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Research Article

Prognostic Factors Associating with Arterial Stiffness in Menopausal Women: A Cohort Study

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Keywords: Pulse wave velocity; Arterial stiffness; Menopause

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Abstract

Background: Menopause is associated with increased arterial stiffness, which in turn is linked to cardiovascular risk. The objective of this study was to conduct a longitudinal assessment of arterial stiffness in pre- and post-menopausal women.

Methods: Arterial stiffness was assessed in 460 out of 823 eligible subjects (362 males were excluded, and 1 woman did not mention her menopausal status at baseline). The sample was divided into pre-menopausal (n = 277) and post-menopausal women (n =183). Pulse wave velocity (PWV) was used as an indicator of arterial stiffness. Anthropometric variables, biochemical markers, and the prevalence of clinical features were also evaluated.

Results: The mean age, fasting blood glucose (FBG), systolic blood pressure, total cholesterol, LDL, and PWV were significantly higher in menopausal women, while other clinical characteristics did not show significant differences. The prevalence of diabetes mellitus, hypertension, metabolic syndrome, and dyslipidemia was also significantly higher in menopausal women. Additionally, post-menopausal women had a 3.723 times greater risk of a PWV >10 m/s after adjusting for confounding factors such as age, smoking, obesity, dyslipidemia, diabetes mellitus, hypertension, and metabolic syndrome compared to pre-menopausal women.

Conclusion: Post-menopausal women recruited for the MASHAD study exhibited significantly higher arterial stiffness compared to pre-menopausal women. Further longitudinal studies are necessary to assess the impact of menopause-related arterial stiffness on cardiovascular disease risk in menopausal women.

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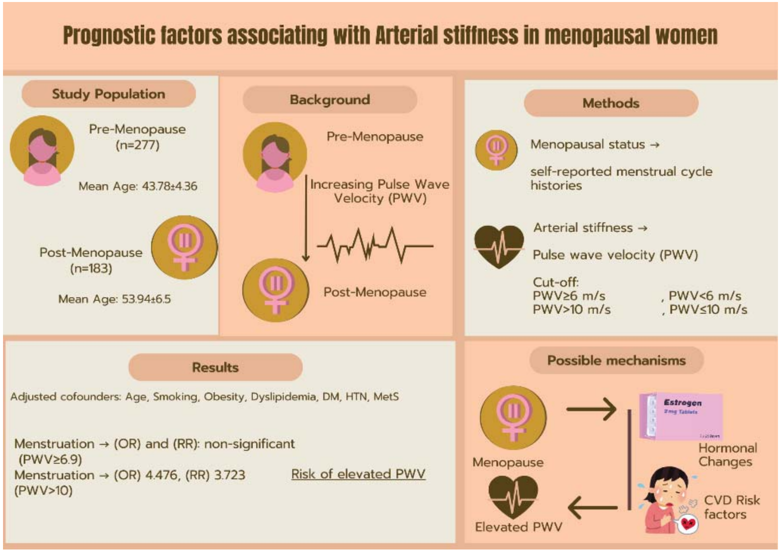

Graphical abstract.

Introduction

Menopause is associated with various complaints such as hot flushes, night sweats, and sleep disorders [1]. Additionally, menopausal women are more susceptible to higher cardiovascular (CV) morbidity and disease, which is the leading cause of death in menopausal women [2]. Natural or surgical menopause results in a lack of the sex steroid estradiol (E2), increasing the risk of CV disease. Menopause significantly impacts a woman's quality of life and long-term health [3,4]. Increased arterial stiffness, an early clinical sign of vascular ageing, predicts future CV disease [5]. Arterial stiffness refers to the reduced ability of arteries to respond to pulse wave energy, affecting aortic pulse wave velocity (PWV) [5]. PWV describes the speed of a pulse wave in the vasculature and is considered an indicator of increased arterial stiffness [4]. Several studies have explored the association between menopause and increased arterial stiffness [4,6]. PWV is lower in women than in men until age 60, after which it becomes similar in both genders, suggesting menopause may play a role in arterial stiffness [7,8]. Additionally, the incidence of known CV risk factors such as hyperlipidemia and hypertension increases in post-menopausal women [2]. This study aims to investigate the association between menopausal status and arterial stiffness assessed using PWV, as well as compare women before and after menopause for other CVD risk factors.

Methods

Participants, sample collection and variables

The individuals recruited for this study were derived from the Mashhad Stroke and Heart Atherosclerotic Disorder (MASHAD) cohort study. Study subjects were recruited between 2007 and 2010 and followed up for ten years. The research Ethics Committee of Mashhad University of Medical Science (Approval Number IR. MUMS.MEDICAL. REC.1398.228) and the Institutional Review Board of Mashhad University Medical Center approved the study. Furthermore, the ethical guidelines of the Helsinki Study were strictly followed in all phases of the study, including maintaining the confidentiality of patient information and obtaining consent for anonymous publication of the research findings. Written informed consent was obtained from all participants. The study was conducted in two steps. In step I, data were collected from participants with and without a history of CVD. In step II, prevalent cases of CAD, stroke, and peripheral arterial disease were excluded, and healthy individuals were followed for the incidence rates of these disorders [9]. Among 9704 health screening participants from the phase I MASHAD cohort study, 7561 completed the study (phase II). Due to grant limitations, 1000 participants were randomly invited to participate, of whom 823 were eligible (meeting criteria like no coffee or sexual activity in the last 24 hours) for assessing arterial stiffness. The female number was 461, of whom 1 was excluded due to incomplete clinical information. A diagram of the subjects' recruitment is shown in Figure 1. The participants were divided into two groups based on menopause at baseline: women pre-menopause (n = 277) and post-menopause (n = 183). Menopausal status was classified based on self-reported menstrual history. Detailed differentiation between natural and surgical menopause was not available in all cases. Pre-menopausal women were identified as having had no change in menstrual cycle regularity over the past three menstrual periods of the recent 12 months (based on their self-report, they did not take estrogen supplementation therapy), while post-menopausal women were defined as not having had a menstrual period in the past 12 months. Weight was measured using a digital scale, and body mass index (BMI) was calculated as weight (Kg) divided by height (m^2). Blood samples were collected for serum concentrations of cholesterol, triglyceride, HDL, LDL, and fasting blood glucose (FBG) after an overnight fast. Arterial stiffness was assessed using a SphygmoCor XCEL System to measure carotid-femoral pulse wave velocity (PWV), Central Augmentation Index (CAI), Cardio-ankle vascular index (CAVI), and Central Aortic Pressure (CAP). Before the investigations, participants were instructed to avoid smoking, alcohol, or caffeine for at least 12 hours and fast for at least 6 hours. After 10-15 minutes of relaxation in

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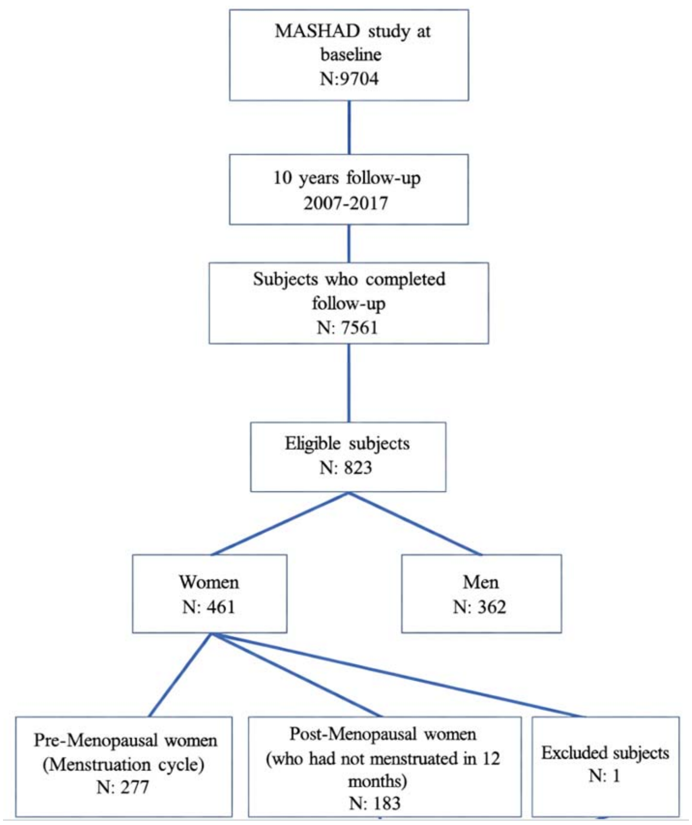

Figure 1: Diagram of subject's recruitment in this study.

the supine posture, the test was conducted non-invasively in two steps [10]. PWV was categorized according to the median of the data to PWV≥6 m/s and based on other studies to PWV>10 m/s [11].

Statistical analysis

Data was presented as mean and standard deviation for quantitative variables, and number and percentage for Qualitative variables. Independent sample t-test and chi-square test were applied to compare the mean of quantitative variables and the number and percentage of qualitative variables, respectively. Although the data were derived from a longitudinal cohort, the present analysis primarily reflects the association between baseline menopausal status and PWV measured at follow-up. Logistic regression was used to estimate odds ratios, and Cox regression was applied to account for time-to-event data over the 10-year follow-up period. All analyses were conducted using SPSS software version 21 at a significant level of 0.05.

Results

There were 460 eligible women divided into pre- and post-menopausal groups. Arterial stiffness was investigated using PWV as a marker. The clinical and biological characteristics of the subjects analyzed in this study are compared and described in Table 1. Results showed that the mean age, FBG, systolic blood pressure, total cholesterol, LDL, and PWV were significantly higher in menopausal females. However, the groups did not differ in other clinical characteristics, including diastolic blood pressure (DBP) and smoking. Serum levels of triglyceride and HDL-cholesterol did not differ significantly between the two groups. The prevalence of clinical features in women before and after menopause is shown in Figure 2. According to the results, the prevalence of diabetes mellitus, hypertension, metabolic syndrome, PWV ≥ 6.9 m/s (median of PWV), and PWV > 10 m/s (other studies) was significantly higher in menopausal women. However, the prevalence of obesity, depression, anxiety, and dyslipidemia did not have significant differences between the two groups.

Table 2 showed the association between menopause status at baseline and PWV≥6.9 m/s (median) and PWV>10 m/s. Based on model 1 (unadjusted model), logistic and Cox regression models showed that menopause has an indirect association with increasing PWV (≥6.9 and >10 m/s) after 10 years of follow-up. After adjustment for confounding factors, the association between menopause and PWV ≥ median (6.9 m/s) was no longer statistically significant. However, the association with PWV >10 m/s remained significant (adjusted RR 3.723; 95% CI 1.391 - 9.963), indicating a stronger relationship with clinically elevated arterial stiffness.

Table 1: Anthropometric variables and biochemical markers in women based on menopause (n: 460).

	Menopausal status		
	pre (n=277)	post (n=183)	p-value
Age, y	43.78 ± 4.36	53.94±6.5	<0.001
BMI, kg/m^2	30.11 ± 4.72	29.32 ± 4.89	0.36
SBP, mmHg	132.85 ± 18.24	144.51 ± 19.18	<0.001
DBP, mmHg	82.39 ± 11.37	83.34 ± 13.08	0.44
Smoking, %	15 (17%)	52 (13.1%)	0.32
FBG, mg/dl	89.13±41.67	103.42±53.24	<0.001
Serum Cholesterol, mg/dl	189.82±41.12	204.02±46.33	<0.001
Serum Triglyceride, mg/dl	136.06±103.51	145.38±81.69	0.25
Serum HDL, mg/dl	44.48±10.49	46.81±13.64	0.082
Serum LDL, mg/dl	107.91±33.64	122.24±39.07	<0.001
PWV, m/s	6.55±2.06	7.34±2.37	<0.001

Data presented as mean ± SD; Sample t-test has been done
BMI: Body mass index; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; FBG: Fasting blood glucose; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; PWV: Pulse Wave Velocity

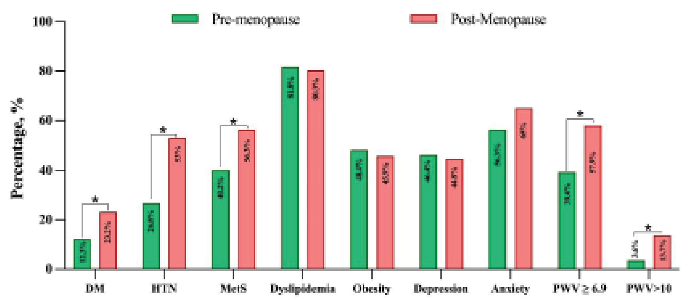

Figure 2: Prevalence of clinical features based on menopause. Data presented as numbers and percentages; a chi-square test has been done.DM: Diabetes Mellitus; HTN: Hypertension; MetS: Metabolic syndrome.

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Table 2: Association between menopause and median PWV and its new cut-off value

	OR (95% CI)	*p*-value	RR (95% CI)	*p*-value
Model 1				
PWV<6.9 m/s: Ref				
PWV≥6.9 m/s (median)	2.122 (1.451-3.102)	<0.001	1.472 (1.127-1.923)	0.005
PWV≤10 m/s: Ref				
PWV>10 m/s	4.225 (1.977-9.027)	<0.001	3.784 (1.818-7.879)	<0.001
Model 2				
PWV<6.9 m/s: Ref				
PWV≥6.9 m/s (median)	1.09 (0.631-1.882)	0.75	1.030 (0.705-1.504)	0.87
PWV≤10 m/s: Ref				
PWV>10 m/s	4.476 (1.575-12.724)	<0.001	3.723 (1.391-9.963)	0.009

OR: odds ratio and reported by logistic regression
RR: relative risk and reported by Cox regression
Model 1: unadjusted; model2: adjusted for age and atherosclerotic risk factors (age, smoking, obesity, dyslipidemia, diabetes mellitus, hypertension, metabolic syndrome)

Discussion

The main finding of the study was that stiffening of large arteries is associated with menopause independently of several other CVD risk factors. Menopause has been consistently associated with increased cardiovascular risk and vascular ageing [11,12]. Due to the diversity of risk factors promoting CV diseases, it cannot be accurately estimated [13]. Our findings align with prior observational studies demonstrating increased arterial stiffness in post-menopausal women [14]. Additionally, it found that some other atherosclerotic risk factors may increase after menopause. However, there is no significant difference in PWV between natural and surgical menopausal groups [15]. In another study, Xia, et al. indicated that age at menopause was independently associated with the thickening and stiffening of large arteries. They also showed that hormone therapy in menopausal women leads to a reduction of PWV [15]. In the present study, we showed that in the menopausal woman, only 49.9% of the cases had PWV< 6.9 m/s, while 70.8% of premenopausal women had a median PWV less than 6.9 m/s (p < 0.001). After adjustment for age and atherosclerotic risk factors, the association between menopause and elevated PWV ≥6.9 m/s was no longer statistically significant. However, the association with clinically elevated PWV (>10 m/s) remained significant. Importantly, menopause was independently associated with clinically elevated PWV (>10 m/s), whereas the association with median-based PWV lost significance after adjustment, suggesting that menopause may have a stronger relationship with advanced arterial stiffening rather than moderate PWV elevation. Several studies have found the increased incidence of known CVD risk factors, including dyslipidemia, hypertension, and diabetes, after menopause. They are associated with coronary artery disease and myocardial infarction and may cause death [16,17]. A meta-analysis by Pu, et al. demonstrated that menopausal women have significant alterations in all indicators of MetS compared to a premenopausal group. In addition, they showed that surgical menopause may lead to a higher incidence of MetS compared to natural menopause [18]. Another study by Figueiredo Neto, et al. reported that the prevalence of hypertension was significantly higher in menopausal women than in the premenopausal group (p = 0.001). Moreover, they suggested that MetS was more prevalent among menopausal women than the premenopausal group. However, menopause was not an independent risk factor for MetS, while age was the leading independent risk factor for the occurrence of MetS [18]. Tandon, et al. also screened 5000 menopausal women and reported that the prevalence of hypertension, dyslipidemia, diabetes, and metabolic syndrome was 56%, 39%, 21%, and 13%, respectively [19]. We showed that the prevalence of hypertension, dyslipidemia, diabetes mellitus, and metabolic syndrome was 66%, 87.7%, 40.8%, and 65.7%, respectively. These are significantly higher in menopausal women than in premenopausal women. The results of the present study confirmed similar studies in terms of the influence of menopause on increasing the stiffness of arteries. In addition, similar to other investigations, we found that some other atherosclerotic risk factors may increase after menopause.

A limitation of the study was the small sample sizes of menopausal women compared to premenopausal women. Participants self-reported the duration of menopause, which may not be accurate. Other intrinsic factors affecting arterial stiffness in menopausal women could not be ruled out. Surgical and natural menopausal women were put in the same group, despite differences in CV risk factors. The assessment of the markers in this study occurred only once, but we can perform follow-up measurements in a longitudinal timeline. Another limitation of the study was that some subjects reported using Strogen themselves (self-report), and we did not adjust the data for the uric acid levels. The other important limitation was that we were unable to separately analyze natural and surgical menopause, which may differ in cardiovascular risk profiles. In addition, detailed data regarding hormone replacement therapy were limited, and its potential impact on arterial stiffness could not be fully evaluated.

Conclusion

In conclusion, the study results revealed that menopause may be independently associated with higher arterial stiffness. Additionally, the prevalence of other CV risk factors, including hypertension, dyslipidemia, diabetes, and metabolic syndrome, was significantly higher in menopausal women. The high level of all these risk factors in menopausal women could be a critical reason for the high rate of cardiovascular diseases in women.

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Declarations

Ethical approval and consent to participate: this project is supported by Mashhad University of Medical Sciences. Funding number: 970117 and ethical approval code: IR.MUMS.MEDICAL.REC.1398.228. All individuals were well-informed, and their written consent was obtained.

Consent for publication: It does not apply to the Consent for Image Publication for this manuscript. The figures were designed only for this manuscript to present the results of the current paper.

Availability of data and materials: The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests: The Authors declare that there is no conflict of interest.

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Authors' contributions

Susan Darroudi, Ala Orafaei, Reza Assaran Darban (wrote manuscript)

Reihaneh Alizadeh, Reihaneh Aryan, Hussein Ahmed Shamkhi Alnayyef (data gathering)

Susan Darroudi, Habibollah Esmaeili (Data analysis and study design)

Gordon A. Ferns (scientific and grammatical editing)

Abbas Abdollahi, Majid Ghayour-Mobarhan (study design)

Mohsen Moohebati, Maryam Saberi-Karimian (corresponding author, designed the study)

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