cross-sectional and longitudinal analyses found that significant depressive symptoms (CES-D 16), dysphoric mood and psychological distress were more likely in early and late perimenopausal women compared to premenopausal women (40). Postmenopausal women in the SWAN study were also more likely to experience depressive symptoms than premenopausal women. Interestingly, we found depressive symptoms were higher in early but not late postmenopausal women compared to premenopausal women, which further supports the hypothesis of brain adaptation to unpredictable hormonal fluctuations, in that the brain adapts to a new stable baseline after prolonged estrogen deficiency, resulting in less mood disturbance.

The increased prevalence of depression with the menopause transition has often been considered a consequence of common menopausal symptoms, such as hot flashes and associated sleep disturbance. In previous studies, the presence of vasomotor symptoms has been associated with an increased risk for depression (8, 41). However, not all studies have shown this association, suggesting that vasomotor and depressive symptoms may share common underlying mechanisms as opposed to a causal relationship. For example, both

estrogen and serotonin have been shown to have both neuromodulatory and thermoregulatory functions (42, 43).

The menopause transition has also been associated with decreased quality of life, thought to be largely a result of menopausal symptoms. For example, in the SWAN study, lower health-related quality of life in early perimenopausal compared to premenopausal women was largely explained by menopausal symptoms, including night sweats, hot flashes and urinary symptoms (44). However, quality of life encompasses multiple domains, some of which may be more influenced by symptoms and health-related factors than others. In the present study, patterns in quality of life measures were similar to those of both depression and menopausal symptoms, with late perimenopausal women reporting the lowest quality of life scores in all domains except for occupational.

Overall, our results are consistent with previous studies which indicate a close relation between menopausal symptoms, depression and quality of life. While menopausal symptoms likely exert a strong influence on mood and quality of life, it is also plausible that common pathways related to fluctuations and declines in estrogen underlie all of these parameters.

Depression, Menopausal Symptoms and Vascular Aging

Depression approximately doubles the risk of developing CVD (45). In postmenopausal women with no history of CVD, baseline depression was associated with an increased risk of cardiovascular mortality over an average of four years of follow up, after adjustment for age, race, education, income, and traditional cardiovascular risk factors (3). A similar association was reported in the Study of Osteoporotic Fractures (46). The association between depression and markers of vascular aging is less clear. A recent meta-analysis reported a moderate effect size for the association between depression and endothelial function, measured by FMD, although there was significant methodologic variability among studies, including differences in cuff occlusion pressure and position, duration of occlusion, measurement interval and testing duration, as well as in measures of depression used (47). Several measures of arterial stiffness have been linked to depression in older adults (48, 49), but studies of women in the context of the menopause transition are lacking. Both depressive symptoms and recurrent major depression have been associated with progression of coronary artery calcification in women in midlife (50, 51).

In the present study, we found no association between either carotid artery compliance or FMD and depressive symptoms. This may reflect our healthy population (48 ± 11 years). For example, a meta-analysis of studies of FMD and depression found a stronger effect in studies of patients with CVD or CVD risk factors, and in studies with a mean age of 55 years or older (47). Studies in patients with current or remitted major depressive disorder also showed a greater effect than those examining depressive symptoms. The CES-D, though a validated measure of depressive symptoms developed for use in community-based populations, is limited to recent symptoms. Interestingly, data from the SWAN Heart study found that subclinical atherosclerosis measured by carotid artery intimal-medial thickening was associated with hopelessness, but not with depression assessed using the CES-D (52). Although the mean age was similar (50 years), the SWAN study enrolled women nearer to

menopause (age 42–52), thus the range of ages was much smaller than in the present study. Mean CES-D scores were similar, 7.2 ± 7.9 , vs. 8.8 ± 6.6 , although the proportion of women with CES-D scores ≥ 16 was higher in the SWAN Heart study (20% vs 13%). Use of antidepressants was not reported in the SWAN Heart study, but were used by 18% of participants in the present study. Studies of the effects of antidepressants on vascular function, including arterial stiffness and endothelial function, have been mixed (53, 54). Our results were not substantively different when we included only non-medicated participants, however, it is possible that factors such as the type and duration of use could have affected our results.

Menopause symptoms, predominantly vasomotor symptoms, have also been linked to increased cardiovascular risk and mortality (55, 56). Hot flashes have been associated with aortic calcification and reduced endothelial function (57, 58). In the present study, the frequency, but not severity, of vasomotor symptoms was associated with greater arterial stiffening, and with reduced endothelial function. These same markers of vascular aging were also associated with both the frequency and severity of general somatic symptoms. Data on the relation between menopausal symptoms other than hot flashes and markers of vascular aging are scarce. Cagnacci et al. reported that overall scores on the Greene Climacteric Scale, which includes vasomotor, somatic, anxiety, depression and sexuality subscores, were associated with several biochemical cardiovascular risk factors (unfavorable lipid profiles, glucose) and with Framingham 10-year cardiovascular disease risk scores (13). To our knowledge, no other studies have examined the associations between menopausal symptoms other than hot flashes and markers of vascular aging such as arterial stiffening and endothelial dysfunction.

Potential mechanisms

Multiple potential mechanisms may underlie the observed associations among menopausal symptoms and vascular aging. Estrogen modulates the synthesis and uptake of serotonin, which has neuromodulatory, thermoregulatory and cardiovascular actions (59). Fluctuating and declining levels of estrogen with the menopause transition may alter serotonin activity; indeed, antidepressants that function as selective serotonin reuptake inhibitors (SSRIs) have demonstrated efficacy in treating hot flashes (60), and in decreasing CVD risk (61).

Another possible mechanism linking menopausal symptoms and vascular aging is an increase in oxidative stress (the imbalance between the production and destruction of reactive oxygen species (ROS)) with menopause. Estrogen is a potent antioxidant. Higher levels of oxidative stress are observed in estrogen-deficient postmenopausal women compared to premenopausal women (62–64), while lower levels of oxidative stress are seen in postmenopausal hormone therapy users compared to non-users (65, 66). Increased ROS can reduce the bioavailability of nitric oxide (NO), a key modulator of arterial stiffness and endothelial vasodilatory function, both by scavenging NO and by suppressing its synthesis. We have previously shown that acute suppression of ROS using a systemic infusion of the antioxidant ascorbic acid improves both brachial artery FMD (35) and carotid artery compliance (16) in estrogen-deficient postmenopausal women, suggesting oxidative stress as one possible mechanism underlying accelerated vascular aging with loss of estrogen.

Women who experience menopausal hot flashes have also been shown to have higher levels of oxidative stress markers than women without hot flashes (66). Furthermore, hormone therapy in women with hot flashes was associated with reductions in both markers of oxidative stress and frequency of hot flashes, suggesting the loss of the antioxidant effects of estrogen with menopause may contribute to this common menopausal symptom.

Together, these data support a role for the loss of the antioxidant properties of estrogen with menopause leading to an increase in oxidative stress and decreased NO bioavailability, which then may contribute to menopausal symptoms such as hot flashes, and accelerated vascular aging.

Strengths and Limitations

Strengths of this study include the well-characterized population, use of state-of-the-art measures of arterial stiffness and endothelial function known to predict CVD events, and well-validated measures of depression, menopause symptoms and quality of life. This study has some important limitations. Menopause stage was based on self-reported cycle characteristics using the older STRAW criteria, as the updated STRAW+10 system (67) had not been released at the time of this study. Bleeding/flow patterns were not collected, thus we cannot update menopause stage to the newer classification system. Women in this study were primarily white and all were healthy non-smokers on no vasoactive medications. It is not known whether the findings extend to other populations. As with all cross-sectional studies, no conclusions about causality can be made. Although the CES-D is a reliable and validated measures of depression, it is limited to assessing symptoms within the past week, thus not capturing chronic or recurrent depressive episodes.

Conclusions

In women, the menopause transition may be a particularly vulnerable time for increase in cardiovascular disease risk given the convergence of hormonal changes, psychological and physical symptoms, and unfavorable changes in blood pressure, lipids, insulin resistance and body composition. Across the stages of menopause, arterial stiffening and endothelial dysfunction were associated with more frequent and severe menopausal symptoms, and a lower quality of life, but not with depressive symptoms. Future studies should explore potential mechanisms underlying the associations among vascular function, mood, quality of life and menopausal symptoms, such as oxidative stress and inflammation. A better understanding of these aspects of the menopause transition will be important for developing effective lifestyle and therapeutic interventions to promote psychosocial well-being and cardiovascular health in aging women.

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Table 1

Baseline characteristics of participants

Variable	Pre N=41	Early Peri N=25	Late Peri N=26	Early Post N=22	Late Post N=24	P-value
Age, years	34±8	49±3	50±4	55±4	61±5	<0.001
Body mass, kg	66.5±15.0	69.7±10.3	66.8±12.4	71.0±12.4	66.7±14.1	0.64
BMI, kg/m ²	24.5±5.7	25.7±3.7	24.3±4.0	26.4±4.8	25.8±5.4	0.44
Total body fat, %	31±7	34±6	36±7	38±5	37±8	0.001
Trunk fat, %	28±9	33±6	34±8	37±7	36±9	<0.001
Waist circumference, cm	79±9	83±10	82±12	87±13	85±12	0.07
WHR	0.79±0.06	0.80±0.06	0.81±0.06	0.83±0.07	0.83±0.06	0.08
VO ₂ peak, mL/kg/min	33.4±7.3	28.0±4.4	28.0±5.7	26.5±3.8	25.4±7.1	<0.001
Seated SBP, mmHg	108±9	112±10	115±12	117±14	120±14	0.001
Seated DBP, mmHg	68±7	72±7	71±8	73±10	72±10	0.07
Resting HR, bpm	65±11	62±7	64±10	63±6	64±8	0.87
Total cholesterol, mg/dL	152±29	168±28	171±31	188±38	199±33	<0.001
LDL cholesterol, mg/dL	88±23	98±26	101±29	109±28	123±28	<0.001
HDL cholesterol, mg/dL	48±11	51±13	51±9	57±20	57±16	0.08
Triglycerides, mg/dL ^a	68 (52–95)	87 (66–104)	90 (79–109)	82 (71–106)	95 (68–123)	0.03
Fasted insulin, µIU/mL ^a	7 (4–9)	4 (3–9)	7 (3–11)	9 (4–14)	5 (3–8)	0.10
Fasted glucose, mg/dL	84±8	85±8	83±8	88±11	86±9	0.18
FSH, mIU/mL	6.3±3.4	22.0±30.0	64.1±35.5	73.1±26.3	82.7±33.2	<0.001
Estradiol, pg/mL ^{a,b}	76 (39–92)	70 (36–141)	34 (10–102)	11 (10–15)	10 (10–15)	<0.001
Progesterone, ng/mL ^a	0.5 (0.2–0.8)	0.5 (0.2–0.9)	0.3 (0.3–0.5)	0.3 (0.1–0.4)	0.2 (0.1–0.4)	0.001
Estrone, pg/mL ^a	59 (37–70)	60 (34–92)	43 (29–70)	28 (23–35)	26 (23–37)	<0.001
Testosterone, ng/dL ^{a,c}	30 (18–43)	22 (17–36)	20 (17–25)	19 (17–23)	17 (17–35)	0.002

Data are mean±standard deviation unless otherwise stated.

^aData are median (interquartile range)^bSensitivity = 10 pg/mL^cSensitivity = 17 ng/dL

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Pre, premenopausal; Peri, perimenopausal; Post, postmenopausal; BMI, body mass index; WHR, waist hip ratio; VO₂ peak, peak aerobic power; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; LDL, low-density lipoprotein; HDL, high-density lipoprotein; FSH, follicle stimulating hormone

Table 2

Vascular and hemodynamic parameters

Variable	Pre N=41	Early Peri N=25	Late Peri N=26	Early Post N=22	Late Post N=24	P-value
Supine SBP, mmHg	103±10	107±9	111±15	113±10	123±13	<0.001
Supine DBP, mmHg	64±8	68±9	68±9	70±6	71±8	0.006
Mean arterial pressure, mmHg	77±8	81±9	82±10	84±6	89±8	<0.001
Pulse pressure, mmHg	39±7	38±6	43±10	44±8	52±11	<0.001
Compliance, mm ² /mmHg×10 ⁻¹	1.24±0.28	0.96±0.31	0.93±0.30	0.93±0.33	0.70±0.25	<0.001
FMD, %	10.4±3.4	8.2±3.1	7.2±2.2	6.2±2.1	5.6±2.8	<0.001

Data are mean ± standard deviation unless otherwise stated

^aData are median (interquartile range)

Pre, premenopausal; Peri, perimenopausal; Post, postmenopausal; SBP, systolic blood pressure; DBP, diastolic blood pressure; FMD, flow-mediated dilation

Table 3

Menopausal symptoms, quality of life and depressive symptoms by menopause stage

Variable	Pre N=37	Early Peri N=24	Late Peri N=26	Early Post N=22	Late Post N=24	P-value
Menopausal symptoms						
Psychological (Range 0–70)						
Frequency	11±9	15±12	23±13	14±13	12±9	0.001
Severity	13±10	15±11	22±13	15±13	13±8	0.01
Vasosomatic (Range 0–60)						
Frequency ^b	4(2–8)	10(3–13)	14(8–21)	13(10–15)	8(5–15)	<0.001
Severity ^b	6(2–8)	9(3–13)	13(7–21)	11(9–15)	10(4–16)	<0.001
General somatic (Range 0–55)						
Frequency	5±5	12±9	23±10	16±7	13±9	<0.001
Severity	6±5	11±9	21±9	16±7	12±8	<0.001
Quality of Life						
Occupational (Range 7–35)	26±5	26±5	26±6	24±6	24±7	0.40
Health (Range 7–35)	26±4	26±4	24±3	24±4	26±6	0.07
Emotional (Range 6–30)	26±4	26±4	24±4	25±4	25±3	0.22
Sexual (Range 3–15)	11±3	11±3	8±3	9±3	10±3	0.01
Total (Range 30–100)	89±10	88±13	82±10	82±10	85±13	0.03
Depression						
CES-D (Range 0–60)	7.8±7.5	7.8±5.9	11.8±5.7	10.4±7.9	6.8±3.7	0.03
CES-D 16 ^a	6 (16)	3 (13)	4 (15)	4 (18)	0(0)	

Data are mean ± standard deviation unless otherwise stated;

^aData are number (percent);^bData are median (interquartile range); Pre = premenopausal; Peri = perimenopausal; Post = postmenopausal; CES-D = Center for Epidemiologic Studies Depression scale.

Table 4

Bivariate correlations between vascular measures and menopausal symptoms, quality of life and depression

Variable	Carotid Artery Compliance	P-value	FMD	P-value
Psychological – frequency	–0.04	0.66	–0.06	0.53
Psychological – severity	–0.02	0.84	–0.03	0.75
Vasosomatic – frequency	–0.18	0.04	–0.18	0.04
Vasosomatic - severity	–0.14	0.12	–0.13	0.14
General somatic - frequency	–0.27	0.002 ^a	–0.25	0.003 ^a
General somatic - severity	–0.25	0.003 ^a	–0.25	0.004 ^a
Quality of Life				
Occupational	0.12	0.16	–0.00	0.97
Health-related	0.17	0.06	0.02	0.81
Emotional	0.10	0.26	0.13	0.17
Sexual	0.16	0.07	0.15	0.09
Total	0.23	0.01	0.11	0.21
Depression				
CES-D score	–0.08	0.35	–0.03	0.74

^a Adjusted P-value <0.05 using the Adaptive Holm method (28).

FMD, flow-mediated dilation; IMT, intima-medial thickness; CES-D, Center for Epidemiologic Studies Depression scale