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Self-Reported Menopausal Symptoms, Coronary Artery Calcification and Carotid Intima-Media Thickness in Recently Menopausal Women Screened for the Kronos Early Estrogen Prevention Study (KEEPS)

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Abstract

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Objective—To determine whether self-reported menopausal symptoms are associated with measures of subclinical atherosclerosis.

Setting—Multi-center, randomized controlled trial.

Patients—Recently menopausal women (n=868) screened for the Kronos Early Estrogen Prevention Study (KEEPS).

Design—Cross sectional analysis.

Interventions—None

Main Outcome Measures—Baseline menopausal symptoms (hot flashes, dyspareunia, vaginal dryness, night sweats, palpitations, mood swings, depression, insomnia, irritability), serum estradiol (E2) levels and measures of atherosclerosis were assessed. Atherosclerosis was quantified using Coronary Artery Calcium (CAC) Agatston scores (n=771) and Carotid Intima-Media Thickness (CIMT). Logistic regression model of menopausal symptoms and E2 was used to predict CAC. Linear regression model of menopausal symptoms and E2 was used to predict CIMT. Correlation between length of time in menopause with menopausal symptoms, estradiol (E2), CAC, and CIMT were assessed.

Results—In early menopausal women screened for KEEPS, neither E2 nor climacteric symptoms predicted the extent of subclinical atherosclerosis. Palpitations (p=0.09) and depression (p=0.07) approached significance as predictors of CAC. Other symptoms of insomnia, irritability, dyspareunia, hot flashes, mood swings, night sweats, and vaginal dryness were not associated with CAC. Women with significantly elevated CAC scores were excluded from further participation in KEEPS; in women meeting inclusion criteria, neither baseline menopausal symptoms nor E2 predicted CIMT. Years since menopause onset correlated with CIMT, dyspareunia, vaginal dryness and E2.

Conclusions—Self-reported symptoms in recently menopausal women are not strong predictors of subclinical atherosclerosis. Continued follow-up of this population will be performed to determine if baseline or persistent symptoms in the early menopause are associated with progression of cardiovascular disease.

Keywords

KEEPS; estrogen; cardiovascular; menopause; CAC; CIMT; palpitations; depression

Introduction

The efficacy of menopausal hormone therapy (MHT) in treating menopausal symptoms is well established and menopausal symptoms remain the primary indication for initiation of MHT in the perimenopausal and early postmenopausal years. Menopause also reflects a time when the risk for cardiovascular disease (CVD) increases, however, the precise effects of MHT on cardiovascular health remain controversial as they have been more difficult to delineate. Many large observational studies suggest that MHT has cardioprotective effects (1–8). However, this dogma was challenged by large, prospective, randomized controlled trials, which failed to show cardiovascular benefit of MHT when initiated remote (>10 yrs) from menopause (9) or in the setting of preexisting CVD (10).

Many preventive strategies have been established to reduce cardiovascular events in patients at risk. However, individuals at risk for CVD are not always easily identified. Baseline data from the Kronos Early Estrogen Prevention Study (KEEPS) were enlightening, revealing that 4% of the early postmenopausal population screened demonstrated an unexpected degree of asymptomatic coronary artery atherosclerosis (11). Additional screening tools to

better define cardiovascular risk may help to individualize the risk/benefit discussion of MHT.

As menopausal symptoms are the primary indication for MHT, it would be important to know if symptoms are related to cardiovascular disease risk. Conflicting evidence on this association exists. Menopausal complaints have been associated with cardiovascular disease risk factors such as hypertension, hypercholesterolemia, and body mass index (BMI) in one study (12). Increased cardiovascular events have been observed in women who experienced baseline vasomotor symptoms (VMS) compared to women who did not have baseline symptoms, but only in the first year after MHT was initiated (13). In the Study of Wommen Across the Nation (SWAN) study, perimenopausal women with VMS had significantly higher coronary artery calcium scores (CAC) when measured near menopause (14). In the Dutch Eindhoven Perimenopausal Osteoporosis Study (EPOS) study, night sweats (but not VMS) were associated with coronary heart disease events (16). Conversely, significantly lower CAC was observed at the end of the estrogen only arm of the Women's Health Initiative (WHI), suggesting that processes underlying atherosclerosis may be mitigated with postmenopausal estrogen therapy (15). Data from the WHI-observational study were particularly intruiguing wherein a decreased hazard for cardiovascular events was observed in women experiencing VMS early in menopause, whereas, VMS occurring late in menopause were associated with increased hazard of cardiovascular events (17). These data suggest that a relationship between atherosclerosis and VMS, if any, may be modulated by the time since menopause. We have herin sought to determine if common menopausal symptoms relate to measurese of atherosclerosis in an early menopausal population of overtly healthy women undergoing screening for KEEPS.

Given that symptoms in early menopause are the primary indication for initiation of MHT and the risks of initiating MHT in the setting of preexisting disease, we sought to characterize measures of atherosclerosis in this population to provide additional clarification on the association between menopausal symptoms with cardiovascular disease.

Materials and Methods

This multicenter trial was approved by an independent Institutional Review Board; in addition, the study was approved by the Institutional Review Board at each study site. Early menopausal women 42 to 58 years of age whose last menstrual period occurred at least 6 months and no more than 3 years previously were screened for eligibility for the KEEPS trial (NCT00154180) at 9 clinical study centers in the United States; study details have been reported elsewhere (18). As per study design, subclinical atherosclerosis was assessed by CAC and carotid intima-media thickness (CIMT). Coronary artery calcium was measured by computed tomography (CT) or electron beam tomography (EBT) and calculated two ways: 1) the mean Agatston score of two measurements and 2), and the mean of two CAC volume scores. Women with mean Agatston scores ≥50 U, taken to indicate coronary artery disease, were excluded from randomization. Women meeting inclusion criteria underwent baseline measurements of CIMT. CIMT was measured by computer image-processed B-mode ultrasound at two visits prior to randomization to study drug, and the average score was used for analysis. Emphasis of ultrasound imaging is on the distal centimeter of the common carotid artery (CCA) because least variability occurs in this area,(19) facilitating reproducible longitudinal imaging necessary for randomized controlled trials.(20–46) In addition, only longitudinal change in the distal centimeter of the (CCA) has been shown to be predictive of clinical coronary events(28); the CCA has been shown to be as good or better than other carotid artery segments in the prediction of cardiovascular events. The far wall is used for statistical purposes since measurement of near wall thickness is less accurate. (47) Per study design, study images were read at central facilities (CAC at the St.

Johns Cardiovascular Research Center, Harbor UCLA Medical Center and CIMT at the Atherosclerosis Research Unit, Core Imaging and Reading Center(25)) by one expert blinded to participant symptom burden and characteristics.

At screening, women were asked to rank the severity of their menopausal symptoms of depression, insomnia, irritability, dyspareunia, hot flashes, mood swings, night sweats, palpitations, and vaginal dryness on a scale of 0 (none), mild (1) to 4 (severe). Serum E2 concentrations were measured in pg/ml. These measures were correlated with self-reported menopausal symptoms and serum estradiol (E2).

Potential confounders for CVD were ascertained as previously reported (11): height (cm), weight (kg), body mass index (BMI, kg/m^2), blood pressure (systolic, diastolic in mm Hg), waist circumference (cm), total cholesterol (mg/dL), low density cholesterol level (LDL, mg/dL), high density cholesterol level (HDL, mg/dL), triglyceride level (mg/dL), fasting glucose (mg/dL), Framingham Risk Score (FRS)(48), cigarette smoking (history of smoking and cigarettes per day), alcohol intake (number of alcoholic drinks consumed per month), and metabolic syndrome. Serum E2 levels (pg/ml) and serum follicle stimulating hormone (FSH, ng/ml) were ascertained at the local study site laboratories. Details of the study design for the randomized trial have been previously reported(11). We chose a more conservative exclusion cut off of CAC>50 to limit the risks to subjects associated with starting HT in the setting of significant heart disease, rather than an exclusion criteria of CAC>100. Women with high cardiovascular factors were excluded.

Statistical Analysis

Continuous data were presented as mean+standar deviation (range) and categorical data as number (%). Data distribution was assessed; since most (80.7%, 700/868) of the Agatston measurements and CAC volumes were scored as zero, this measure was recoded into a dichotomous variable as absent (0 score) or present (score>0). Logistic regression analysis was used to investigate the relationship between CAC (present/absent) and menopausal symptoms while controlling for the effects of the covariates (height, weight, BMI, blood pressure, waist circumference, total cholesterol, LDL, HCL, triglycerides, fasting glucose, FRS, smoking, alcohol use, metabolic syndrome, E2, and FSH). Linear regression analysis was performed to investigate the relationship between CIMT and the 9 measures of menopausal symptoms while controlling the effects of the same covariates as included in the logistic regression model. Spearman's rank correlation was used to test for correlation between years of menopause and each of the nine menopausal symptoms, Agatston score, and CAC volume since the former (years of menopause) is a continuous variable and the others are ordinal. Pearson's correlation (correlation coefficient, CC) test was used for testing correlations between years of menopause and CIMT and E2 given that all variables involved are continuous. Additional sensitivity analyses were conducted by atherosclerosis disease severity. Statistical analyses were performed using the statistical software R 2.11.1. A p-value of less than 0.05 is considered statistically significant.

RESULTS

Data from n=868 subjects screened for the KEEPS trial were included in the analysis. A summary of the important variables is shown in Table 1. The average age of women screened was 52.7±2.6 SD (42–58) years. As was the aim of the study design, all women were within 3 years since their last menstrual period. Participants had low levels of atherosclerotic burden, given the young age and early menopausal status of the study population(11). Due to the length of time since menopause, E2 values were skewed as expected.

Association between CAC and Menopausal Symptoms

For the logistic regression analysis, mean Agatston score and mean CAC volume were exactly the same after recoding into dichotomous variables as absent (0 score) or present (score>0). Therefore we only report the CAC result for the mean Agatston score. First, a logistic regression of CAC on all variables was performed with n= 771 fully observed records. The p-value from the unweighted sum-of-squares goodness-of-fit test was 0.283 (where the null hypothesis is that the model is fit to the data well) could not be rejected, suggesting that the model was fit to the data well. After excluding noncontributory covariates (specifically, E2 and alcohol use were excluded since they have P-values 0.826 and 0.738, respectively), a logistic regression model was refit by using the 9 measures of menopausal symptoms and the history of smoking whose p-value (0.073) was close to 0.05 in the original model. Under the re-fit model, n=822 records, including n=684 zero readings and n=138 nonzero readings for mean Agatston, were fully observed and used for analysis. Of the menopausal symptoms studied, palpitations and depression were the closest predictors of CAC. The p-value of 0.302 from the same goodness-of-fit test suggests that the null hypothesis that the model still fit the data well could not be rejected.

On univariate analyses summarized in Table 2, none of the nine menopausal symptoms were significantly associated with CAC, where the listed values indicate the log of the Odds Ratio and direction of the relationship in predicting CAC by a positive or negative coefficient. Two measures of menopausal symptoms, palpitations and depression, had p-values 0.091 and 0.070, respectively. Smoking history was shown to be strongly associated with CAC (p= 0.006).

For univariate logistic regression of mean Agatston on each of the nine symptoms, only depression approached significance (p=0.098). However, hot flash was significantly related to mean Agatston among women with evidence of calcification (univariate linear regression of mean Agatston (including only subjects with mean Agatston>0 and with log transformation of mean Agatston), p value = 0.047. However, the R-squared for the univariate model with hotflash is only 0.029. All other eight symptoms were not significant.

For univariate linear regression of mean Agatston (including only subjects with Mean Agatston>50) on each of the nine symptoms, hotflash is marginally significant (p=0.054) and sweats is significant (p= 0.043). The R-squared for the two univariate models are 0.104 and 0.115, respectively. All other seven symptoms are not significant. After controlling for the described confounders, an association between menopausal symptoms and CAC was also assessed in the subgroups with the highest disease burden (defined as CAC>0 and CAC>50) using linear regression. The R-squared measures are 0.08 and 0.18 respectively, suggesting that the menopausal symptoms have little value in predicting CAC.

Association between CIMT and Menopausal Symptoms

After excluding records with missing values, data from n=759 subjects were available for analysis. Intraobserver CIMT variability was estimated from 2 pretreatment scans on each patient, which were performed <6 (mean 3.9 ± 4.2) weeks apart. Coefficients of variation (SD/mean) were, on average, <1.0% (0.83 ± 0.98%). The results from the linear regression analysis are summarized in Table 3. The R square measure is a relatively low 0.131, which suggests that the current set of predictive variables is not adequate for modeling CIMT. In addition, the P-values for all the 9 menopausal symptoms and E2 are far larger than 0.05, showing that it is very unlikely that these variables are associated with CIMT.

Years Since Menopause Correlates with CIMT

The results of the correlation tests between years since menopause with atherosclerotic measures, menopausal symptoms and E2 levels are summarized in Table 4. Time since menopause (years) was significantly associated with E2 (CC=−0.084, P=0.015), CIMT (CC=0.075, P=0.029), dyspareunia (CC=0.084, P=0.015), and vaginal dryness (CC=0.151, P=1.0e-5), but not with CAC or other menopausal symptoms.

Discussion

As menopausal symptoms are the driving force for initiation of MHT, it is critical to understand the cardiovascular characteristics of the women who experience them. This will not only help with counseling women about the benefits and risks of MHT, but could also prove to be a valuable clinical tool to identify high risk patients for further evaluation and preventive strategies. However, menopausal symptoms are not statistically significantly correlated with CAC or CIMT, in this population of recently menopausal women screened for the KEEPS trial. The lack of linkage between menopausal symptoms and evidence of heart disease should provide some reassurance to clinicians about the cardiovascular safety of prescribing MHT to recently menopausal women.

Depression has been shown to be associated with clinical heart disease, but association with subclinical, asymptomatic disease is less studied. Other groups have shown that in asymptomatic middle aged women, coronary calcification is associated with recurrent major depression (49) as well as progression of disease (50), but single depressive episodes were not associated with CIMT plaque (51). However, the menopausal status and symptomatology of these women was not well characterized.

In this study, palpitations approached significance in predicting atherosclerosis measures. Although palpitations specifically have not previously been described to correlate with either clinical heart disease or subclinical markers of atherosclerosis, abnormal heart rate turbulence was found to be associated with cardiac mortality risk, and atrial fibrillation is well known to correlate with risk of stroke (52).

Interestingly, vasomotor symptoms of hot flashes and/or night sweats anytime up to enrollment in the estrogen only arm of the WHI were associated with reduced odds for CAC>0 at the conclusion of the study (15), contrasting findings were noted in a Dutch study (16). However, the women enrolled in the WHI had to be asymptomatic in order to be randomized, which represents a significant recruitment bias to study outcomes associated with menopausal symptoms. It will be interesting as KEEPS continues to assess how progression of CAC relates to vasomotor symptoms and if differences in early versus late symptoms will relate to changes in vascular anatomy (17, 53). Most studies have found some positive association of menopausal symptoms with cardiovascular disease (12–17, 54, 55), while only one study showed a reduced risk (15). Given that most of the participants in KEEPS had low CAC scores, we cannot know if the presence and severity of symptoms may relate to advanced CAC, as was likely present in the WHI subjects.

The strengths of this study include the narrow range of time since menopause of women enrolled in KEEPS. In addition, current and recent symptoms are ascertained, which are less subject to recall bias when recalled distantly. Further, the screened population in KEEPS is representative of the general population of recently menopausal women given that CAC measures were undertaken in all who were screened. Specifically, patients were not excluded for or against menopausal symptoms, which could significantly skew the population studied. The strength of these observations with regard to CIMT is that the relationship was defined in a population which was found to have a low CAC burden (<50)

and deemed at low risk for CVD (low risk low density lipoprotein cholesterol, triglycerides, systemic blood pressure and fasting blood glucose levels).

The cross-sectional study design, the relatively low CVD risk profile of the studied population, and the fact that this study was initiated post hoc following completion of the screening process and hence not designed to specifically assess a relations between atherosclerotic measures and self-reported symptoms are recognized as study limitations. Potential reasons why we failed to detect a significant association between common menopausal symptoms and atherosclerotic markers in this population could include that current and recent symptoms were reported by qualitatively assessment; a more specific, prospective, symptom journaling could potentially reveal an association. Since the evaluation of symptoms was retrospectively self-reported on a broad and subjective scale, it is possible that a prospective assessment of palpitations and depression would reach statistical significance as factors in predicting subclinical atherosclerotic disease. An alternative explanation for the negative study with regard to CIMT may be the study design wherein participants with CAC>50 were excluded from undergoing CIMT assessment; a relationship between menopausal symptoms and established atherosclerosis is thus still plausible.

Conclusion

In this cohort of relatively healthy early menopausal women screened for participation in KEEPS, we did not detect an association between self-reported common menopausal symptoms or E2 with CIMT or CAC. Results of this study support previous findings which suggest that symptoms do not predict atherosclerotic burden in early menopause.. The KEEPS cohort will provide an opportunity to further assess whether persistence and severity of menopausal symptoms relate to progression of atherosclerosis and if MHT modulates such a relationship.

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Table 1

Baseline Characteristics of Subjects Screened for the KEEPS Trial

Variable (n=868 women)	Average	Range	SD*
Demographics			
Age of women screened (years)	52.7	42–58	2.6
Weight (kg)	68.8	42–104	11.7
Number of years in menopause	1.4	0.5–3.0	0.7
FSH (ng/ml)	87.6	6.3–194	33.4
E2 (pg/ml)	23.5	2–298	21.9
Drinks per month	11.9	0–122	17.9

	(N)
Marital Status	
Married	538
Never Married	153
Divorced	16
Separated	24
Partner-not married	24
Widowed	105
Race/Ethnicity	
Caucasian/White	671
Black/African American	65
Hispanic	57
Asian/Indian	13
Chinese	9
Philipino	4
Japanese	1
Korean	1
Other Asian	1
Decline to answer	38
Education	
Grade School	4
Some High School	3
High School Diploma or GED	67
Some College/Vocational	172
College Graduate	337
Some Graduate/Professional School	40
Graduate or Professional Degree	228
Declined to Answer	17
Employment Status	
Disabled	572
Employed full-time	130
Homemaker	66

	(N)
Employed part-time	35
Not working	28
Retired	21
Not answered	16
Hypertension	
Yes	75
No	784

Variable (n=868 women)	Average	Range	SD*
Baseline Atherosclerosis Measurements			
CIMT (mm)	0.721	0.532–1.168	0.1
Mean Agatston score	9.3	0–1091	54.3
Mean Agatston Vol	8.2	0–720.750	41.9
Baseline Menopausal Symptom Scores			
Depression score	0.483	0–3	
Insomnia score	1.096	0–3	
Irritability score	0.793	0–3	
Dyspareunia score	0.915	0–4	
Hot flashes score	1.362	0–3	
Mood swings score	0.764	0–3	
Night sweats score	1.096	0–3	
Palpitations score	0.349	0–3	
Vaginal dryness score	0.933	0–3	

Table 2

In a Logistic Regression Model, Menopausal Symptoms Do Not Predict CAC Scores

Variable (n=822)	Coefficient Estimate*	Std. Error	P
Hot flashes	−0.032	0.145	0.825
Dyspareunia	0.030	0.073	0.684
Vaginal dryness	0.008	0.108	0.944
Night sweats	−0.019	0.128	0.884
Palpitations	−0.298	0.176	0.091
Mood swings	0.126	0.189	0.505
Depression	0.280	0.155	0.070
Insomnia	0.044	0.113	0.696
Irritability	−0.244	0.188	0.194

* Log of Odd Ratio

Table 3

In a Linear Regression Model, Menopausal Symptoms Do Not Predict CIMT Measurements

Variable (n=759)	Coefficient Estimate*	Std. Error	P
HOTFLASH	0.004	0.005	0.419
DYSP	−0.002	0.003	0.392
VAGDRY	−0.003	0.004	0.393
SWEATS	0.002	0.005	0.691
PALPIT	−0.001	0.006	0.817
MOODSW	−1.2E-04	0.007	0.985
DEPR	−0.003	0.006	0.58
INSOM	−0.001	0.004	0.861
IRRIT	0.002	0.007	0.806
E2	−7.0E-06	1.7E-04	0.967

* Log of Odd Ratio

Table 4

Correlation of Menopausal Symptoms, Estradiol and Atherosclerosis Measures with Time Since Menopause

Variable	Correlation coefficient (CC)	P
Hot flashes	0.016	0.651
Dyspareunia	0.084	0.015
Vaginal dryness	0.151	1.0e-5
Night sweats	−0.059	0.090
Palpitations	0.031	0.365
Mood swings	−0.032	0.357
Depression	0.051	0.142
Insomnia	0.019	0.595
Irritability	−0.031	0.373
Mean Agatston	− 0.006	0.857
Mean Agatston Vol	−0.006	0.857
CIMT	0.075	0.029
E2	−0.084	0.015