

Original Article

Early menopause for prognosis of coronary artery disease in women: a prospective study

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Abstract: Objective: To examine the characteristics of coronary artery disease (CAD) in early menopausal women and their correlation with clinical outcomes of CAD in the population, and to provide evidence for effective strategies for CAD prevention and treatment. Methods: A prospective cohort study with 1,875 CAD women undergoing coronary angiography in Cangzhou Central Hospital, Hebei Medical University was conducted from January 2011 to December 2013. The patients were assigned to the early menopause group or the control group. Clinical data were collected from all the patients, and then the general data, the number of diseased arteries and the Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery (SYNTAX) scores of the patients were compared between the two groups. All the patients were followed for 3 years. During the follow-ups, the rates of major adverse cardiac events and echocardiographic indicators at the last follow-up were compared between the two groups. The Logistics regression analysis was performed to assess the correlation between early menopause and the major adverse cardiac events. Results: Significant differences in hypertension, diabetes, hyperglycaemia, smoking, the lipid and glucose levels were noted between the two groups (all $P < 0.05$). Most patients in the early menopause group had three-vessel CAD whereas most in the control group had one-vessel CAD. The SYNTAX scores and the rates of major adverse cardiac events increased considerably among the patients in the early menopause groups as compared with those in the control group (all $P < 0.05$). The echocardiographic measurements did not differ substantially between the two groups (all $P > 0.05$). In addition, in the logistic regression analysis, early menopause and three-vessel CAD were associated with the rates of major adverse cardiac events in CAD women. Conclusion: Early menopause is an independent risk factor for major adverse cardiac events in CAD women, so more attention should be paid to its early prevention and treatment.

Keywords: Early menopause, coronary artery disease, female, prognosis

Introduction

Coronary artery disease (CAD) is one of the most common cardiovascular diseases that seriously threaten human health. Most previous studies have focused on men or elderly patients [1, 2]. Few studies have reported CAD in women, the understanding and recognition of CAD in perimenopausal women, in particular. Inadequate importance has been put on angina or myocardial infarction in perimenopausal women whom are not treated as actively as male CAD patients. CAD women have shown to have higher mortality and poorer prognosis [3].

Some studies have demonstrated that there is an association of menopause at an early age with the risk of CAD [4]. The probability of recur-

rent angina increased substantially in women with early menopause, compared with that of normal menopausal women [5]. Early menopause is an independent risk factor for CAD [6, 7]. Therefore, it is urgent to explore effective protocols for the management of women with CAD in the perimenopausal period. The purpose of the present study was to clarify the characteristics of coronary artery lesions and the prognosis in CAD women with early menopause and provide more data in support of its early prevention strategies.

Materials and methods

Participants

This study was in line with the ethical criteria of the Cangzhou Central Hospital, Hebei Medical

Early menopause for women's disease prognosis

Table 1. Demographic and clinical characteristics

Characteristic	Early menopause (n=368)	Control (n=1,507)	P value
Age mean \pm sd (years)	62.3 \pm 8.6	61.6 \pm 9.2	0.185
Menopause type (n, %)			<0.001
Natural	55 (14.9)	1,336 (88.7)	
Hysterectomy	188 (51.1)	109 (7.2)	
Oophorectomy	125 (34.0)	62 (4.1)	
Hypertension (n, %)	132 (35.9)	434 (28.8)	0.008
Diabetes (n, %)	133 (36.1)	441 (29.3)	0.010
Hyperlipidemia (n, %)	152 (41.3)	510 (33.8)	0.007
Family history of CAD (n, %)	60 (16.3)	272 (18.0)	0.432
Smoking status (n, %)			0.031
Current	63 (17.1)	354 (23.5)	
Former	69 (18.8)	262 (17.4)	
Never	236 (64.1)	891 (59.1)	
Fasting glucose (mg/dL)	124.3 \pm 17.3	121.6 \pm 16.8	0.006
HbA1c (%)	6.6 \pm 1.8	6.3 \pm 1.9	0.006
TC (mg/dL)	238.7 \pm 19.2	233.1 \pm 17.6	<0.001
LDL (mg/dL)	129.9 \pm 17.3	125.7 \pm 18.7	<0.001
HDL (mg/dL)	52.9 \pm 9.6	54.0 \pm 10.2	0.061
TG (mg/dL)	120.1 \pm 23.4	114.8 \pm 24.6	<0.001
BMI (kg/m ²)	25.7 \pm 2.6	23.2 \pm 1.9	<0.001

Note: SD, standard deviation; CAD, coronary artery disease; TC, cholesterol; LDL, low density lipoprotein; HDL, high density lipoprotein; TG, Triglyceride; BMI, body mass index.

Study methods

Demographics of all the patients including age, early menopause type, hypertension, diabetes, hyperlipidemia, a family history of CAD, a smoking history, fasting blood glucose, glycosylated hemoglobin, cholesterol (TC), triglyceride (TG), high density lipoprotein (HDL), low density lipoprotein (LDL), body mass index (BMI) were collected and documented. The biochemical indicators were obtained by drawing and measuring some fasting blood from the elbow of patients with the use of an automatic biochemical analyzer.

Coronary angiography was performed on all female patients with the use of the Siemens digital flat-panel angiography (US) by the Judkin method (interventional radiology); the severity of coronary artery stenosis was assessed according to estimated visual diameter.

University, and approved by the ethical reviewers. All the participants signed written informed consent. A prospective analysis was made on 1,875 CAD women (40-75 years of age) undergoing coronary angiography from January 2011 to December 2013 in our hospital. Early menopause is considered as menopause which occurs in women younger than 45 years of age as a result of surgery or natural reason. The patients were assigned to the early menopause group or the control group based on the presence or absence of early menopause. Of the enrolled patients, 368 were assigned to the early menopause group (mean, 62.3 \pm 8.6 years), whereas 1,507 were assigned to the control group (mean, 61.6 \pm 9.2 years). The CAD women older than 40 years of age were eligible for inclusion in this study if their left main, anterior descending, circumflex artery or any right coronary artery had a stenosis of 50% or more as show in angiography. Any patient who had severe hepatic or renal dysfunction, hematological disease, tumor, the immune disorder or severe complications during coronary angiography was excluded from the study.

The diseased coronary arteries were calculated by two senior angiographers based on the coronary angiography images. The anterior descending, circumflex artery and right coronary artery were calculated as one vessel, respectively. One-vessel CAD was involved in the anterior descending, circumflex artery or any one right coronary artery; two-vessel CAD was involved in two vessels or the left main coronary artery and three-vessel CAD was involved in three coronary arteries. The coronary artery lesions were assessed according to the Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery (SYNTAX) score, which reflects a comprehensive angiographic assessment of the coronary vasculature.

All the patients made clinical preventative visits or telephone calls every 3 months for three years. The primary outcome of follow-up was major adverse cardiac events, including cardiac death, new myocardial infarction and coronary revascularization.

At the last follow-up, all the patients were examined with the use of echocardiography, and the

Early menopause for women's disease prognosis

Table 2. Coronary artery lesions of patients in the two groups

Group	Coronary artery lesions		
	One-vessel	Two-vessel	Three-vessel
Early menopause	84 (22.8%)	88 (23.9%)	196 (53.3%)
Control	645 (42.8%)	318 (21.1%)	544 (36.1%)
χ^2 value	16.782		
P value	0.000		

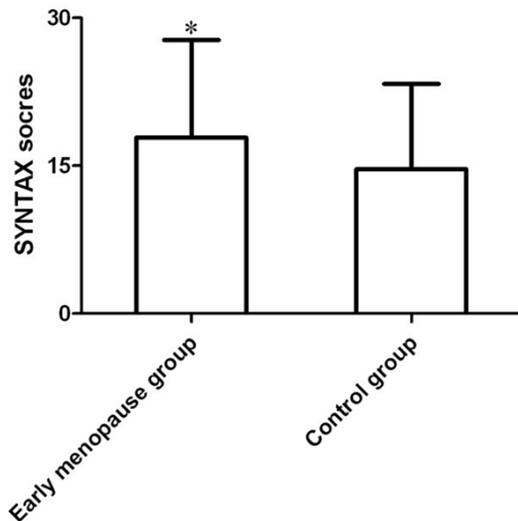


Figure 1. SYNTAX scores of all the patients. * $P < 0.05$ for comparison with the control group; SYNTAX, Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery.

examined factors included the left atrial diameter, the left ventricular diastolic diameter, and the left ventricular ejection fraction.

Statistical analysis

All statistical analyses were conducted using the SPSS software, version 20.0. Measurement data were presented as mean \pm standard deviation ($\bar{x} \pm sd$), and comparisons between the groups were made by means of the independent t-test. Count data were expressed as percentage and comparison between the groups were conducted with the χ^2 test. The Logistic regression analysis was employed to assess the risk factors for major adverse cardiac events. Of the basic clinical data, the variables with significant differences between the two groups were subjected to the regression analysis. The P value of less than 0.05 was deemed statistically significant.

Results

Demographic and clinical characteristics

Demographics and clinical characteristics of all the patients, including age, risk factors for CAD, and factors of early menopause, were shown in **Table 1**.

The two groups were significantly different in factors of early menopause, hypertension, diabetes, hyperlipidemia, smoking, levels of blood lipid and glucose except in the family history of CAD, age and HDL levels ($P > 0.05$).

Coronary artery lesions

The majority of the patients in the early menopause group (53.3%) were involved in three-vessel CAD, 22.8% in one-vessel CAD, and 23.9% in two-vessel CAD; most of the patients in the control group (42.8%) were involved in one-vessel CAD, 21.1% in two-vessel CAD, and 36.1% three-vessel CAD; the differences between the early menopause group and the control group were significant ($P < 0.05$, **Table 2**). The SYNTAX scores of the early menopause group increased more considerably than those in the control group (17.85 ± 9.91 vs. 14.66 ± 8.65 ; $P = 0.000$, **Figure 1**).

Rates of major adverse cardiac events

During the three years of follow-up, major adverse cardiac events occurred in 59 patients in the early menopause group, including 8 patients with myocardial infarction, 9 with cardiac death, and 42 coronary revascularization; major adverse cardiac events were noted in 132 patients in the control group, including 18 patients with myocardial infarction, 10 with cardiac death and 104 coronary revascularization, and the rate of major adverse cardiac events in the early menopause group was significantly different from that of the control group ($P < 0.05$, **Table 3**).

Echocardiographic outcomes

At the last follow-up, no significant differences between the two groups were observed in the left atrial diameter, the left ventricular diastolic diameter, and the left ventricular ejection fraction (all $P > 0.05$, **Table 4**).

Early menopause for women's disease prognosis

Table 3. Major adverse cardiac events

Group	Myocardial infarction	Death from cardiovascular causes	Coronary revascularization	No. and rates of overall major adverse cardiac events
Early menopause	8 (2.17%)	9 (2.45%)	42 (11.41%)	59 (16.03%)
Control	18 (1.19%)	10 (0.66%)	104 (6.9%)	132 (8.75%)
χ^2 value	5.468	9.545	9.257	17.108
P value	0.020	0.009	0.010	0.000

Table 4. Echocardiographic measurements

Group	Left atrial diameter (mm)	Left ventricular diastolic diameter (mm)	Left ventricular ejection fraction
Early menopause	36.7±6.8	49.4±4.3	61.4±9.8
Control	36.5±6.4	49.6±4.7	62.7±10.3
t value	1.504	0.579	1.089
P value	0.314	0.544	0.452

Risk factors related to major adverse cardiac events

With adverse cardiac events as dependent variables, and early menopause, hypertension, diabetes, hyperlipidemia, smoking, BMI, SYNTAX scores and the number of diseased coronary arteries as independent variables, the values assigned to all the variables were shown in **Table 5**. The multivariate Logistic regression analysis revealed that three-vessel CAD and early menopause were correlated with the occurrence of major adverse cardiac events in CAD women (**Table 6**).

Discussion

Young females show a low rate of CAD because of protective estrogen. However, with the development of aging population, the number of perimenopausal women has increased substantially, which comes with a dramatic rise in the rate of CAD in perimenopausal women. Consequently, CAD has become the number one women killer in China [8, 9]. The perimenopausal period is not the peak period of CAD in women, but CAD in perimenopausal women is characteristic of atypical symptoms, difficult diagnosis and high rates of misdiagnosis or misdiagnosis. Few current studies are involved in CAD in women and even fewer studies in the conditions and prognosis of CAD in perimenopausal women. Some scholars reported that the studies on prevention and treatment of cardiovascular diseases in women are far from sufficient [10]. All these have urged us to reconsider and think over the CAD patients in

the perimenopausal period, and further delve into the causes and prognosis of CAD for better early prevention and treatment.

Previous studies have demonstrated the role of multiple risk factors in the

onset and progression of coronary artery disease [11, 12]. As compared with premenopausal women, postmenopausal women have shown higher prevalence of hypertension and hyperlipidemia and other diseases, leading to higher risks for CAD [13-15]. In the present study, more traditional high-risk factors for CAD were noted in the patients in the early menopause group than those in the control group, suggesting that early menopause affects the occurrence and development of CAD by making further damage to the vascular endothelial cells through elevated blood pressure and lipid and glucose levels.

To our knowledge, CAD is less severe in premenopausal women than in men but more severe in postmenopausal women [16]. The results of our present study indicated that patients in the control group mostly had one-vessel CAD while those in the early menopause group mostly had three-vessel CAD, and the substantially higher overall SYNTAX score in the early menopause group than in the control group suggests that early menopause has an effect on the severity of CAD. Female patients with acute myocardial infarction have proven to have poorer short or long-term prognosis than male patients, and female patients younger than 60 years of age have markedly higher mortality of acute myocardial infarction [17, 18]. Further study will be required to explore the association of early menopause with the severity of major adverse cardiac events. The results of our present study revealed that the rate of new myocardial infarction represented 2.17%, deaths from cardiac causes was 2.45%

Early menopause for women's disease prognosis

Table 5. Values assigned to the variables

Variable	Assigned value
Early menopause	0: No; 1: Yes
Hypertension	0: No; 1: Yes
Diabetes	1: No diabetes; 2: Diabetes under favorable glycemetic control; 3: Diabetes under poor glycemetic control
Hyperlipidemia	0: No; 1: Yes
Smoking	1: Current smoking; 2: Former; 3: Never
BMI	1: Lower than 18.5 kg/m ² ; 2: 18.5-24.9 kg/m ² ; 3: Higher than 25 kg/m ²
SYNTAX score	1: ≤25; 2: >25
No. of diseased coronary artery	1: One-vessel; 2: Two-vessel; 3: Three-vessel

Note: BMI, body mass index; SYNTAX, Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery.

Table 6. Risk factors related to major adverse cardiac events

Factor	Regression coefficient	Standard error	Adjusted OR	95% CI	P value
Early menopause	1.683	0.712	2.731	1.238±18.054	0.021
No. of diseased coronary artery (≥2)	1.915	0.674	6.782	2.674±14.798	0.014

and coronary revascularization was 11.41% in the early menopausal group, significantly higher than those of the control group ($P < 0.05$). What's more, in the Logistic regression analysis, three-vessel CAD and early menopause were correlated with the rates of major adverse cardiac events, which might be attributable to early menopause affected the severity of CAD, which led to higher rates of major adverse cardiovascular events in women with early menopause. This demonstrates the importance of early prevention and treatment of CAD in women. These results were basically consistent with those reported in previous studies [19-21].

In conclusion, as compared with women with normal menopause, CAD women with early menopause are associated with higher rates of hypertension, diabetes, smoking and major adverse cardiac events as well as higher blood lipid levels. Therefore, clinicians should pay more attention and make active follow-ups to CAD women with early menopause, striving to strictly control the risk factors for CAD and realize its early prevention and treatment. There were some limitations in this study. For example, it was a single-center, prospective study. Prospective and multicenter with large sample size are needed to make further validation in the future. Moreover, the effect of early menopause on coronary artery lesions was not reflected in the nature of CAD, such as bifurca-

tion, main branch or calcified lesions, which is also a direction of future research.

Disclosure of conflict of interest

None.

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Early menopause for women's disease prognosis

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