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Comparison of Risk Factor Profiles and Angiographic Disease Patterns in Premenopausal and Postmenopausal Women Presenting to a Tertiary Care Hospital

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Abstract: ***Background: Coronary Artery Disease (CAD) is increasingly becoming the disease of the young. Not much is known regarding the risk factors and pattern of CAD in pre-menopausal Indian women. Aim of this study was to study the differences in risk factor profile and coronary angiographic pattern of disease among pre- and post-menopausal women. Methods: A total of 1260 consecutive female patients who underwent coronaryangiogram for suspected ischemic heart disease over a period of 2 years from Jan 2019 to Dec 2020 were enrolled. Patients were divided into 2 groups, premenopausal group consisted of 240 (19.04%) patients and postmenopausal group1020 (80.95%). Detailed risk factor profiles and angiographic patterns of disease were recorded and analyzed. Results: Premenopausal women were more likely to be obese (58.3% Vs 47%, p=0.05), hypothyroid (25% Vs 11%, p<0.0001) and more likely to have a positive family history of premature CAD (39.7% Vs 5.89%, p<0.0001). On the other hand, postmenopausal women were more likely to be diabetic (23.2% Vs 12.7%, p=0.007), hypertensive (73.8% Vs 52.3%,p<0.0001), smokers (31% Vs 20%, p=0.01) and had >3 risk factors more frequently (43.5% Vs 31%, p=0.0071).Atypical chest pain was more common as presenting diagnosis among premenopausal women (24.4% Vs 11.4%,p<0.0001). They were also more likely to have positive exercise stress test (63.5% Vs 38.3%, p<0.0001) and normal coronary angiogram (60.1% Vs 33.3%, p<0.00024) with endothelial dysfunction (85.8% Vs 67.6%, p<0.0001) than post-menopausal women. Post-menopausal women had greater burden of obstructive CAD characterized by more prevalent multi vessel disease in the form of double vessel (18.3% Vs 7.8%, p=0.071) and triple vessel disease (21.2%Vs 6.4%, p<0.00023). Conclusion: The risk factor profile and angiographic disease pattern among women vary significantly depending on their menopause status. Recognizing these distinctions would aid in a deeper understanding of the connection between menopause and the production of CAD.***

Keywords: Menopause; Coronary artery disease; Risk factors; Coronary angiography

1. Introduction

Coronary Artery Disease (CAD) for long has been called “men’s disease”; however these days an increasing trend of CAD is observed in women [1, 2]. There are major differences in the prevalence of various risk factors such as diabetes mellitus, hypertension, family history of CAD, dyslipidaemia, obesity and cigarette smoking probably because of advanced age of women at presentation and greater co-existence of co-morbidities such as diabetes and hypertension as compared to men. The presenting symptoms also differ as women are more likely to present with atypical chest pain, neck pain, nausea, fatigue and dyspnoea making the diagnosis more difficult subjecting women to suboptimal and less aggressive care [3, 4].

Coronary artery disease is the leading cause of mortality and morbidity of both men and women accounting for over one third of total deaths [5]. In women, the annual mortality rate from CAD is high. Epidemiological studies from various parts of India have reported the rising trends and ahigh burden in the levels of conventional risk factors such as diabetes, hypertension and metabolic syndrome [6, 7].

CAD risk increased along with an increase of age, interestingly, premenopausal women had much lower incidence of CAD compared with males, just only 1:3-10, but the incidence rate of CAD increased fast in postmenopausal women, and there was a nearly incidence of CAD between males and women with the age of 65 years, women, over 75 years of age, had higher incidence of CAD than men [8].

Despite the importance of CAD for women, there is persistent perception that CAD is a man’s disease. Contributing to this notion is the observation of differences in incidence rates according to age; the incidence of CAD in women is lower than men, but rises steadily after fifth decade. The distribution of CAD risk factors varies between men and women across age ranges and failure to consider these differences may have contributed to the belief that women are at lower risk of CAD compared with men. In addition, women are more likely to have symptoms considered atypical compared with men. There is an urgent need to better understand the presentation of cardiac symptoms in women, in order to facilitate diagnosis and treatment, to initiate aggressive risk factor intervention and to improve the quality of life [9].It is still unclear how menopause affects coronary artery disease. There are hardly any studies which have systematically recorded the risk factor profiles and compared them with the angiographic pattern of disease, according to the status of menopause. The aim of this study was to study the differences in risk factor profile and coronary angiographic pattern of disease among pre- and post-menopausal women.

2. Materials and Methods

This observational study was done at the Department of Cardiology, in a Tertiary Care Hospital during a period of 2 years from Jan 2019 to Dec 2020. During this study period total 3790angiographies were done of them total 1260 female angiographies were done. All these female patients (1260) who presented with clinical suspicion of coronary ischemia, based on the presence of angina with or without an abnormal stress test, were considered for participation in the study. Patients with acute coronary syndrome (ACS) were also included. ACS patients were then categorized into ST segment elevation myocardial infarction (STEMI) or non-ST segment elevation myocardial infarction/unstable angina (NSTEMI/UA). STEMI was diagnosed if ECG showed evidence of ST segment elevation in > 2 contiguous leads. Those without ST segment elevation were labeled as NSTEMI/UA based on the presence of elevated cardiac enzymes. Patients with valvular heart disease, cardiomyopathy, pulmonary artery hypertension, congenital heart disease, renal failure and pregnancy were excluded from the study. Those refusing to give consent were also excluded.

A detailed medical history for assessing nature and duration of chest pain, menstrual status and risk factor profile were recorded. Examination was carried out to examine the pulse, blood pressure and body mass index (BMI) using appropriate and validated tools. The clinical presentation of patients was categorized as STEMI, NSTEMI/UA, typical chest pain and atypical chest pain. Chest pain was labeled as typical if it met all three of the following criteria: (1) retrosternal chest discomfort described as pressure, tightness or heaviness with duration no more than 10 minutes in most of the cases(2) provoked by exertion or emotional stress and (3) relieved by rest and/or nitrates. Atypical angina was defined as meeting 2 of the above characteristics. International cut off points of the body mass index (BMI) for Asian populations were used to assess overweight (BMI≥ 23 kg/m2 to 24.99 kg/m2) and obesity (≥ 25 kg/m2). Smokers were defined as all those patients who regularly smoked an average of one or more cigarettes a day for at least 1 year. Patients on oral hypoglycemic agents or Insulin and/or those having fasting blood sugar >126 g/dl were regarded as having diabetes mellitus. Hypertension was diagnosed if blood pressure >140/90 mmHg was recorded twice or in those on antihypertensive drugs. A diagnosis of dyslipidemia was made if total Cholesterol was >160 mg/dl, triglycerides >150 mg/dl, low densitylipoprotein (LDL) cholesterol >130 mg/dl and high density lipoprotein (HDL) cholesterol was <50 mg/dl. Women with history of ischemic heart disease in first degree male relatives of less than 55 years or in female relatives less than 65 years were regarded as having family history of premature coronary artery disease. Menopause was considered to be present when there was no history of menstrual periods for the lastone year. Modified Minnesota leisure time questionnaire [7] was used to define the physical activity of patient as heavy, medium and light/sedentary. Baseline transthoracic echo cardiographic examination was done in all patients to assess regional wall motion abnormalities and left ventricular function, using American Society of Echocardiography guidelines [8, 9]. Coronary angiography was performed with Siemens Artis Zee Cath Lab Equipment through standard radial or femoral artery approach. Angiographic data was analyzed by using quantitative coronary analysis software by two different cardiologists independently and any discrepancies in analysis were settled at the same time. Obstructive CAD was diagnosed if lesion causing luminal narrowing≥50% was observed in one or more epicardial coronary arteries. It was further classified into single vessel disease (SVD), double vessel disease (DVD) and triple vessel disease (TVD). Non-obstructive CAD was defined if only lumen irregularities were seen and/ or if stenosis was seen causing <50% luminal narrowing. Normal epicardial coronaries were defined as having no luminal irregularities and luminal stenosis. In patients with normal epicardial coronaries, endothelial dysfunction was diagnosed by corrected TIMI (Thrombolysis in Myocardial Infarction) frame count >21 at a frame rate of 30 mm/sec. The presence of a myocardial bridge was defined by ≥10% systolic compression of the epicardial coronary artery during the cardiac cycle.

3. Statistical Analysis

Continuous variables were presented in means ± standard deviation. Categorical variables were presented as proportions. Differences between pre- and postmenopausal women were compared using the student t-test for continuous variables and the chi-square test for categorical variables. P value<0.05 was taken as statistically significant. All analyses were performed using SPSS version 21.

4. Observations and Results

A total of 1260 female patients underwent coronary angiography at our center over a period of 2 years from Jan 2019 to Dec 2020. All these patients were divided into 2 groups, first group premenopausal consisted of 240 (19.04%) patients and remaining 1020 (80.95%) postmenopausal women formed the second group. The differences between the baseline characteristics and risk factors among the two groups are detailed in Table 1. The mean age in premenopausal group was 43.11 ± 5.31 years and the mean age of postmenopausal women was 58.87 ± 7.21.

i) Risk factor profile

In comparison to postmenopausal women, premenopausal women were more likely to be obese (58.3% Vs 47.05%, p=0.05), hypothyroid (25% Vs 10.98%, p<0.0001), more likely to have a positive family history of premature CAD (39.58% Vs 5.88%, p<0.0001) and a LDL Cholesterol level >100 mg/dl (69.16% Vs 59.6%, p<0.0001), than the postmenopausal women. On the other hand, postmenopausal women were more likely to be diabetic (23.2% Vs 12.5%, p=0.007), hypertensive (73.82% Vs 52.5%, p<0.0001), smokers (31.07% Vs 20%, p=0.01), also had >3 risk factors more frequently for CAD (43.52% Vs 31.25%, p=0.0071) and a serum HDL Cholesterol level of less than 40 mg/dl (44.5% Vs 29.58%, p=0.0015) than the premenopausal women.

Table 1: Baseline characteristics and risk factors among the two groups

Parameters		Premenopausal (n=240)	Postmenopausal (n=1020)	P value
Mean Age (years)		43.11 ± 5.31	58.87 ± 7.21	0.0165
≥ 3 Risk Factors		75 (31.25%)	444 (43.52%)	0.0071
Sedentary Lifestyle		158 (65.83%)	605 (59.31%)	0.0142
Obesity/Overweight (BMI ≥ 23 kg/m2)		140 (58.33%)	480 (47.05%)	0.05
Diabetes Mellitus		30 (12.5%)	237 (23.23%)	0.007
Hypertension		126 (52.5%)	753 (73.82%)	0.0001
Dyslipidemia	LDL>100	166 (69.16%)	608 (59.60%)	0.0001
	HDL<40	71 (29.58%)	454 (44.50%)	0.0015
Smoking		48 (20%)	317 (31.07%)	0.011
Family history of premature CAD		95 (39.58%)	60 (5.88%)	0.0001
Hypothyroidism		60 (25%)	112(10.98%)	0.0001

ii) Differences in presentation pattern

The main presentation diagnosis in both the groups was chronicstable angina. However, a significantly higher number of premenopausal women presented with atypical chest pain than postmenopausal women (24.4% Vs 11.4%, p<0.0001). STEMI as the presenting diagnosis was more commonly seen in postmenopausal women (7.94% Vs 3.33%, p<0.0001). Significantly higher proportion of postmenopausal women presented with LV systolic dysfunction in comparison to premenopausal women. Premenopausal women were also more likely to have positive exercise stress test (63.33% Vs 37.94%, p<0.0001) than post-menopausal women.

Table 2: Differences in presentation pattern

Parameters		Premenopausal (n=240)	Postmenopausal (n=1020)	P value
Presentation Diagnosis	STEMI	8 (3.33%)	81(7.94%)	0.0001
	NSTEMI/UA	25 (10.41%)	72 (7.05%)	0.0001
	Chronic Stable Angina	132 (55%)	684 (67.05%)	-
	Atypical Angina	73 (30.41%)	204 (20%)	-
Exercise stress test in non-ACS Patients		152 (63.33%)	387 (37.94%)	-
LV Dysfunction		24 (10%)	183 (17.94%)	0.021

iii) Differences in coronary angiographic profile

The differences in coronary angiographic profile based on menopausal status are depicted in Table 3. Normal epicardial coronaryarteries were seen in a significantly higher number of premenopausal women (60.1% Vs 33.3%, p<0.00024). In those with normal coronaryangiogram, endothelial dysfunction was also observed more commonly in premenopausal women (85.83% Vs 67.6%, p<0.0001). The proportion of women with SVD was not statistically different between the two groups (24.5% Vs 25.39%, p=0.842). On the other hand, DVD (18.3% Vs 7.91%, p=0.071) and TVD (21.17% Vs 6.25%, p<0.00023) were more prevalent in the postmenopausal women (Figure 1).

Left main coronary artery (LMCA) was more prevalent among postmenopausal women (7.05% Vs 2.0%, p=0.015). While left anterior descending (LAD) artery was the most commonly involved artery inpostmenopausal women, it was Right coronary artery (RCA), which was the more frequently affected in premenopausal women (Figure 2).No calcification lesions were seen in premenopausal women in comparison to 18% of postmenopausal women having calcification lesions on angiogram. Spontaneous dissections were more common among premenopausal women (10% Vs 1.0%, p<0.0001). Myocardial bridge was seen with equal frequency in the two groups (8.3% Vs 8.5%).

Table 3: Differences in Coronary angiographic profile of the study groups

	Premenopausal (n=240)	Postmenopausal (n=1020)	P value
Normal Coronary Arteries	144 (60.1%)	340 (33.33%)	0.00024
Endothelial dysfunction in absence of obstructive lesions	206 (85.83%)	690 (67.64%)	0.0001
Non-obstructive Disease	7 (2.91%)	75 (7.35%)	0.000214
Number of vessels SVD	59 (24.58%)	259 (25.39%)	0.842
DVD	19 (7.91%)	187 (18.33%)	0.071
TVD	15 (6.25%)	216 (21.17%)	0.00023
Left main coronary artery	5 (2.08%)	72 (7.05%)	0.015
Calcification	0 (0.0%)	184 (18.03%)	0.0001
Dissection	24 (10%)	10 (0.98%)	0.0001
Myocardial bridge	20 (8.33%)	87 (8.52%)	0.423

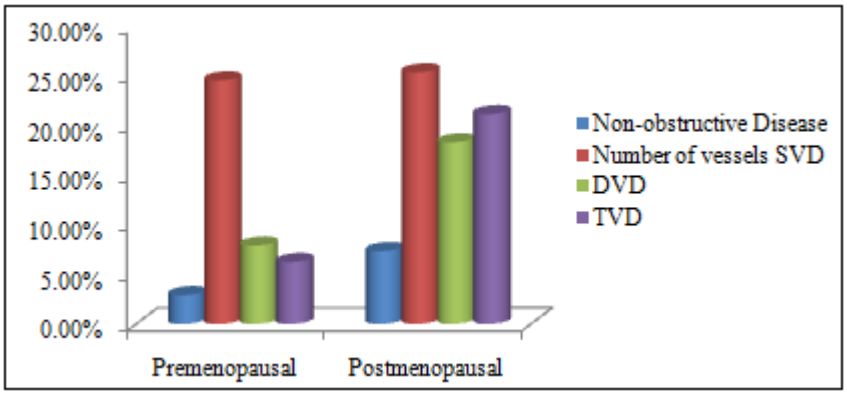

Figure 1: Angiographic distribution among study population based on the number of vessels involved

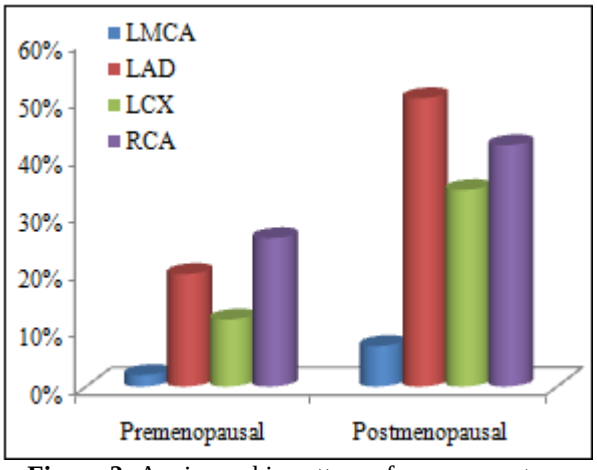

Figure 2: Angiographic pattern of coronary artery involvement among the study groups

5. Discussion

The incidence of coronary artery disease in women after menopause is two to three times than that in women at the same age before menopause [10] Numerous studies have also indicated that estrogen exerts a cardiovascular protective action including improving the lipid profile, enhancing blood flow, [11, 12] and other beneficial effects on primary and secondary prevention of coronary artery disease [13, 14].In the current study the premenopausal women present more commonly with atypical chest pain and they were more likely to be obese with positive family history of premature CAD. But overall, the risk burden of CAD was lesser in them as compared to postmenopausal women. Exercise stress test was often under used in women as a diagnostic test before coronary angiogram, more so in postmenopausal women. A positive result is seen more commonly inpremenopausal women despite greater prevalence of normal coronary angiogram in them. The prevalence of normal coronary angiogram and endothelial dysfunction was more commonly observed in premenopausal women. SVD was the most common mode of presentation of CAD in premenopausal women; it is the multivessel involvement (DVD and TVD) that predominates in postmenopausal women. The similar pattern of increasing risk of CAD after menopause has been documented in previous studies [15-17]. Almost one-fifth of women in the present study presented with atypical chest pain, more commonly the premenopausal women.

There was increase in the prevalence of cardiovascular risk factors with age. In the present study increase in CAD risk factors observed in postmenopausal women which is comparable with the previous studies [18, 19]. Postmenopausal women had higher prevalence of diabetes, hypertension and smoking and majority of them had three or more risk factors in comparison to premenopausal women. Interestingly, premenopausal women had higher prevalence of obesity and LDL cholesterol >100 mg/dl. This reflects the effects of lifestyle changes in young females, thereby making them more prone to develop CAD. The postmenopausal women had a higher prevalence of a low HDL cholesterol <40 mg/dl. Low HDL cholesterol predicts CVD strongly in women. It is known that the risk of coronary events increases significantly in women with low levels of HDL cholesterol [20]. Thus, low HDL cholesterol levels along with an overall greater risk factor burden could be the contributing factors for increased prevalence of CAD in postmenopausal women in the present series.

Overall 46% of women undergoing coronary angiogram in the present study were found to have normal or non-obstructive epicardial coronary arteries which are similar to study done by, This is lesser than reported in earlier studies where 50% of women undergoing coronary angiography for suspected IHD are found to have normal or non-obstructive epicardial coronary arteries [21, 22]. Atherosclerotic burden is greater in postmenopausal women than premenopausal women as understood from the higher prevalence of obstructive CAD especially DVD, TVD and left main coronary artery disease in postmenopausal group and that of normal epicardial coronaries in the premenopausal women. Previous angiographic studies in women have also documented a rise in DVD and TVD as the age advances [23, 24].Premenopausal women also had greater prevalence of endothelial dysfunction. This along with higher prevalence of a positive stress test suggests a higher prevalence of micro-vascular angina in premenopausal women [25]. This is important since data from the women's ischemia syndrome evaluation (WISE) study suggests that such patients are more likely to have recurrent hospital admissions, rapid progression to obstructive CAD and greater cardiovascular mortality and morbidity when compared to the general population [26].

6. Conclusion

The present study showed a various differences in the pattern of CAD between the premenopausal and postmenopausal women, witha greater incidence of atypical angina, positive exercise stress testand angiographically normal epicardial coronaries with endothelial dysfunction in the premenopausal women. These women are morelikely to develop obstructive CAD in future, warranting aggressive lifestyle and risk factor modification. On the contrary, postmenopausal women have higher risk factor burden and more atherosclerotic disease burden reflected by more multivessel disease. Aggressive evidence based management of already established disease and risk factorswould decrease the cardiovascular mortality and morbidity in them.

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