A Case – Control Study of Risk Factors for Coronary Artery Disease in Pakistani Females

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Objectives: To establish the strength of association of conventional risk factors for coronary artery disease in native Pakistani females.

Methods: We conducted a case – control hospital based study on 198 females (age 30 – 80 years) scheduled for their first coronary angiography at Punjab Institute of Cardiology, Lahore. Patients were divided into pre-menopausal group (age: 45.1 ± 6.3) and post-menopausal group (62.1 ± 9.1). For each risk factor, patients with significant CAD ($\geq$ 50% luminal diameter stenosis) were regarded as cases an those without significant CAD were taken as controls. Odds Ratios (OR) and their 95% confidence intervals (CI) were calculated by univariate analysis.

Results: In total study cohort, Diabetes mellitus (OR 3.65 95% CI 2.0 – 6.5), Family history of premature coronary artery disease (OR 2.3, 95% CI 1.2 – 4.4), and increased waist circumference (OR 2.11, 95% CI 1.2 – 3.8) were strongly associated with significant CAD. In post menopausal age group, diabetes mellitus (OR 2.66 CI 1.3 – 5.1), hyperlipedemia (OR 2.25 CI 1.2 – 2.3) and increased waist circumference (OR 2.16 CI 1.1 – 4.2) reached statistical significance. In pre-menopausal females only diabetes was strongly associated with significant coronary artery disease (OR 10 CI 2.6 – 37.4). Association of hypertension was not significant in any of subgroups studied. Very few cases of smoking (6 / 198) were found in our study to merit any further statistical analysis.

Conclusions: Diabetes mellitus was the only risk factor in pre-menopausal females associated with coronary artery disease While diabetes, hyperlipedemia and increased waist circumference were significantly associated with CAD in post-menopausal females.

Key words: Coronary risk factors; pre-menopausal females, post-menopausal females, case control study.

Abbreviations: CAD: coronary artery disease; OR: Odds Ratio; CI: Confidence Intervals, CABG: coronary artery bypass grafting: QCA: Quantitative coronary angiography.

Introduction

Coronary artery disease is the leading cause of morbidity and mortality in developed countries and is also becoming the leading cause of death in underdeveloped countries world wide. Many risk factors, first documented in males, were also found to similarly affect females. Hence once established in a country or region, coronary artery disease affects males and females equally.[1] Although recent decades have shown decreasing CAD related mortality in western male population, death rates have either been stable or increased in females.[2,3] In particular, women younger than 55 years, have worse prognosis after acute myocardial infarction than their male counterparts, with greater recurrence and higher mortality.[4]

Currently, Indian Subcontinent is experiencing rapid increase in the rates of CAD.[5] Consequently there is a great interest in clarifying epidemiology of coronary artery disease in this region. Various studies have been carried out in Subcontinent immigrants in developed countries[6,7] and locally in indigenous population.[8,9] These studies suggest an earlier onset of aggressive coronary artery disease with higher rate of complications afterward. Clustering of risk factors was also commonly found in Asians.

The current study is a standardized hospital-based case-control study that seeks to define the strength of association of conventional coronary risk factors in the angiographically proven cases of females with significant coronary artery disease, from an urban community of Punjab.

Methods

This prospective case – control study was conducted at Punjab Institute of Cardiology, Lahore in 2004. Punjab Institute of Cardiology is a dedicated cardiology hospital, serving to both urban and rural population of Punjab.

Cases

In 2004, during a period of six months, 506 consecutive male and female patients undergoing their first diagnostic angiography for suspected ischemic heart disease were interviewed.

Study population consisted of 218 female patients from this cohort. Informed consent was taken from the patients or their guardian. Twenty patients (9%) declined to be included in the study. Remaining 198 female patients or their guardians were interviewed before coronary angiography by a trained doctor. Any missing information was collected from

patient's charts. All the information was collected on a performa which was completed once angiographic findings were made available. A total of 98 females were found to have significant coronary artery disease and were regarded as cases.

Controls

Patients were enquired about seven coronary artery disease risk factors. Within each risk factor group, patients without significant coronary artery disease served as control. One hundred such patients served as controls for this study.

Exclusion Criteria:

Patients with previous evidence of coronary artery disease like previous myocardial infarction, coronary intervention or CABG were excluded from the study. Patients who already had coronary angiogram were also excluded. Similarly patients taking lipid lowering therapy and those with valvular heart disease, cardiomyopathies or myocarditis were also excluded.

Definition of terms:

Significant coronary artery disease:

Fifty percent or more diameter stenosis in any major coronary artery or its major branch (> 2.5 mm) was considered as significant. Each lesion on coronary angiogram was reviewed by two cardiologists who were blinded about the risk profile of the patient. Each lesion was reviewed in two orthogonal planes. In case of disagreement among cardiologist, QCA using Philips Xcelera (PIE Medical CAAS 2000) system was performed.

Risk Factors

Patients on oral hypoglycemic drugs, Insulin or those having fasting blood sugar > 126 g/dl were regarded as having diabetes mellitus. Those with blood pressure > 140 / 90 mmHg taken twice or those on antihypertensive drugs were defined as hypertensives. All the patients had their fasting lipid levels checked one day before coronary angiography. A diagnosis of hyperlipedemia was made if total Cholesterol

is > 160 mg/dl, Triglycerides > 150 mg/dl, and LDL > 130 mg/dl. Waist circumference was measured by a staff nurse at the level of anterior superior iliac spine. A waist circumference greater than 35 inches (89 cm) was considered abnormal.[10] Females 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 history of premature coronary artery disease in the family. Menopause was considered to be present when there was no history of menstrual periods for the last one year. Current smokers were defined as those who smoked any form of tobacco in the previous 6 months while former smoker were those who had quit more than 6 months earlier. History of vascular disease in peripheral limbs, carotid or renal, mesenteric arterial involvement was defined and peripheral vascular disease and considered a positive risk factor.

Statistical Analysis

Independent variables (Risk factors) and main outcome variable (Coronary artery disease) were treated as categorical variables. These are represented by numbers and percentages. Age was regarded as continuous variable and measure of central tendency was mean and standard deviation.

Cases and controls within each risk factor group were used to calculate Odds Ratio and their 95% confidence intervals in univariate analysis.

Results

Between February 2004 and July 2004, a total of 506 patients undergoing their first coronary angiogram for ischemic heart disease were recruited. This study presents the data of 198 female patients from this cohort. Depending upon history of menstrual periods, females were divided into two groups, post – menopausal and pre-menopausal. Presence or absence of significant coronary artery disease was noted for each coronary artery disease risk factor group. Within each risk factor group, those showing significant CAD were regarded as cases while those showing mild coronary artery disease or normal coronaries were regarded as controls.

Table 1: *Baseline characteristic of study population.*

Total Patients: 506	Females: 198			
	Post – Menopausal (n: 147)		Pre – Menopausal (n: 51)	
Clinical Presentation	Cases (n: 79)	Controls (n : 68)	Cases (n: 19)	Controls (n : 32)
Chest pain	40	52	10	28
Acute MI	12	3	3	0
Unstable Angina	25	7	6	4
Cardiac failure	2	5	0	0
Arrhythmias	0	1	0	0

Table 2: *Coronary Artery Disease Risk Factors in Study Population (n: 198).*

Variable	Total *n.* 198 (%)	Post-menopausal *n.* 147 (%)	Pre-menopausal *n.*51 (%)
Age Cases / Controls (Years ± SD)	59.2 ± 11.4 / 56.3 ± 10.9	62.7 ± 9.3 / 61.5 ± 8.8	44.8 ± 7.4 / 45.2 ± 5.7
Diabetes Mellitus	94 (49)	73 (50)	21 (43)
Hypertension	66 (34)	51 (35)	15 (29)
Hyperlipedemia	102 (53)	72 (50)	30 (59)
Waist Circumference >35"	96 (50)	84 (57)	12 (23)
Smoking	06 (3)	06 (4)	0 (0)
PVD / Stroke	4 (2)	4 (3)	0 (0)

SD: Standard deviation; CAD: Coronary artery disease; PAD: Peripheral vascular disease

Table 3: *Clustering of Risk Factors in Patients with significant Coronary Artery Disease.*

No of Risk factors	Total female Cases (n=98)	Post-menopausal Cases (n=79)	Pre-menopausal Cases (n=19)
Single risk factor	17 (17%)	17 (21%)	12 (66%)
Two risk factors	60 (60%)	46 (58%)	5 (24%)
Three risk factors	23 (23%)	16 (20%)	2 (5%)

* Percentages and numbers were rounded to nearest figure

Table 4: Association of Risk factors with Coronary Artery Disease in Total Female Population (*n*: 198)

Variables *n*	CAD *n*	OR (95% CI)	*P*	Odds Ratio (95% CI)
Diabetes Mellitus *94*	62	3.65 (2 – 6.5)	< 0.0001	
Family H/O IHD *15*	33	2.3 (1.2 – 4.4)	0.01	
Waist Circumference "> 35 cm"	57	2.11 (1.2 – 3.8)	0.01	
Hyperlipedemia *102*	57	1.7 (1.0 – 2.9)	0.08	
Hypertension *66*	36	1.3 (0.7 – 2.4)	0.3	

Table 5: *Association of Risk factors with Coronary Artery Disease in Post- Menopausal Female Population (n: 147).*

Variables *n*	CAD *n*	OR (95% CI)	*P*	Odds Ratio (95% CI)
Diabetes Mellitus *73*	*48*	2.66 (1.3 – 5.1)	*0.006*	
Hyperlipedemia *72*	46	2.25 (1.2 – 2.3)	*0.01*	
Waist Circumference ">35 cm" *84*	52	2.16 (1.1 – 4.2)	*0.02*	
Family H/O IHD *40*	26	1.8 (0.8 – 4.0)	*0.09 (NS)*	
Hypertension *51*	30	1.3 (0.7 – 2.7)	*0.36 (NS)*	-.5 1 2 3 4

Table 6: *Association of Risk Factors with Coronary Artery Disease in Pre-Menopausal Female Population (n: 51).*

Variables *n*	CAD *n*	Odds Ratio (95% CI)	*P*
Diabetes Mellitus *21*	14	10 (36 – 37.4)	0.0001
Family H/O IHD *11*	7	4.0 (1.0 - 16)	0.07 (NS)
Hyperlipedemia *30*	11	0.9 (0.3 – 2.9)	0.09 (NS)
Hypertension *15*	6	1.17 (0.3 – 4.0	0.8 (NS)
Waist Circumference ">35 cm" *12*	5	1.2 (0.3 – 4.7)	0.07 (NS)

Baseline Characteristics of the Study Groups

Table 1 shows the baseline characteristics of the study population. Mean age between cases and controls within the two main groups did not differ significantly, while mean age of pre-menopausal group was 17 years lower than mean age of post-menopausal group. Majority (62.5%) of post-menopausal females underwent coronary angiogram due to complaint of exertional chest discomfort. However proportion of patients with acute myocardial infarction and unstable angina was much higher (25%) in those with significant coronary artery disease than those without (7%). Majority of pre-menopausal females underwent coronary angiography due to chest pain on exertion.

Prevalence of Risk Factors

Table 2 shows the prevalence of six main risk factors for coronary artery disease among cases and controls of post-menopausal and pre-menopausal groups. Hyperlipedemia, was the most prevalent risk factor in total female study (53%) population as well as in post (50%) and pre-menopausal (59%) groups. About half of the total female population had increased waist circumference, however it proportion was low (23%) in pre-menopausal group than in post-menopausal group (57%). Diabetes mellitus was found in almost half of the total females and in both main groups. Hypertension was the next most prevalent risk factor. Predictably very few cases of smoking and peripheral vascular disease were noted.

Table 3 shows that clustering of risk factors was common in our study population with coronary artery disease. 60% of total female cases had two coronary artery disease risk factors. Same proportion was noted in post menopausal group. Three risk factors were noted in 23% of the total cohort and 20% of post menopausal group. In pre-menopausal group majority (66%) had single coronary risk factor while 24% had two risk factors. Only few pre-menopausal females had three coronary risk factors.

Association of Risk Factors with Significant Coronary Artery Disease

Table 4 shows the overall odds ratios for individual risk factors in total study population. Diabetes mellitus emerged as strongest risk factor (p < 0.0001), followed by family H/O ischemic heart disease and increased waist circumference. Hyperlipedemia and hypertension, did not reach statistical significance.

Table 5 shows Odds Ratios for individual risk factors in post-menopausal females. Here again diabetes mellitus showed the strongest association with coronary artery disease (p < 0.006). Hyperlipedemia and increased waist circumference were also significantly associated with coronary artery disease. In post menopausal females, family history of ischemic heart disease and hypertension did not reach statistical significance.

Table 6 shows results in pre-menopausal females. Diabetes mellitus was the only risk factor associated with coro-nary artery disease in pre-menopausal females. Other risk factors had no statistically significant association with coronary artery disease in this young population.

Discussion

The study was designed to assess the prevalence of conventional coronary risk factors, and their strength of association with coronary artery disease in native female population. Diabetes mellitus, hypertension, hyperlipedemia, increased waist circumference and family history of premature heart disease were analyzed by univariate analysis to assess their strength of association with angiographically proven significant CAD.

A total of 198 females who were scheduled for coronary angiography due to suspected coronary artery disease, participated in this study. Common coronary risk factors were noted in all the patients and every patient underwent coronary angiogram. We divided females into two groups according to their menopausal status instead of grouping by patient's age. This was done to clarify the nature of CAD risk factors in younger females of child bearing age. It is not uncommon these days to see pre-menopausal females admitted with coronary artery disease. However no study in Pakistan and very few in other countries has studied this segment of female population.

We noted high prevalence of coronary artery disease risk factors in our study population.

Prevalence of diabetes mellitus was around 50% in total female and post-menopausal cohorts and 43% in pre-menopausal group. Similarly, high prevalence of hyperlipedemia (53%), increased waist circumference (50%) and hypertension (34%) were noted. This proportion is high if one considers that prevalence of diabetes mellitus in Pakistani females population is estimated to be 3.5% and 2.5% in urban and rural areas respectively, while prevalence of overall glucose intolerance is 17.5%.[11] Similarly estimated prevalence of hypertension in adult Pakistani females is 32.7%, Hyperlipedemia in 20.9% and obesity is estimated to be 22.6%.[12] However this high prevalence of risk factors in female patients undergoing coronary angiography was also noted in Indian studies. Dave TH et al[13] found a prevalence of diabetes mellitus as 44.3%, Hyperlipedemia 58%, obesity 58.3% and hypertension 52.9% in female population undergoing coronary angiography at their center. Oomman A et al[14] also cited similarly high prevalence of conventional risk factors in female population scheduled for coronary angiography at their hospital.

Clustering of risk factors was also common in study population. Majority of the total female cases and post-menopausal females cases had more than one coronary artery disease risk factors. In younger females of pre-menopausal group however majority had single coronary artery disease risk factor.

This high prevalence of risk factors in our study population could be due to selection bias of a hospital based study. But it also reflects high prevalence of multiple risk

factors at a younger age in our community and fact that diabetes mellitus is known clinically to be a strong risk factor of ischemic heart disease in females, leading to low threshold of investigating chest pain.

This study showed a strong association of diabetes mellitus, increased waist circumference, hyperlipedemia and family history of IHD with significant coronary artery disease. However their relative importance differed in various groups. Diabetes Mellitus was found to be most strongly associated with CAD in all the three groups. This was particularly so in pre-menopausal age group where it was the only significant risk factor found. Diabetes eliminates the usual gender gap in CAD mortality and may induce accelerated atherogenesis to a greater extent in women than in men.[15]

Increased waist circumference (more than 35") was also significantly associated with significant coronary artery disease in total female population as well as in post-menopausal females. Cutoff point of 90 cm (35 inches) was chosen before lower ethnic – specific measures for waist circumference (less than 80 cm / 31.5 inches) were recommended by various health advisory groups.[16] This lower cutoff point would have resulted in more females being included in this risk category. Increased waist circumference is one of the five criteria of underlying metabolic syndrome. Many of our patients had clustering of risk factors constituting metabolic syndrome, however we did not evaluated this syndrome as an independent coronary artery disease risk factor.

Hyperlipedemia showed a statistically significant relationship in post-menopausal females only. Despite its high prevalence in total female and pre-menopausal population it did not reach statistical significance in these subgroups. LDL and total cholesterol, as we measured in this study has shown modest and weaker relationship with coronary artery disease in native[17] and immigrant[18] Pakistani population. In contrast, some Indian studies[19] have found strong relationship of ambient lipid levels with sub-clinical atherosclerosis. However modest hyperlipedemia as found in Indo – Pak population is not expected to produce significant coronary artery disease in relatively young pre-menopausal females unless there is some rare heritable defect in handling of lipid metabolism. Secondly had we measured HDL levels in patients, results would have been more consistent across the subgroups.

Family history of premature coronary artery disease was strongly and significantly associated with significant coronary artery disease in our total female cohort. The odds of having CHD were 2.3 in those who had positive family history of premature CHD in their first degree relatives. However in subgroup analysis in post and pre-menopausal females, though it achieved odds of more than one, it did not reached statistical significance. Although it is widely regarded as an independent risk factor for CAD in multivariate analysis in several studies,[20,21] it is controversial whether family history of premature coronary artery disease act as an independent risk factor. In INTERHEART, when family history was added to the information from other significant risk factors, the overall PAR rose from 90.4% to only 91.4%, indicating that although family history is an independent risk factor for MI, most of the associated risk burden can be accounted for by other risk factors.[1]

Prevalence of hypertension was between 30 and 40% in total and both sub-groups. This is consistent with population based studies from this country.[12] However it failed to show any positive statistical relationship with significant coronary artery disease in our study population. This discrepancy may be due to high prevalence of hypertension in our control population. One reason for this could well be the stress of oncoming coronary angiography in patients which admittedly would have affected controls more than cases.

Conclusions

In this case control study we have shown that female Pakistani population has high prevalence and clustering of traditional risk factors. This necessitates integrating these risk factors into a global risk score to better predict future coronary events in the females. Similarly preventive measures should address not only single risk factors but should be more encompassing. Physically active life style to control abdominal obesity and diabetes, heart healthy diet and use of statins to control hyperlipedemia should be encouraged. Every attempt should be made to keep cigarette consumption in females at the current level. These measures are economically feasible in our developing country.

Limitations

Ideally, to identify association of risk factor to a disease should be done through a prospective cohort study, but time constraint and limited resources forced us to choose a hospital based case-control study. Clustering of risk factors was common in our study population. To mitigate against confounding effects of multiple risk factors present in a patient, logistic regression analysis should have been done. Additionally socio-economic and psychological analysis as a risk factor for CAD should have been done, but it was beyond the scope of this study.

Finally, the excessively high Odds Ratios and wide 95% Confidence intervals noted in pre-menopausal group are probably due to limited number of cases per risk factor. However our study has shown some light on risk factors in this hitherto untouched group in Pakistan. A more extensive study in future will be very helpful in resolving this issue.

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