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RESEARCH ARTICLE

ANGIOGRAPHIC AND RISK FACTORS EVALUATION OF CORONARY ARTERY DISEASE IN PREMENOPAUSAL FEMALE POPULATION

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ABSTRACT

Objective: This study was designed to evaluate the risk factors and angiographic profile of coronary artery disease in premenopausal females. Traditionally premenopausal females are thought to be at low risk for coronary artery disease but only few studies have been done to exactly look for the risk factors and angiographic picture in this subset of patients. **Background**: Coronary artery disease in premenopausal females appears to have particularly poor prognosis. Evaluation of risk factors associated and relative importance of risk factors in this subset of population needs more studies. **Methods**: We evaluated 100 premenopausal patients who presented with acute coronary syndrome or chest pain considered to be anginal in origin. Traditional risk factors were reviewed in all patients and association with angiographically detectable corornary artery disease was made. Also,cases were compared with age and sex matched controls who had normal coronaries. **Results**: Out of 100 patients 33 patients presented with Effort Angina (EA), 15 with Unstable Angina (UA) ,4 with NSTEMI and 48 with STEMI. The mean age was 45.67±6.28 years. Only 2 patients had no risk factors and 17 patients had all the 4 risk factors evaluated. Out of all cases 17 patients had normal coronaries, 16 had non-obstructive disease and 65 had significant disease. Amongst patients with obstructive disease 37 had SVD, 17 had DVD, 8 had TVD and 5 had significant LMCA disease. Among the traditional risk factors analyzed no significant difference amongst the three angiographic groups were seen. On comparative analysis between cases and controls significant difference was present with reference to diabetes, hypertension, total cholesterol, LDL,TG and BMI. After multivariate analysis DM (p=0.016), HTN (p=0.000) and BMI (p=0.002) were found to be significantly associated with the patient group. **Conclusion**: Premenopausal females with coronary artery disease are not so uncommon entity as initially thought. These patients have high prevalence of conventional risk factors as compared to normal population. Majority of these patients had significant disease in our study. However conventional risk factors failed to predict the presence of angiographically significant disease in this group of patients.

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INTRODUCTION

Coronary artery disease is highly prevalent in Indian subcontinent. It affects the population across all demographics. However males and smokers are traditionally thought to be affected more in population and females that too young premenopausal females are considered relatively resistant to coronary artery disease. As per Framhingham study overt coronary artery disease occurs in 1/1000 women in age group 30-39 yrs and manifested as myocardial infarction in only 19% of these women (Kargan, 1962).

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There are no large prospective studies to estimate the incidence of coronary artery disease in India. However as per one meta-analysis prevalence of coronary artery disease in urban females in age group 30-39 was estimated to be 7.64% and in 40-49 yr age group was estimated to be 4.86% in 1995. It was estimated to be low in rural population with corresponding figures of 2.63% and 1.31% respectively. Prevalence was estimated on the basis of ECG changes and history (Rajeev gupta, 1996). Besides the adverse societal effects of coronary artery disease in young females the outcome is also poor in these patients. It is the leading killer in premenopausal females (Vaccarino, 1999). Among patients <50 years of age, the mortality rate for the women is twice that for the men in patients presenting with myocardial infarction.

Differences in medical history, severity of the infarction and early managementaccounted only for about one third of the difference in risk (Vaccarino, 1999). This excess risk appears to be sustained among young women who initially survive an AMI, their subsequent mortality risk is about 50% higher than men two years after AMI (Vaccarino, 1999; Vaccarino *et al*., 1998; Vaccarino, 2001). Young Asian women also showed same poor outcome after acute MI. The reasons for higher mortality in younger women are poorly understood and may be related to the presence of different risk factors in women, co-morbidities, severity of infarction, and response to treatment (Jenkins, 1994; Kam, 2002). Even though more than a decade has passed since the publication of initial studies reporting an excess mortality risk for young women with heart disease, there is currently little information about the etiology of premature heart disease or factors that may contribute to this excess risk (Harlan, 2010). Women are relatively spared from coronary artery disease (CAD) before menopause and in order for it to occur, it is mostly accompanied by the presence of cardiovascular risk factors, especially smoking (Zimmerman, 1995).However in asian Indians women it is almost non-existent (Sharma, 1990; Pinto, 1992; Dave, 1991; Pahlajani, 1989). Young women with CAD comprise an especially interesting group given the protective effect of estrogen, but which factors are predictive in this distinctly unusual cohort is poorly understood (Jalowiel, 1989).

Materials and methods:
All premenopausal female patients who presented with acute coronary syndrome (ACS) or with complaints of chest pain,which was thought to be angina in origin, to Sri Jayadeva Institute of cardiovascular sciences & research between July 2011 to July 2012, who subsequently underwent coronary angiography were included in this study.

Inclusion criteria for cases

- Age >18 years and premenopausal
- Admitted with ischemic heart disease- EA, UA/NSTEMI or STEMI
- Exclusion criteria for cases:
- Concomitant valvular heart disease or cardiomyopathy
- Congenital heart disease
- Refusal for CAG
- Baseline serum creatinine >2 mg/dl
- Pregnancy
- Surgical menopause (bilateral oopherectomy or hysterectomy)

Patients were divided in 3 groups on the basis of coronary angiogram: normal coronary arteries group, non-obstructive coronary artery group (<50% lesion in epicardial coronary artery) and obstructive group (≥ 50% involvement of any of the epicardial coronary artery). Standard coronary artery disease risk factors were evaluated amongst all patients. Control group were recruited from a group of patients who were admitted to our hospital for surgery of valvular heart disease and had no history of chest pain and normal coronaries in coronary angiogram. These were sex and age matched to the case group.

Definition of risk factors: Hypertension was defined as blood pressure of ≥140/90 mm Hg, or use of blood pressure lowering medication at the time of index event.

Dyslidemia was defined as either presence of total cholesterol ≥200mg/dl or HDL≤50mg/dl or LDL≥130mg/dl or prior use of statins. Diabetes was defined as per history from patient or prior use of oral hypoglycemic or insulin or random blood sugar of ≥200mg/dl. Obesity was defined as body mass index (BMI) ≥ 23, or waist/hip ratio of 0.85.

Coronary angiographic analysis: Coronary angiograms were reviewed by 2 interventional cardiologists and were classified into 3 groups. First group include patient with normal epicardial coronary arteries, second group classified as non-obstructive coronary artery disease with <50% lesion in epicardial coronary arteries and third group with obstructive coronary artery disease with ≥50% lesion in coronary arteries. Patients with obstructive coronary artery disease were further classified as having single vessel, double vessel, triple vessel and significant LMCA disease.

Statistical analysis: Continuous variables were expressed as mean±standard deviation. Categorical variables were expressed as number and percentages. Continuous variables were compared by ANOVA amongst the 3 groups in cases. Categorical variables were compared with the chi-square square test or the Fisher exact test where indicated. Multivariate analyses were done using those variables with p <0.5 in the univariate analysis. All probability values were 2-sided, and values of p <0.05 were considered statistically significant.

RESULTS

Out of 100 patients there were 33 patients presented with Effort Angina (EA), 15 with Unstable Angina (UA) ,4 with NSTEMI and 48 with STEMI.

Table 1. Angiographic Findings

	No of patient
Normal	17
Insignificant	16
SVD	37
DVD	17
TVD	8
LMCA	5
Significant involvement of vessel	
LAD	45
LCX	20
RCA	21

The mean age was 45.67±6.28 years. Hypertension was present in 53 patients, diabetes in 45 patients,dyslipidemia in 85 patients and obesity in 71 patients. Only 2 patients had no risk factors and 17 patients had all the 4 risk factors evaluated. Only one patient in cases group used tobacco while 4 patients gave history of coronary artery disease in family. Of all MI patients (n=48) all patient except one had history of chest pain. Only 3 patients presented within 3 hrs of symptom, 10 presented between 3-6hr duration and 17 patients presented after 24 hrs. Of all the STEMI patients 21 received thrombolysis and 25 patients were not lysed as duration of symptoms were >12hrs. Out of all cases 17 patients had normal coronaries, 16 had non-obstructive disease and 65 had significant disease. Amongst patients with obstructive disease 37 had SVD, 17 had DVD, 8 had TVD and 5 had significant LMCA disease. There was significant involvement of LAD in 45 patients,LCX in 20 patients and RCA in 21 patients.

Table 2. Baseline Parameters

Parameters	Normal (N=17)	Diffuse non-obstructive disease (N=16)	Obstructive CAD (N=67)	p value
Age (years)	47.05±6.28	45.06±4.80	45.4±6.73	0.598
Diabetes mellitus	7(41.2%)	7(43.8%)	31(46.3%)	0.926
Hypertension	10(58.8%)	9(56.2%)	34(50.7%)	0.804
Dyslipidemia	15(88.2%)	14(87.5%)	56(83.6%)	0.851
Obesity	14(82.4%)	9(56.2%)	48(71.6%)	0.251
Presentation				
EA	10(30.3%)	7(21.2%)	16(48.5%)	0.015
UA	4(26.7%)	1(6.7%)	10(66.7%)	
STEMI/NSTEMI	3(5.8%)	8(15.4%)	41(78.8%)	
Lvef				
EF<30%	0	0	1(1.5%)	0.187
EF 30-45%	2(11.8%)	2(12.5%)	21(32.3%)	
EF 45-55%	2(11.8%)	4(25%)	16(24.6%)	
EF >55%	13(76.5%)	10(62.5%)	27(41.5%)	
Waist<81cm	8(47.1%)	4(25%)	20(29.9%)	
Waist≥81cm	9(52.9%)	12(75%)	47(70.1%)	0.321
Mean waist size	84.3±8.47	84.6±6.51	84.6±7.15	0.990
Waist :hip ratio <0.85	8(47.1%)	12(75%)	47(70.1%)	0.148
Waist :hip ratio ≥0.85	9(52.9%)	4(25%)	20(29.9%)	
Mean Waist :hip ratio	0.84±0.04	0.84±0.04	0.83±0.05	0.760
BMI<25(kg/ m^2)	8(47.1%)	9(56.2%)	29(43.3%)	0.643
BMI ≥25 (kg/m^2)	9(52.9%)	7(43.8%)	38(56.7%)	
Mean BMI	26.2±5.91	25.9±3.86	26.07±4.22	0.977
Total cholesterol <200mg/dl	12(70.6%)	12(75%)	48(71.6%)	0.955
Total cholesterol ≥200mg/dl	5(29.4%)	4(25%)	19(28.4%)	
Mean cholesterol	194±32.13	186±34.1	190.4±39.12	0.827
HDL<50mg/dl	13(76.5%)	12(75%)	47(70.1%)	0.838
HDL>50mg/dl	4(23.5%)	4(25%)	20(29.9%)	
Mean HDL	45.6±9.19	45.7±8.57	45.1±9.32	0.967
LDL<130mg/dl	12(70.6%)	14(87.5%)	50(74.6%)	0.472
LDL≥130mg/dl	5(29.4%)	2(12.5%)	17(25.4%)	
Mean LDL	119.11±26.22	107.7±29.15	113.01±35.72	0.619
Parameters	Normal (N=17)	Diffuse non-obstructive disease (N=16)	Obstructive CAD (N=67)	p value
LDL<100mg/dl	5(29.4%)	4(26.7%)	22(34.9%)	0.789
LDL≥100mg/dl	12(70.6%)	11(73.3%)	41(65.1%)	
TG<150mg/dl	9(52.9%)	10(62.5%)	38(56.7%)	0.855
TG≥150mg/dl	8(47.1%)	6(37.5%)	29(43.3%)	
Mean TG	146.6±49.4	153.8±69.5	162.4±80.5	0.713
TCH/HDL<3.5	4(23.5%)	5(31.2%)	16(23.9%)	0.820
TCH/HDL≥3.5	13(76.5%)	11(68.8%)	51(76.1%)	
TCH/HDL	4.37±1.03	4.15±1.00	4.36±1.16	0.780
LDL/HDL<2.5	7(41.2%)	10(62.5%)	39(58.2%)	0.382
LDL/HDL≥2.5	10(58.8%)	6(37.5%)	28(41.8%)	
LDL/HDL	2.70±0.81	2.43±0.79	2.56±0.87	0.650
No of risk factors				
0	0	0	2(3%)	0.797
1	1(5.9%)	4(25%)	7(10.4%)	
2	6(35.3%)	4(25%)	22(32.8%)	
3	7(41.2%)	5(31.2%)	26(38.8%)	
4	3(17.6%)	3(18.8%)	10(14.9%)	
<2 Risk factors	7(41.2%)	8(50%)	31(46.3%)	0.876
≥2 Risk factors	10(58.8%)	8(50%)	36(53.7%)	
BP Systolic<140mmHg	12(70.6%)	9(56.2%)	50(74.6%)	0.346
BP Systolic≥140mmHg	5(29.4%)	7(43.8%)	17(25.4%)	
Mean systolic BP	137.1±19.8	141±19.5	132.2±23.5	0.329
BP Diastolic<90mmHg	15(88.2%)	14(87.5%)	54(80.6%)	0.659
BP Diastolic≥90mmHG	2(11.8%)	2(12.5%)	13(19.4%)	
Mean diastolic BP	84.1±7.95	86.5±9.45	84.4±10.8	0.741
Metabolic syndrome	8(47.1%)	9(56.2%)	38(56.7%)	0.770

Table 3. Risk Factors

	CASES(N=100)	CONTROLS(N=100)	P VALUE
AGE	45.63±6.27	46.78±5.55	0.171
DIABETES	45	12	0.000
HYPERTENSION	53	7	0.000
DYSLIPIDEMIA	85	98	0.001
HYPERCHOLESTROLEMIA	28	20	0.185
TOTAL CHOLESTROL	190.36±37	172.39±39.67	0.001
HDL	45.34±9.09	39.12±7.45	0.000
LDL	113.21±33.16	104.37±31.35	0.05
TG	158.37±74.12	137.69±72.41	0.04
BMI	26.09±4.45	21.34±4.98	0.000

Table 4. Statistical Analysis

	P VALUE	ODD'S RATIO	95% CI FOR EXP(B)	
			LOWER	UPPER
DM	0.016	3.346	1.251	8.949
HTN	0.000	7.983	2.901	21.972
DYSLIPIDEMIA	NS	-	-	-
BMI	0.002	1.156	1.056	1.264
TOTAL CHOL	NS	-	-	-
HDL	0.024	1.070	1.009	1.136
LDL	NS	-	-	-
TG	NS	-	-	-

Table 5. Comparitive Studies

		Htn	Dm	Hyper-cholestro Lemia (>200mg/dl)	Whr	Obesity	Smoking	Dyslipidemia	Family h/o
PINTO *et al* (n=47)	NOR	5	2	0			0		
	OBSTR	9	6	5 [n]			0		
CHINESE (n=565)	NON OBSTR (%)	99 (34.7)	21 (7.4)				12 (4.2)	47 (16.5)	15 (5.3)
	OBSTR (%)	154 (55.0)	42 (15.0) [n]				26 (9.3) [n]	67 (23.9) [n]	21 (7.5)
WISE STUDY (n=95)	NON OBSTR	49%	16%		0.83 (0.07)		24%	28%	77%
	OBSTR	46%	46% [n]		0.90 (0.08) [n]		23%	30%	67%
OUR STUDY (n=100)	NOR(%)	10(58.8)	7(41.2)			14(82.4)		15(88.2)	
	NON OBST (%)	9(56.2)	7(43.8)			9(56.2)		14(87.5)	
	OBSTR (%)	34(50.7)	31(46.3)			48(71.6)		56(83.6)	
CASS (n=391)	NON OBSTR			214±47			P<0.001		
	OBSTR			235±63 [n]					

[n] p value significant

(Table-1) Significantly less number of patients who presented with MI had normal coronaries as compared with effort angina and unstable angina group. Among the risk factors analyzed i.e. presence of hypertension, dyslipidemia, obesity, diabetes no significant difference amongst the three angiographic groups was seen. Also variables like BMI, waist circumference, waist hip ratio, presence of metabolic syndrome, total cholesterol, HDL, LDL, TCH/HDL ratio didn't showed significant difference amongst the three groups. Similarly when cases were analyzed into three groups according to presentation i.e.: Effort angina, Unstable angina, Myocardial infarction (NSTEMI/STEMI) no difference was seen with reference to risk factors.

Comparison of cases and controls: On comparative analysis between cases and controls it was found that there was significant difference between the groups with reference to risk factors. Significant difference was present with reference to diabetes, hypertension, total cholesterol, HDL, LDL, TG and BMI. Dyslipidemia was more common in controls.After multivariate analysis DM, HTN and BMI were found to be significantly associated with the patient group. Diabetes had an odds ratio of 3.3 and hypertension had an odds ratio of 7.7. (Table-2) Interesting observation was that HDL was found to be significant but in opposite direction after multivariate analysis

DISCUSSION

In our study we examined wide prevalence of conventional risk factors in premenopausal females.

Only 2 patients had no risk conventional factors. However we couldn't find any significant association between the prevalence of risk factors and angiographically demonsrated coronary artery disease. Similar study conducted in India by Pinto *et al*. (1989) demonstrated significant difference with reference to hypercholesterolemia (Total cholesterol >200mg/dl) between the normal coronaries group and group with obstructive coronary disease. The difference in results between our and this study may be due to the duration between the index event and performance of coronary angiogram. In study by pinto *et al*. (1989) on an average angiogram was done after 182 days of MI in one group and 30 days in other group while in our study angiogram was done during the episode of index event in cases of acute coronary syndrome. With reference to Chinese study (Ke-fei, 2008) which showed correlation between DM, dyslipidemia, smoking and prevalence of obstructive and non-obstructive disease in premenopausal females it has to be considered that this study included patient presenting with chest discomfort and no details regarding number of patients with acute myocardial infarction is available. In our study acute MI accounted for nearly 50% of patients. Beside criteria for classifying as HTN and dyslipidemia are not clear in study. Also prevalence of smoking and retrospective nature of study would also have affected the overall outcome. In the WISE sub group study (Noel Bairey Merz, 2003) there was significant difference between the obstructive and non-obstructive group with reference to presence of diabetes and waist-hip ratio. However after multivariate analysis these factors were not found to be significant. This was in accordance with our study.

CASS study (Vlietstra, 1980) revealed data in female's ≤45 yrs which showed significant difference between non obstructive and obstructive group with reference to current smoking and cholesterol levels. The difference can be explained with the fact that only one patient in our study used tobacco so prevalence of smoking varies widely when compared to population in CASS study. Also the average level of cholesterol in ours study was lower as compared to CASS study. In our study only 28 patients had total cholesterol >200mg/dl and after multivariate analysis there was no significant difference even between the cases and controls. Coronary artery disease patients from India are known to have low cholesterol values (Krishnaswami, 1989). Comparison of cases with controls with normal coronary angiogram revealed significant difference between the groups with to diabetes, hypertension, total cholesterol, HDL, LDL, TG and BMI.

However on multivariate analysis DM, HTN and BMI were found to be significantly associated with the patient group. Diabetes had an odds ratio of 3.3 and hypertension had an odds ratio of 7.7. These observations were in accordance to other studies done with premature coronary artery disease in females (Gupta, 1999; Barbara, 2010). Interesting observation was that HDL was found to be significant but in opposite direction after multivariate analysis and more controls had dyslipidemia as compared to cases. The opposite odds ratio with reference to HDL could be explained by the nature of control group. Control group was composed of patients who were planned to undergo surgery for severe valvular heart disease both rheumatic and degenerative. Various studies have shown negative correlation of HDL with severity of rheumatic heart disease and degenerative aortic stenosis (Mehmet Birhan Yilmaz, 2006; Busseuil, 2008; Yilmaz, 2004). This may be reason of low HDL in our control group. Low HDL in control group was responsible for presence of more dyslipidemic patients in the control group as HDL<50 was included as one of the criteria for classifying as dyslipidemia.

Limitations: There are few limitations of our study. First it is a single centre study, second we didn't evaluated hormonal levels of the patient presenting to us which have been shown particularly important in this subgroup of patients. Third no non conventional risk factors like Lp(a), stress were evaluated which would have shown correlation with the angiographic profile of patients. Also it would have been better if we had larger sample size. The cross sectional nature of study precludes causal relationship to be established.

Conclusion

Premenopausal females with coronary artery disease are not so uncommon entity as initially thought. These patients have high prevalence of conventional risk factors as compared to normal population. Majority of these patients had significant disease in our study. However conventional risk factors failed to predict the presence of angiographically significant disease in this group of patients.

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