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Coronary Artery Disease In Premenopausal Versus Postmenopausal Women - Risk Factors, Clinical Profile and Angiographic Characteristics

Dr.J.Nambirajan[1], Dr.P.Praveen Kumar[2], Dr.D.Chakkravarthi[3], Dr.J.Jegadeesh[4], Dr.A.N.Senthil[5]

1-Associate Professor And Head Of Department – Cardiology, Government Coimbatore Medical College Hospital, Coimbatore, Tamilnadu, India.
2- Senior Resident, Department of Cardiology, Government Coimbatore Medical College Hospital, Coimbatore, Tamilnadu, India.
3,4,5-Assistant Professor, Department of Cardiology, Government Coimbatore Medical College Hospital, Coimbatore, Tamilnadu, India.

Abstract
The onset of occurrence of heart disease in women was much later than in men. The purpose of this study was to determine the differences between premenopausal and postmenopausal coronary artery disease (CAD) risk factors, clinical manifestation, cardiovascular features, rates of recurrence, and influencing factors. Premenopausal (n = 57) and postmenopausal (n = 178) CAD women hospitalized during the same period were en- rolled. All patients were followed-up, and the combined recurrence of major adverse cardiovascular events was recorded as the clinical outcome. Differences were compared between the 2 groups. Fewer premenopausal women suffered from hypertension (43.86% versus 75.28%, P < 0.001), type 2 diabetes (12.28% versus 35.96%, P = 0.001), and hyperlipidemia (5.26% versus 34.83%, P < 0.001), but more had a positive family history of premature CAD (40.35% versus 25.28%, P = 0.03). Acute coronary syndrome (ACS) was more fre- quently seen in premenopausal women (82.46% versus 48.88%, P < 0.001), and their left anterior descending branch was the vessel most often involved (65.33%). The cumulative recurrence rate was 1.76 times higher in postmenopausal patients than premenopausal patients. Clinical diagnosis (HR = 2.54, 95%CI: 1.21-4.85, P = 0.02) and type 2 diabetes (HR = 4.10, 95%CI: 2.37-8.83, P = 0.004) were two factors that influenced recurrence in premenopausal subjects, while the clinical diagnosis (HR = 1.93, 95%CI: 1.59-3.46, P = 0.03) and Gensini score (HR = 1.20, 95%CI: 1.11-1.45, P = 0.02) were influencing factors in the postmenopausal patients. Symptoms among younger women were atypical, but the onset of disease was faster and more urgent.

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I. Introduction

The onset of occurrence of heart disease in women was much later than in men, and young women suffer less from heart disease due to the vascular protective action of estrogen which helps in preventing atherosclerosis. In fact, coronary artery disease (CAD) is an important killer of women, regardless of race and ethnicity, and it also strikes at younger ages than most people think. The incidence of CAD has declined among men while it has risen among women since the 1950s. Postmenopausal and premenopausal women differ in the symptoms, risk factors, disease characteristics, prognosis, and recurrence of CAD. However, due to the low incidence of CAD in premenopausal women, research on this particular population has not been sufficient. The purpose of this study was to determine the special nature of CAD in pre- menopausal women by comparing the difference from postmenopausal women.

II. Methodology

The female CAD patients were drawn from the cardiology department from January 1, 2018 to December 31, 2018 . The subjects were enrolled in accordance with the criterion of diameter stenosis > 70% in at least one coronary angiograph with Judkins catheters. Patients with pulmonary embolism, aortic aneurysm, congenital heart disease, rheumatic heart disease, myocarditis, or cardiomyopathy were excluded. A total of 57 premenopau- sal cases and 178 postmenopausal cases were enrolled accord- ing to their status at the time of diagnosis. All patients underwent percutaneous coronary intervention and were given conventional drug therapy for coronary artery disease during follow-up. Routine drug therapy included antiplatelet agents (aspirin), lipid lowering agents, beta blockers, and angiotensin converting enzyme inhibitors/angiotensin II receptor antago- nists according to the

patients' existing conditions. No patients were treated with hormone replacement therapy. This study was approved by the ethical committee of the institution.

Clinical data collection: The following clinical data were collected: 1) demographic data and traditional risk factors, such as age, hypertension, hyperlipidemia, type 2 diabetes, smoking, obesity, and a positive family history of premature CAD; 2) clinical classification of disease, such as stable angina and acute coronary syndrome (ACS) including unstable angina, ST-elevation myocardial infarction, and non ST-elevation myocardial infarction; 3) clinical measurements including body mass index (BMI), blood pressure, blood biochemical variables, 4) the severity of CAD was defined using the angio- graphic Gensini scores according to coronary angiography with Judkins catheters. Coronary angiography test results included lesion location, the number of vascular stenosis, and the severity of stenosis.

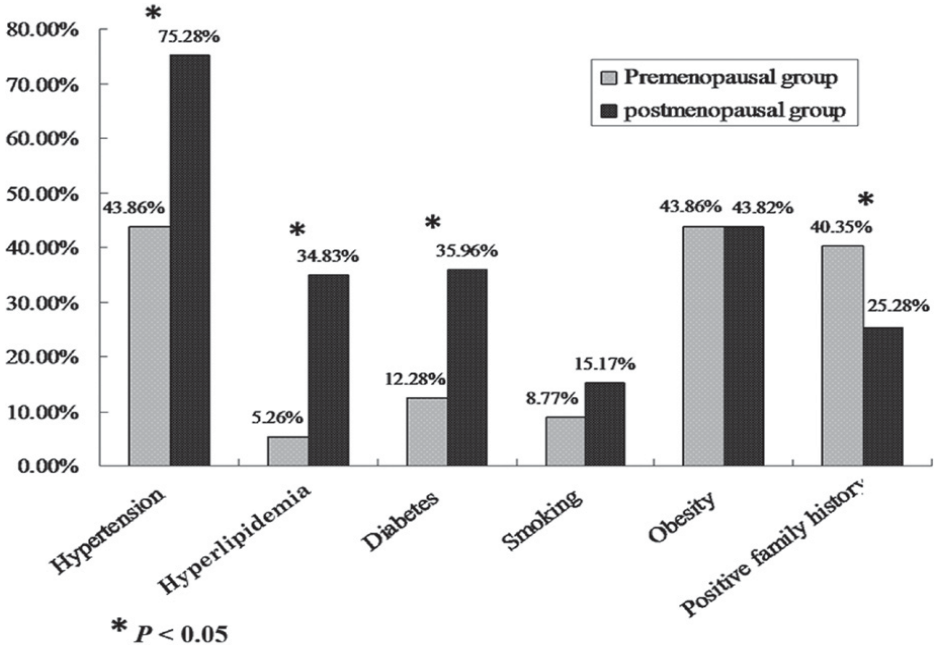
Clinical follow-up: All patients were contacted by telephone every 6 months until June 2020, and their medical records were followed regularly. The endpoint was the combined recurrence of major adverse cardiovascular events, including death, targeted vascular revascularization, heart failure, ACS, and transient ischemic attack (TIA)/stroke. Death and targeted vascular revascularization with percutaneous coronary inter- vention or coronary bypass surgery were confirmed by a re- view of the medical records. Heart failure was defined as dyspnea and/or edema that was accompanied by pulmonary congestion on a chest roentgenogram and left ventricular dysfunction on an echocardiogram. ACS was defined as a rise in cardiac troponin I with ischemic symptoms and/or characteristic electrocardiographic changes. TIA/stroke was defined as the presence of a new neurological deficit verified by either magnetic resonance imaging or computed tomography.

Data analysis: Statistical analyses were performed using SPSS version 17.0. Discrete variables were com- pared with the chi-square test or Fisher Exact test.

III. Results

Comparison of CAD traditional risk factors: The mean age of the 57 premenopausal cases was 46.70 ± 4.40 years, while the mean age of the 178 postmenopausal subjects was 67.62 ± 9.86 years. The differences in traditional risk factors between the two groups are summarized in Figure 1.

Figure 1. Comparison of risk factors between premenopausal and post- menopausal groups.



Compared with the postmenopausal group, the prevalences of hypertension (43.86% versus 75.28%, χ^2 = 19.48, P < 0.001) and hyperlipidemia (5.26% versus 34.83%, χ^2 = 18.86, P < 0.001) were significantly lower. Furthermore, fewer premenopausal patients suffered from type 2 diabetes (12.28% versus 35.96%, χ^2 = 11.48, P = 0.001). Yet, there were more premenopausal patients with a positive family history of premature CAD (40.35% versus 25.28%, χ^2 = 4.77, P = 0.03). There were no significant differences in smoking and obesity.

Symptom presentation and clinical diagnosis: Eight cases (14.04%) had typical angina before the onset in premenopausal CAD women, while the percentage was much higher in postmenopausal patients (82.58%) (χ^2 = 90.35, P < 0.001). Based on the clinical manifestation, CAD was divided into stable angina and acute coronary syndrome, the latter including unstable angina (UA), acute ST-segment elevation myocardial infarction (STEMI), and acute non-ST-segment elevation myocardial infarction (Non-STEMI). Table I shows the main onset of disease in premenopausal women was ACS, which was significantly more frequent than in the post menopausal group (82.46% versus 48.88%, χ^2 = 19.87, P < 0.001).

Comparison of clinical parameters: Comparison of the clinical and biochemical markers between the premenopausal and postmenopausal women revealed that the systolic pressure (140.48 ± 20.54 mmHg versus 126.73 ± 18.25 mmHg, t =4.51, P < 0.001) and diastolic pressure (78.96 ± 9.72 mmHg versus 72.28 ± 11.35 mmHg, t = 4.33 mmHg, P < 0.001), fasting blood glucose (6.78 ± 2.34 mmol/L versus 6.01 ± 2.48 mmol/L, t = 2.13, P = 0.003), total cholesterol (5.43 ± 1.24 mmol/L versus 4.97 ± 1.92 mmol/L, t = 2.11, P = 0.04) and low density lipoprotein cholesterol (3.27 ± 1.08 mmol/L versus 2.90 ± 1.25 mmol/L, t = 2.16, P = 0.03) of postmenopausal patients were higher than those of the premenopausal women. There were no differences in other blood lipids markers, BMI, blood coagulation markers, or hsCRP. **Characteristics of coronary lesions:** The number of stenotic vessels was significantly less in the premenopausal group com- pared with postmenopausal cases (1.28 + 0.50 versus 2.43 + 0.89, P < 0.001). In the premenopausal group, the left anterior descending branch was the stenosis vessel most often involved (65.33%), followed by the left circumflex (18.67%) and right coronary artery (16.00%). However, there was more left circumflex stenosis (30.55%) and right coronary artery (30.28%) stenosis in the postmenopausal group. The location of the vessel stenosis was significantly different between the two groups (Fisher's exact test, P < 0.001). Gensini's degree integral was applied to identify the se- verity of coronary narrowing. The Gensini scores of premenopausal patients were significantly lower than those of postmenopausal patients (10.48 ± 7.23 versus 56.49 ± 26.97, P < 0.001).

Disease recurrence and influence factors: Six patients dropped out of the study because they had changed their phone numbers or addresses for communication and did not return after discharge from the hospital. A total of 99 cases of recurrence of major adverse cardiovascular events occurred: 8 cases of death, 62 cases of acute coronary syndrome, 3 cases of TIA/ stroke, 9 cases of targeted vessel revascularization, and 17 cases of heart failure. There were 13 patients in the premenopausal group and 86 in the postmenopausal group (22.81% versus 48.31%, χ^2 = 11.52, P = 0.001). The cumulative recurrence rate was 1.76 times higher in postmenopausal patients than premenopausal patients (15.94 per person-month versus 9.07 per person-month).

Table I. Comparison of Clinical Diagnosis Between Premenopausal and Postmenopausal Groups

	Acute coronary syndrome (n, %)	Stable angina (n, %)	χ^2	P
Premenopausal group	47 (82.46%)	10 (17.54%)	19.87	$<0.001^{**}$
Postmenopausal group	87 (48.88%)	91(51.1%)		

Table II. Comparison of Clinical Measurements and Biochemical Variables

	Premenopausal group ($n = 57$)	Postmenopausal group ($n = 178$)	P
BMI (kg/m^2)	26.92 ± 5.15	25.87 ± 3.64	0.09
Blood pressure (mmHg)			
Systolic pressure	126.73 ± 18.25	140.48 ± 20.54	< 0.001**
Diastolic pressure	72.28 ± 11.35	78.96 ± 9.72	< 0.001**
Blood lipids			
TC (mmol/L)	4.97 ± 1.92	5.43 ± 1.24	0.04*
TG (mmol/L)	1.96 ± 1.50	2.05 ± 1.20	0.64
HDL-C (mmol/L)	1.28 ± 0.41	1.27 ± 0.29	0.84
LDL-C (mmol/L)	2.90 ± 1.25	3.27 ± 1.08	0.03*
apoA1 (g/L)	1.48 ± 1.06	1.35 ± 0.26	0.13
apoB (g/L)	0.88 ± 0.24	1.00 ± 0.62	0.16
LPA (mg/L)	210.10 ± 153.15	231.42 ± 188.55	0.44
FBG (mmol/L)	6.01 ± 2.48	6.78 ± 2.34	0.03*
hsCRP (mg/L)	3.46 ± 4.11	3.47 ± 3.29	0.20
Blood coagulation			
PT	12.93 ± 2.95	13.43 ± 1.94	0.14
APTT	29.28 ± 10.75	26.84 ± 17.15	0.31
INR	1.02 ± 0.23	0.98 ± 0.17	0.15

Table III. Coronary Angiographic Features of Premenopausal and Postmenopausal CAD Women

	Lesion location				Number of stenotic vessels	Gensini score
	LM	LAD	LCX	RCA		
Premenopausal group	0 (0.00%)	49 (65.33%)	14 (18.67%)	12 (16.00%)	1.28 ± 0.50	12.48 ± 7.23
Postmenopausal group	5 (1.31%)	145 (37.86%)	117 (30.55%)	116 (30.28%)	2.43 ± 0.89	46.49 ± 26.97
P	< 0.001**				< 0.001**	< 0.001**

LM indicates left main coronary artery; LAD, left anterior descending branch; LCX, left circumflex; and RCA, right coronary artery. *$P < 0.05$, **$P < 0.001$.

Table IV. Multivariate Cox Regression of Risk Factors of Recurrence

	Premenopausal patients			Postmenopausal patients		
	HR	95.0% CI	P	HR	95.0% CI	P
Age	1.02	0.87-1.21	0.80	1.04	0.98-1.03	0.74
Clinical diagnosis	2.54	1.21-4.85	0.02*	1.93	1.59-3.46	0.03*
Hypertension	1.66	0.97-6.97	0.07	1.28	0.60-5.68	0.06
Hyperlipidemia	2.19	0.09-56.42	0.64	1.39	0.89-2.17	0.15
Diabetes mellitus	4.10	2.37-8.83	0.004*	1.03	0.66-1.62	0.89
Smoking	5.99	0.70-51.24	0.10	1.18	0.65-2.13	0.57
Obesity	1.38	0.88-2.15	0.16	1.24	0.69-2.23	0.47
Number of stenoses vessels	0.84	0.15-4.69	0.84	0.87	0.62-1.21	0.40
Gensini score	1.01	0.92-1.11	0.88	1.20	1.11-1.45	0.02*

*$P < 0.05$.

Cox regression analysis was conducted to investigate the factors influencing recurrence (Table IV). Age, clinical diagno- sis, risk factors of CAD, number of stenotic vessels, and Gensini scores were independent variables. Clinical diagnosis (HR = 2.54, 95%CI: 1.21-4.85, P = 0.02) and type 2 diabetes (Hazard ratio (HR) = 4.10, 95%CI: 2.37-8.83, P = 0.004) were two factors that influenced recurrence in premenopausal sub- jects, while clinical diagnosis (HR = 1.93, 95%CI: 1.59-3.46, P = 0.03) and Gensini score (HR = 1.20, 95%CI: 1.11-1.45,P= 0.02) were factors in postmenopausal patients.

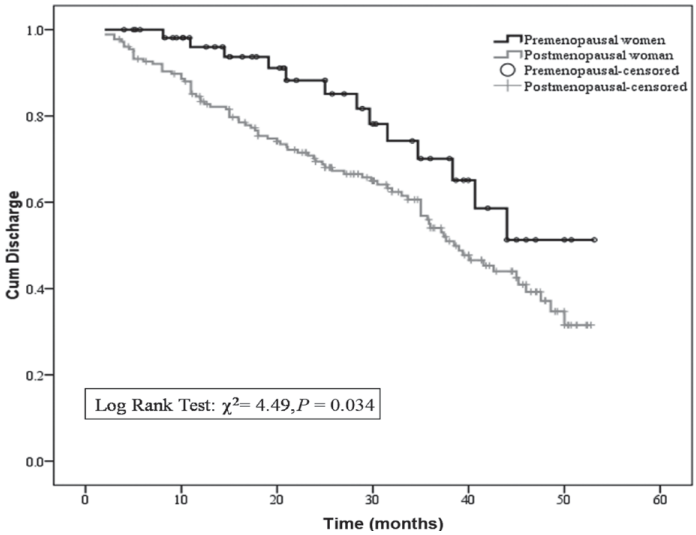


Figure 2. Kaplan-Meier analysis of non-recurrence in the 2 study groups indicates cumulative rate of non-recurrence at different follow-up,

IV. Discussion

Recognition of prodromal symptoms was reported to be critical for preemptive coronary heart disease screening and effective diagnosis and treatment. It was important to recognize the symptoms which are associated with acute subsequent cardiac events. However, symptoms among younger women were atypical, and patients with silent myocardial ischemia usually had more extensive and severe disease. A previous study also indicated that young women were more likely to have CAD without chest pain. Another study in a Canadian cohort of patients whose age was under 55 years with acute coronary syndrome supported this pattern. Our study showed that 48.88% of postmenopausal cases were identified as ACS, compared to 82.46% of premenopausal patients identified as ACS. Premenopausal women had a rapid onset and no typical angina, but myocardial infarction typically occurred. Autopsy research has demonstrated that coronary artery lesions in young women contain less calcium and dense fibrous tissue than those of men and older women. Coronary atherosclerotic plaque of young patients was comprised mainly of fatty deposits, which was extremely easy to rupture and caused acute coronary thrombosis that led to acute cardiovascular disease.

Coronary angiography of the premenopausal patients showed the coronary artery stenosis was limited to a single vessel, and the left anterior descending artery was the most frequently affected vessel, while the involvement of the left circumflex and right coronary artery was significantly less. It reported that left anterior descending branch stenosis and Q-wave myocardial infarction were common in young women. Another recent study found that left anterior descending branch stenosis was more common in young people; 63.9% of patients in the ≤ 35 years old age group, 41.7% in the 35 to 55 age group, and 33.7% in the older than 55 age group exhibited atherosclerosis in the left anterior descending artery (P < 0.01).[18)] At present, there is no authoritative statement about why LAD disease occurred more often in the premenopausal group. Taking the anatomical structure of the left anterior descending artery into account, it was most likely because pre- menopausal women are more active, and the left ventricle needs to consume more oxygen and nutrients. The left anterior descending artery is more easily involved as it is the main blood supply artery of the left ventricle, and it supports large areas of the ventricle.

In addition, the Gensini scores of premenopausal patients were much lower, which meant the lesions were confined mostly to single or double blood vessels. A previous study re- ported age-related differences in percent luminal stenosis at the site of thrombus and extent of coronary disease. There were relatively few narrowed segments of coronary arteries in younger women compared with women over 50 years of age. This was probably because young women were more likely to have inflammation, coronary spasm, plaque erosion, or rupture. The clinical manifestations of postmenopausal patients were more complex, and collateral circulation was easily formed as they had a longer disease duration and long-term progress of the disease course. Our study results suggest that angiography in premenopausal women might underestimate the severity of the disease in younger women. These findings emphasize that premenopausal women and postmenopausal women who experience CAD may represent a heterogeneous group.

Cardiovascular risk factors were highly valuable predictors of the presence and severity of CAD. The prevalence of hypertension, hyperlipidemia, and type 2 diabetes were significantly lower in the premenopausal group. In menopause, women have significant effects on lipid metabolism, which is mainly manifested by an increase in LDL-C and decrease in HDL-C. However, there was no difference in other blood li-pid markers, with the exceptions of total cholesterol and LDL. This suggested that abnormal metabolism occurred early on in the premature

menopause CAD women. In other words, it appeared to lessen the cardio-protective effect associated with age. Smoking was reported as the most prevalent risk factor which caused endothelial dysfunction, spontaneous platelet aggregation, coronary spasm, and adverse hemostatic effects. However, due to the low smoking rate among Chinese women, smoking was a less significant risk factor in this study. Among all the 6 main risk factors, only the proportion of the family history of the premenopausal women was significantly higher, which suggests that females with a positive family history of premature CAD should be more concerned with the occur- rence of CAD before menopause.

The cumulative recurrence rate was higher in postmenopausal patients, which was partly attributable to their older age and partly because their coronary lesions were much more complex, even though the onset of disease was faster and more urgent in premenopausal patients. The premenopausal group had a lower recurrence rate within a relatively short period of time. In our study, the influencing factors for each group were not exactly identical. However, the initial clinical diagnosis before follow-up was the influencing factor in both groups. The risk of recurrence of cardiovascular events remains high after acute coronary syndrome.

The description of other symptoms in the absence of typical angina pectoris was not identified, and we did not analyze it in our study. Secondly, the sample size was not large. It was because the incidence of CAD in pre-menopausal women was not particularly high, and all enrolled subjects underwent coronary angiography in order to compare the coronary artery lesions.

V. Conclusion

Our study clarified the differences between postmenopausal and premenopausal women with respect to risk factors, clinical symptoms, cardiovascular features, and recurrence rate, and provided a reference for further study on the mechanism and prognosis in postmenopausal or premenopausal CAD patients.

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