

Original Article**Premature menopause and severity of coronary artery disease**

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Abstract

BACKGROUND: Relationship between premature menopause and presence, severity and life-threatening events of coronary artery disease (CAD) has been suggested in recent observations. The present study tried to assess relationship between age of menopause and severity of CAD in a sample of women with suspected CAD.

METHODS: In a cross-sectional study, we included 189 consecutive women with suspected CAD that were candidate for coronary angiography and admitted to the Shafa hospital in Kerman city. Our final population for analysis included women who underwent natural menopause (n = 148) or premature menopause (n = 41). CAD severity was classified according to the number of coronary artery stenosis $\geq 50\%$ in coronary angiography.

RESULTS: Among 189 study patients with suspected CAD, 22.0% of those with early menopause and 23.6% of those with normal menopause suffered three coronary vessels involvement, while normal angiography features was shown in 39.0% and 40.5%, respectively. Regarding severity of CAD and left main lesions, no significant differences were found between the patients with and without premature menopause. According to the multivariable logistic regression model and with the presence of other patients' variables as cofounders, age of menopause could not predict the presence and severity of CAD in patients with suspected CAD. However, patients' age (OR: 1.11, $p < 0.001$) and family history of CAD (OR: 2.05, $p = 0.04$) were main predictors of the severity of CAD in these patients.

CONCLUSIONS: Premature menopause does not predict occurrence or severity of CAD in women with suspected CAD, but women age and their family history of CAD are main predictors of the severity of CAD.

KEYWORDS: Coronary Artery Disease, Risk Factor, Age, Menopause, Premature Menopause.

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The use of exogenous estrogen has been hypothesized to be associated with reducing the risk of coronary artery disease (CAD) during postmenopausal period.¹ It has been also demonstrated that the surgical menopause in younger individuals results in the increase of CAD risk if hormone therapy is not taken.² Although relationship between premature menopause and presence, severity, and even life-threatening events of cardiovascular disease has been suggested, a few studies focused on demonstrating the relationship of a

broad range of ages at menopause with risk of CAD. In a study by van der Schouw and his colleagues,³ the rate of cardiovascular mortality was not significantly associated with later age at natural menopause. This non-significant association was also observed in similar studies.^{4, 5} Contrarily, McVay et al.⁶ observed an overall significant association between risk of CAD and younger age at menopause among women who experienced natural menopause and never used hormone therapy. It seems that the obtained results were strongly influenced

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by some study limitations such as effects of other important cofounders such as smoking or inappropriate age cut-off points.^{6,7}

Hence, the present study tried to assess relationship between age of menopause and severity of CAD with the presence of other affecting factors in a sample of women with suspected CAD.

Methods

In a cross-sectional study, we included 189 consecutive women with suspected CAD that were candidate for coronary angiography and admitted to the Shafa hospital in Kerman city between February 2009 and September 2010. Early diagnosis was based on clinical evidences and non-invasive tests, including typical chest pain, increase in serum creatine kinase (CK) level, and diagnostic specific changes in ECG.⁸ We excluded women who reported having a previous history of coronary heart disease (CHD) or underwent coronary interventions at baseline. On the questionnaires filled by the trained practitioners, menopausal status was determined by asking whether the participants' menstrual periods had ceased permanently and, if so, at what age and for what reason (occurring naturally or after radiation treatment or surgery). Our final population for analysis included women who underwent natural menopause (n = 148) or premature menopause (n = 41) and never received hormone therapy or had previous history of hysterectomy. Premature menopause was defined as cessation of menses before age 40 years.⁹ The study was approved by the ethics committee of the Kerman University of Medical Sciences and informed consent was obtained from all patients.

Demographic characteristics and clinical information of these patients were extracted from hospital recorded files as well as face to face interviewing if required and entered into a computerized database form. Information on other potential CHD risk factors were assessed including participants' age, smoking, weight, drug history within two months before admis-

sion, and history of diabetes (symptoms of diabetes plus at least one of the following conditions: plasma glucose concentration ≥ 11.1 mmol/l, fasting plasma glucose ≥ 7.0 mmol/l or 2-hpp ≥ 11.1 mmol/l),¹⁰ hypertension (systolic blood pressure ≥ 140 mmHg and/or diastolic ≥ 90 mmHg and/or on antihypertensive treatment)¹¹, hypercholesterolemia (total cholesterol ≥ 5.0 mmol/l, HDL-cholesterol ≥ 1.0 mmol/l in men, or ≥ 1.1 mmol/l in women, and triglycerides ≥ 2.0 mmol/l),¹² and opium addiction (regularly consumption of opium by inhalation more than three times per week and/or daily oral opium defined based on the DSM-IV Criteria for Substance Dependence).¹³ Patients underwent two-dimensional echocardiography for assessing left ventricular ejection fraction and ruling out other structural abnormalities as well as coronary angiography for determining presence and severity of CAD. All coronary angiography procedures were performed by the femoral approach using the standard Judikin's technique¹⁴ and the coronary angiograms were analyzed by a cardiologist. The lesion in the left main coronary artery (LM), left anterior descending coronary artery (LAD), left circumflex coronary artery (LCX) and right coronary artery (RCA) were recorded, the 1-vessel disease, 2-vessel disease and 3-vessel disease was classified according to the number of coronary artery stenosis $\geq 50\%$.

Results were reported as mean \pm standard deviation (SD) for the quantitative variables and percentages for the categorical variables. Variables between the two subgroups were compared using the chi-square test for categorical variables and the student-t test or Mann Whitney U test for the continuous variables. Multivariate logistic regression analysis was used to investigate association between age of menopause and presence of CAD while the model was adjusted for baseline data as cofounders. P-values of 0.05 or less were considered statistically significant. All the statistical analyses were performed using SPSS version 13.0 (SPSS Inc., Chicago, IL, USA) for Windows.

Results

There were no significant differences between the two study groups with premature and normal menopause in terms of mean age (58.61 ± 7.27 versus 60.26 ± 7.06 , $p = 0.20$) as well as mean weight (64.49 ± 15.08 versus 63.79 ± 10.20 , $p = 0.78$). Among general risk factors for coronary artery disease (Table 1), except for opium addiction that was more prevalent in the group with early menopause, overall prevalence of other risk factors was similar between two groups. Furthermore, cardiovascular-related drugs were similarly administered in the two groups. The mean of left ventricular ejection fraction was significantly higher in the patients with premature menopause (57.50 ± 5.24 versus 49.33 ± 11.21 , $p = 0.01$). The number of parity in the patients with and without early menopause was similar (7.43 ± 2.92 versus 7.55 ± 2.65 , $p = 0.80$). No significant difference was also observed in the

number of babies between them (6.15 ± 2.24 versus 6.44 ± 2.22 , $p = 0.47$).

Among study patients with suspected CAD, 22.0% of those with early menopause and 23.6% of those with normal menopause suffered three coronary vessels involvement, while normal angiography features was found in 39.0% and 40.5%, respectively (Table 2). Regarding severity of CAD and left main lesions, no significant differences were found between the patients with and without premature menopause (Table 2).

According to the multivariable logistic regression model (Table 3) and with the presence of other patients' variables as cofounders, age of the menopause could not predict the presence and severity of CAD in patients with suspected CAD. Among other factors, patients' age (OR: 1.11, $p < 0.001$) and family history of CAD (OR: 2.05, $p = 0.04$) were the main predictors of the severity of CAD in this study.

Table 1. Baseline characteristics and clinical data of the study subjects

Characteristics	Menopause age \leq 45 years (n = 41)	Menopause age $>$ 45 years (n = 148)	p-value **
Risk factors:			
Systolic hypertension *	29 (70.7)	95 (64.2)	0.43
Diabetes mellitus †	17 (41.5)	54 (36.5)	0.56
Hyperlipidemia ‡	30 (73.2)	97 (65.5)	0.35
Cigarette smoking	4 (9.8)	8 (5.4)	0.31
Opium addiction	9 (22.0)	15 (10.1)	0.04
Family history of CAD	17(41.5)	55 (37.2)	0.61
Oral medication:			
Aspirin	30 (73.2)	106 (71.6)	0.84
Clopidogrel	10 (24.4)	40 (27.0)	0.73
Statin	30 (73.2)	89 (60.1)	0.12
ACE ‡‡:inhibitors	22 (53.7)	85 (57.4)	0.66
Nitrates	36 (87.8)	127 (85.8)	0.74
Beta-blockers	27 (65.9)	98 (66.2)	0.96

The results are expressed as n (%)

* Systolic blood pressure \geq 140 mmHg and/or diastolic \geq 90 mmHg and/or on antihypertensive treatment¹⁰

† Symptoms of diabetes plus at least one of the following conditions: plasma glucose concentration \geq 11.1 mmol/l, fasting plasma glucose \geq 7.0 mmol/l, and 2-hpp \geq 11.1 mmol/l⁹

‡ Total cholesterol \geq 5.0 mmol/l, HDL-cholesterol \geq 1.0 mmol/l in men, or \geq 1.1 mmol/l in women, and triglycerides \geq 2.0 mmol/l¹¹

‡‡ angiotensin-converting enzyme

** Data were compared using the chi-square test

Table 2. Severity of coronary artery disease according to the angiography features

Characteristics	Menopause age \leq 45 years (n = 41)	Menopause age $>$ 45 years (n = 148)	p-value**
Coronary artery disease			
None	16 (39.0)	60 (40.5)	
One-vessel disease	9 (22.0)	20 (13.5)	0.58
Two-vessel disease	7 (17.1)	33 (22.3)	
Three-vessel disease	9 (22.0)	35 (23.6)	
Left main lesions	1 (2.4)	3 (2.0)	0.99

The results are expressed as n (%)

** Data were compared using the chi-square test

Discussion

In general, no significant association was found in this study between the appearance of early menopause and severity of CAD among women who had natural or earlier menopause and never used hormone therapy. We even hypothesized that the relation between premature menopause and CAD severity might be influenced by some potential confounders such as current smoking or opium use, however, this relationship was not proved using multi-variable models when it was adjusted for confounding factors. Recently, it has been proposed that the early menopause can be directly associated with higher risk of angina after myocardial infarction, independent of other co-morbidities, and even severity of infarction.¹⁵

The largest previous study was conducted by van der Schouw et al.³ who examined the relation of age at menopause with total cardiovascular mortality. There was a significant increased risk with decreased age at menopause for each 1-year, but this inverse association was not statistically significant among women with natural menopause. They found that the inverse association was limited to non-current smokers, but they did not examine the association specifically among never smokers.

PRECADIW study revealed that besides smoking, parental history of premature CVD, diabetes, menopause and hypertension that were the strongest risk markers for premature CAD, early menopause was the most important determinant of premature CAD in a model

Table 3. Multivariable analysis of the role of age of menopause for predicting presence and severity of CAD

Variables	Multivariate p-value	Odds Ratio*	95% Confidence Interval
Age of menopause \leq 45 yrs	0.829	0.913	0.397 – 2.097
Advanced age ($>$ 60 yrs)	$<$ 0.001	1.114	1.056 – 1.175
Weight ($>$ 70 kg)	0.324	0.981	0.943 – 1.020
Height ($<$ 170 cm)	0.869	0.994	0.925 – 1.068
Systolic hypertension	0.125	1.745	0.857 – 3.551
Diabetes mellitus	0.108	1.778	0.881 – 3.590
Hyperlipidemia	0.575	1.229	0.597 – 2.528
Cigarette smoking	0.487	0.574	0.120 – 2.742
Opium addiction	0.225	1.956	0.662 – 5.783
Family history of CAD	0.047	2.055	1.009 – 4.185

* Analysis was performed using the multivariable logistic regression model

including the early and late stages of menopause.¹⁶ Thus, according to our result, age of menopause does not induce extension of infarction in affected patients, but based on similar researches, early menopause might be a trigger for angina after myocardial infarction or even induced severe CAD that needs further evaluation.

As shown in previous studies,¹⁶⁻¹⁹ both cigarette smoking and opium addiction are power-

ful risk factors for CAD. In our study, current smoking decreased the age of natural menopause by about 1.5 years and opium addiction decreased it by 2.5 year. Thus, incomplete adjustment for smoking or opium addiction in some other studies might have artificially increased the risk of CAD associated with early age of natural menopause. Hence, it is better to reconsider evaluation of this association among never smokers or opium users.

Conflict of Interests

Authors have no conflict of interests.

Authors' Contributions

HN drafted the manuscript, MSh conducted the statistical analysis, YM collected samples and performed the study and this manuscript was derived from his thesis and, AF participated in the study.

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