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Identification of Risk Factors Associated with Coronary Artery Disease in Haryana: is There a Need to Screen Genetic Risk Factors in Young Patients?

KEYWORDS: Coronary artery disease, hypertension, dyslipidemia, diabetes, family history

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ABSTRACT *Background: Coronary artery disease (CAD) accounts for high morbidity and mortality worldwide. The incidence of CAD is in epidemic proportion in India and state Haryana due to lack of awareness about the associated risk factors of the disease. Study was designed to assess the age and gender specific associated risk factors in CAD patients from Haryana and to evaluate the risk factors in young patients.*

Materials and Methods: Out of 406 CAD (postmyocardial infarction-110, ischemic heart disease -296) patients, 303 were male and 103 were female with mean age of 50.62±12.73 years. The Patients were recruited on the basis of ECG, clinical examinations and investigations.

Results: Smoking was most prominent risk factor in males followed by dyslipidemia, hypertension, diabetes and obesity while dyslipidemia was most frequent in females followed by hypertension, obesity and diabetes. Significant age associated differences was observed in incidence of hypertension, diabetes, family history, either of or no modifiable risk factor and no known risk factor in males ($p<0.05$) while family history, either of or no modifiable risk factor and no known risk factor in females ($p<0.05$). High incidence of positive family history and no known risk factor was found in young patients.

Conclusion: Reducing exposure to smoking and collective management of dyslipidemia, hypertension and diabetes may significantly reduce the burden and risk of CAD. Risk factors in young patients were nearly same as of other participants but the high incidence of positive family history and no known risk factors in young patients suggest the genetic screening to uncover risk factor.

Introduction

Coronary artery disease (CAD) is one of the major causes of death and disability in India and across the world.[1-4] The CAD develops due to buildup of atherosclerotic plaque in coronary arteries that leads to the disease condition which includes acute coronary syndromes (ACS), myocardial infarction (MI), ischemic heart disease (IHD) etc. Although, the CAD related death rate declined in the developed counties due to increasing awareness of the CAD risk factors in the society and public health interventions but in the low income and developing countries the CAD is rising in significant proportion of the population.[1,3] The South Asian populations including Indians are believed to be at higher risk of CAD as compared to western countries.[5] The prevalence of CAD is consistently increasing in India.[6,7] Hence, the knowledge of predominant risk factor of the disease needs to be known.

CAD is a multifactorial disorder which is associated with environmental and genetic factors. The well determined modifiable risk factors of CAD include hypertension, diabetes, smoking, obesity, alcohol consumption, lack of exercise, dyslipidemia and; non-modifiable risk factors are age, gender, race and family history.[6,7] These risk factors have been widely explored worldwide and management of these risk factors is useful in reducing the burden of CAD.

CAD has been considered as a disease of over the age of 40 years but the younger male and female may also affected. The silent process of CAD in younger patients limits the scope of estimating the prevalence of disease.[8] In view of gender, the coronary manifestation arises usually 10 years later in female due to effect of estrogen than in male and, also the risk of MI is 10 years later in female than in male. The risk of CAD is equal in male and female at the age of 80 years.[7, 8]

Among adults over the age of 20 years, the estimated prevalence of CAD is around 3-4 % in rural areas and 8-10 % in urban areas, representing a two-fold rise in rural areas and a six-fold rise in urban areas between 1960 and 2000 from India.[6,7] The CAD has been projected as major cause of morbidity and mortality in the developing counties by the year 2020. [4,9,10] It's of prime importance to understand the risk factors in young patients to reduce the disease burden at early age since mortality in young age have significant influence on the patients family and society particularly in India and the state like Haryana.

Haryana is a small state in North India with the population of 25.4 million with male and female sex ratio of 1000: 879 according to 2011 census.[11] The rural population contributing 65.12% while urban 34.88%. With the

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development of economy and changing lifestyle in the last decades particularly among the young aged people in Haryana, the knowledge of the CAD associated risk factor may be helpful in reducing the burden of CAD in Haryana. The patient's race and positive family history of CAD add an extra risk factor for the occurrence of the disease. Non-modifiable risk factor like age, gender, genetics and family history cannot be change but the risk can be minimized with prior information or knowledge.

Therefore, a study has been designed with the objectives to identify the risk factors associated with the CAD, to identify precise risk factors in young aged patients if any and; what next to be evaluated in the CAD patients with no known risk factor of CAD in Haryana ?

Material and Methods

Patients: The study subjects were the patients who were on treatment or on follow up in the ward and outpatient department of department of Cardiology at Pt. B.D. Sharma PGIMS, Rohtak from April 2015 to September 2015. The institution is located in the center of the state of Haryana. Most of the patients visiting this hospital were from various districts (Rohtak, Jhajjhar, Jind, Bhiwani, Sonepat and Panipat) of Haryana and have mixed urban and rural population. Total of 406 patients of coronary artery disease (Post MI- 110, IHD-296) were recruited in this study. The patients were grouped with respect to their age (≤30, 31-40, 41-50 and ≥51 years) and gender for analysis of associated risk factor. The incidence of risk factors of the patients of the age of ≤40, ≤50 years and rest were also evaluated. The disease was categorized on the basis of ECG findings, clinical examinations, investigations and medical records. Ischemic heart disease is evident in coronary angiogram or having TMT (Treadmill test) positive. Post-myocardial infarction patients having history of percutaneous coronary intervention with or without stenting or coronary bypass graft or medical management with fibrinolytics or heparins.[12]

Risk factors: - Smoking /Tobacco chewing: Patients who have reported history of smoking of >10 bidies, cigarettes and hukka or chewing tobacco per day for at least one year prior to visit to our hospital for treatment. Dyslipidemia: Patients having total cholesterol >240 mg/dL, triglycerides (TG) >150 mg/dL, low- density lipoprotein (LDL) > 130 mg/dl, high-density lipoproteins (HDL) <40 mg/dL (males) / <50 mg/dL (females) or on lipid lowering drugs. Hypertension: Patients having systolic BP (SBP) ≥ 140 and or diastolic BP (DBP) ≥ 90 mm Hg or patients are on antihypertensive drugs were defined as hypertensive. Diabetes: Fasting blood sugar ≥126 mg/dL, Post prandial 2 h blood sugar ≥200 mg/dL. Obesity: BMI 18.5-24.9 kg/m^2 defined as normal, 25.0-29.9 kg/m^2 as overweight and ≥30 kg/m^2 as obesity. Alcohol: Patients who have ≥4 alcoholic drink per day for at least a year were considered alcoholic. Family history: The patients whose parents and siblings had an event of premature cardiovascular disease before the age 45 years in male and 55 years in female were labeled as positive family history of CAD.

Statistical analysis: - The continuous variables were represented as mean ± S.D. and the ordinal variables as percentage. The prevalence rates of the risk factor in various age groups at decade intervals have been shown in percentage. The statistical significant difference of the trend of the prevalence of risk factor was determined by Mantel-Haensezel X ^{2} for trend of ordinal variables using SPSS software, version 16.0. The p values <0.05 was considered as statistically significant.

Results

Out of 406 (Post MI-110, IHD-296) coronary artery disease patients recruited in this study, 303 (74.63%) were male and 103 (25.36%) were female. The mean age of the patients was 50.62 ± 12.73 years. The mean age of male patients was 50.5 ± 12.86 years and of female patients was 50.99 ± 12.38 years. The age wise distribution of the male and female patients in the disease categories have been shown in Fig 1 a & b.

Of the male study participants, the 6.93 %, 18.48%, 28.71% and 45.87% of patients were in the age group of 23-30, 31-40, 41-50 and 51-87 years respectively (Table-1). Among female participants, 6.79%, 15.53%, 26.21% and 49.51% of patients were in the age group of 24-30, 31-40, 41-50 and 51-81 years respectively (Table-2). The prevalence of CAD is increasing in higher age groups in both male and female. The 25.4% male and 22.3% of female patients were ≤40 years of age (Table-3) while 54.1% of male and 48.5% of female patients were ≤50 years of age (Table 4). The high incidence of the disease evident in patients in age of 41-50 years of this study with ~25% of the CAD patients was ≤40 years.

Smoking was the most prominent risk factor of the coronary artery disease among the male patients in this study. 70.6% of the male of this study were smokers while 10.6 % of the female were smokers. The significant age associated increase in incidence of smokers was not observed in male and female patients (p>0.05). (Table 1 & 2) However, the high incidence of smokers was found in all age group of males. Similarly, the consumption of alcohol was risk factor associated with males in this study. History of alcohol consumption was found on 24.4% of the males while none of the females. (Table 1&2)

Of the study patients, dyslipidemia was found in 42.5% of the male and 38.8% of the female patients. 23.8% of the male and none of the female patients below the age of 30 years had dyslipidemia. The significant age associated increase in incidence of dyslipidemia was not observed in male and female patients (p>0.05). (Table 1 & 2) Nearly all the participants of this study consumed clarified butter, oils in their food prior to an episode of MI or diagnosis of IHD. Only 31.03% of the study participants were doing physical exercise for ≥30 minutes/ day.

The incidence of hypertension was 25.08% in male and 32.08% of the female. None of the male and female patients below 30 years of age were hypertensive. The significant age associated increase in incidence of hypertension was observed in male (p <0.05) but not in female patients (p>0.05). (Table-1 & 2)

Diabetes mellitus was found in 20.01% of the male and 24.2% of the female patients of this study. None of the male and female patients below 30 years of age have evidence of diabetes mellitus. The significant age associated increase in incidence of diabetes was observed in male (p <0.05) but not in female patients (p>0.05). (Table-1 & 2)

Obesity was found in 16.8% of the males and 28.1% of the female of this study. None of the male and female patients below 30 years of age had obesity. The significant age associated increase in incidence of obesity was not observed in male and female patients (p>0.05). The highest incidence of obesity 37.03% was recorded in female

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patients of the age group of 41-50 years. (Table 1& 2)

Of the patients studied for modifiable risk factor of the CAD, 84.1% of the male and 62.13% of the female showed the presence of at least any one of the modifiable risk factor. No modifiable risk factor was found in 15.8% of male and 37.8% females of the study. The significant age associated difference in incidence of either of modifiable risk factor and no modifiable risk factor was observed in male and female patients ($p<0.05$). (Table 1 & 2)

The positive family history of the disease was observed in 16.1 % of the male and 30.09% of the female patients. The much higher incidence of positive family history was observed in younger patients. The CAD patients who do not have any of the modifiable and non-modifiable risk factor evaluated in this study were mentioned as patients with no known risk factor of disease. No known risk factor was found in 11.2% of the male and 18.4% of the female participants. The significant age associated difference in incidence of positive family history and no known risk factor was observed in male and female patients ($p<0.05$). (Table 1 & 2)

The 32.46% of male and 60.9 % female study participants of ≤40 years of age had positive family history. Also, no known risk factor was found in 18.1% of male and 30.04% of the female study participants of ≤40 years of age. (Table-3) In the group of patient of ≤50 years, 23.78% of male and 48% female study participants have positive family history and no known risk factor was found in 15.85% of male and 30% of female. (Table-4) Two to three times higher incidence of positive family history and no known risk factors was observed in younger (≤40, ≤50 years) patients compared to rests (Table 3 & 4).

Discussion

In the present study, the mean age of the study patients were 50.62±12.73 Years, which is lesser than the mean age of the studies reported from western countries. Occurrence of heart diseases in India is considered as 5 to 10 years earlier than in other populations around the world.[13] According to the INTERHEART study, the median age 53 years has been reported for the first presentation of acute MI in the South Asian (Bangladesh, India, Nepal, Pakistan, Sri Lanka) population while 63 years that in Western Europe, China and Hong Kong.[14] However, mean age of 63 years has been reported from a north Indian study but there is no improvement from Haryana according to this study .[15] Nearly 25% and 50% of the CAD patients were ≤40 and ≤50 years of age respectively revealed that the patients are getting exposed to risk factor of CAD at an early age in Haryana.

On evaluation of the frequency of the risk factor, the smoking was found as the most prominent risk factor of the CAD in males contributing 70.6% of the patients which is higher than other Indian studies.[2, 6, 7] 42.8% of the male patients between 23-30 years were also smokers. No age associated statistical significant increase in incidence of smoking showed that the patients in all age groups have exposure to this risk factor equally. The low incidence of 10.6% smokers in the female subject considered as insignificant factor. None of the female patient between 23-30 years was a smoker. The low incidence of the smokers among female may be due to unavailability of the tobacco products to the females due social scenario but it's a good sign which reduces the prevalence of CAD in females. High prevalence of male patients than female in this study may be because of the higher exposure of males to smoking.

The uses of clarified butter, vegetable oils are the part of traditional diet in this region. Peoples believe that consumption of fat rich diet is good for the health and same is reflecting in the results. Dyslipidemia is the second highest risk factor in the patients studied. The evidence of dyslipidemia was revealed in 42.5% of the male and 38.8% female which is comparable to each other. 23.8% of male while none of the female ≤30 years of age had dyslipidemia. No age associated statistical significant increase in incidence of dyslipidemia in both male and female showed that the patients in all age groups have exposure to the risk factor equally. The pathogenesis of dyslipidemia is well established in the CAD. The increased level of low-density lipoprotein cholesterol (LDL-C) and triglycerides and decreased concentration of high-density lipoprotein cholesterol (HDL-C) is an important risk factor for CAD. The studies from India demonstrated upto 70% of the participants having evidence of dyslipidemia. Dyspilidemia was reported 18.7 % to 58 % from various part of the world and contributed significantly as a risk factor in the progress of arthrosclerosis process.[13-17]

The incidence of hypertension was 25.08% in male and 32.03% in female patients. None of the male or female patient was hypertensive below the age of 30 years. Hypertension contributing as risk factor in significant proportion after 50 years of age cases of this study. Age associated statistical significant increase in incidence of hypertension seen in males while insignificant in females. It shows that the risk factor of hypertension in male patients increases with age while not in female. According to the WHO global health statistics 2012, 23.10% men and 22.6% women over 25 years old suffer from hypertension in India.[18] Therefore, the hypertension alone cannot be considered as significant risk factor in the young patients of this study having comparable incidence.[16]

Diabetes has been identified in 20.1% of male and 24.2% of the female patients. Trend of diabetes is like of hypertension in various age groups. Incidence of Diabetes mellitus reported to be increased from 32 million to 50 million in past decades and projected to be 87 million by 2030 in India.[19] Like hypertension, diabetes alone cannot be considered as significant risk factor in the young patients of this study but required monitoring in such patients since diabetes is known for accelerating the process of atherosclerosis.[15, 16]

Obesity was found in 16.8% of male and 28.1% of the female according to the BMI. The evidence of obesity was not found in male and female patients of below age of 30 years. No age associated statistical significant increase in incidence of obesity in both male and female showed that the patients of all the age groups have been exposed to the risk factor equally. Long-term studies indicated that obesity independently as such does not predict arthrosclerosis. Nevertheless, the co morbidities associated with the CAD may be related to fat distribution.[2,6] Alcohol consumption was evident in 24.4% of male while none of the female patients consumed alcohol. The moderate quantity of alcohol consumption (1 drink per day for females and up to 2 drinks for males) can be protective while heavy drinking (4-5 drink per day) may be a risk.[20]

The evidence of the any one of the modifiable risk factor studied was found in 84.1% of male and 62.13% of female

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patients of this study. Age associated statistical significant increase in incidence of any one of the modifiable risk factor in male and female showed that it is very crucial to address the risk factors collectively to reduce the burden of CAD in Haryana. Since the risk factors occur in clusters and may have synergistic effect in the progress of the process of atherosclerosis. The awareness of no smoking, management of dyslipidemia, hypertension, diabetes by drugs and changing lifestyle may significantly reduce the burden of CAD in Haryana.

None of the modifiable risk factor was observed in 15.8% of male and 37.8% of the female patients and there is outmost need of addressing the non modifiable factors such as family history, genetics factors in such patients. The 16.1% of male and 30.09% of female study participants have positive family history of the diseases. The age associated significant difference in incidence of positive family history and unknown risk factor was observed in male and female patients implies the need to address these factors particularly in young patients. The higher frequency of patients with no modifiable, positive family history and unknown risk factor for the diseases in the young aged patients (Table 3 &4) suggest the need to look for the genetic interventions. Individual with genetic susceptibility are on higher risk of developing the diseases at early age.[21] Family history of premature CAD in first degree relatives is associated with development of CAD in young patients from India.[22]

A large number of studies on screening the candidate genes and genome-wide association analysis for the identification of the CAD risk factor and; some have promising signals. In Asian Indian families, role of Interleukin-6 gene polymorphisms have been described in the regulation of key atherogenic markers and genetic factors in premature CAD.[22] Low molecular weight isoforms of lipoproteins were reported to be associated with a positive family history of premature CAD in Indian patients. [23] The genetic factors may have strong association with one of the major modifiable risk factor dyslipidemia in this study. The screening and analysis of genetic factor may be helpful for the management of dyslipidemia and also helpful in executing the preventive strategies where the risk factors are not known in the young CAD patients of Haryana.

In conclusion, the mean age of CAD patients from Haryana are comparable with South Asian studies which is 5-10 years earlier than western countries. Smoking was found to be the most predominant risk factor in the male patients of this study. Many of the patients have two or more risk factors. More than one risk factors of the CAD in the study may induce synergistic effect in the progress of the process of atherosclerosis. The study highlighted that dyslipidemia; hypertension and diabetes are the potential risk factor and need to be targeted. Reducing exposure to smoking in males and; management of dyslipidemia, hypertension and diabetes in both male and females by means of changing lifestyle, food habits and drugs may significantly reduce the burden of CAD in this region. The risk factors associated with the CAD in young patients were almost the same as of other participants with 2-3 times higher incidence of positive family history and unknown risk factor. Such patients needs to be the screened for other parameters like homocysteine, c-reactive proteins, lipoproteins and genetic factors to identify the associated risk factor of the disease for early management and precautions. Our research group will focus on these associated risk factors in young patients in future.

Table: - 1 Frequency of associated risk factors and their trend in male patients of coronary artery disease in different age group.

Risk Factor	Number of cases (%) in different age groups					P Value (X^2 trend)
	23-30 years	31-40 years	41-50 years	51-87 years	23- 87 years	
	21 (6.93)	56 (18.48)	87 (28.71)	139 (45.87)	303 (100)	
Smoking	9 (42.8)	41(73.2)	67 (77.01)	97 (69.7)	214 (70.6)	>0.05
Dyslipidemia	5 (23.8)	26 (46.4)	39 (44.8)	59 (42.4)	129 (42.5)	>0.05
Hypertension*	-	9 (16.07)	15 (17.2)	52 (37.4)	76 (25.08)	<0.05
Diabetes*	-	8 (14.2)	12 (13.7)	41 (29.4)	61 (20.1)	<0.05
Obesity*	-	11 (19.6)	13 (14.9)	27 (19.4)	51 (16.8)	>0.05
Alcohol	1 (4.7)	15 (26.7)	21 (24.1)	37 (26.6)	74 (24.4)	>0.05
Either of Modifiable risk factors (MRF)	11 (52.4)	45 (80.35)	72 (82.75)	127 (91.4)	255 (84.1)	<0.05
No MRF	10 (47.6)	11(19.6)	15 (17.2)	12 (8.6)	48 (15.8)	<0.05
Positive Family History	10 (47.6)	15 (26.7)	14 (16.09)	10 (7.1)	49 (16.1)	<0.05
No known Risk factor	4 (19.04)	10 (17.8)	12 (13.7)	8 (5.7)	34 (11.2)	<0.05

* In the age group of 23-30 years where no patients is associated with a parameter were not included for statistical analysis.

Table: - 2 Frequency of associated risk factors and their trend in female patients of coronary artery disease in different age group.

Risk Factor	Number of cases (%) in different age groups					P Value (X^2 trend)
	24-30 years	31-40 years	41-50 years	51-81 years	24- 81 years	
	7 (6.93)	16 (15.53)	27 (26.21)	53 (49.51)	103 (100)	
Smoking*	-	1 (6.2)	4 (14.8)	6 (11.3)	11 (10.6)	>0.05
Dyslipidermia*	-	5 (31.2)	12 (44.4)	23 (43.3)	40 (38.8)	>0.05
Hypertension*	-	4 (25)	8 (29.6)	21 (39.6)	33 (32.03)	>0.05
Diabetes*	-	2 (12.5)	6 (22.2)	17 (32.07)	25 (24.2)	>0.05
Obesity*	-	3 (18.7)	10 (37.03)	16 (30.1)	29 (28.1)	>0.05
Alcohol*	-	-	-	-	-	
Either of Modifiable risk factors (MRF)*	0 (0)	7 (43.75)	16 (59.25)	41 (77.35)	64 (62.13)	<0.05
No MRF*	7 (100)	9 (56.2)	11 (40.7)	12 (22.6)	39 (37.8)	<0.05
Positive Family History	5 (71.4)	9 (56.2)	10 (37.03)	7 (13.20)	31 (30.09)	<0.05
No known Risk factor	2 (28.5)	5 (31.2)	8 (29.6)	4(7.5)	19 (18.4)	<0.05

* In the age group of 24-30 years where no patients or all patients associated with a parameter were not included for statistical analysis.

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Table-3: Gender wise comparison of the frequency of the risk factors in CAD patients of age ≤40 years and ≥ 40 years of age.

Risk factor	Number of cases (%)			
	Male (N=303)		Female (N=103)	
	≤40 years	≥ 40 years	≤40 years	≥ 40 years
	77 (25.4)	226 (74.6)	23 (22.3)	80 (77.7)
Either of Modifiable risk factors (MRF)	56 (72.72)	199 (88.05)	7 (30.4)	57 (71.25)
None of MRF	21 (27.27)	27 (11.94)	16 (69.56)	23 (28.75)
Positive Family History	25 (32.46)	24 (10.61)	14 (60.9)	17 (21.25)
No known Risk factor	14 (18.1)	20 (8.84)	7 (30.04)	12 (15)

Table-4: Gender wise comparison of the frequency of the risk factors in CAD patients of age ≤50 years and ≥ 50 years of age.

Risk factors	Number of cases (%)			
	Male (N=303)		Female (N=103)	
	≤50 years	≥ 50 years	≤50 years	≥ 50 years
	164 (54.1)	139 (45.9)	50 (48.5)	53 (51.5)
Either of Modifiable risk factors (MRF)	128 (78.04)	127 (91.36)	23 (46)	41 (77.3)
None of MRF	36 (21.95)	12 (8.6)	27 (54)	12 (22.6)
Positive Family History	39 (23.78)	10 (7.1)	24 (48)	7 (13.2)
No known Risk factor	26 (15.85)	8 (5.7)	15 (30)	4 (7.5)

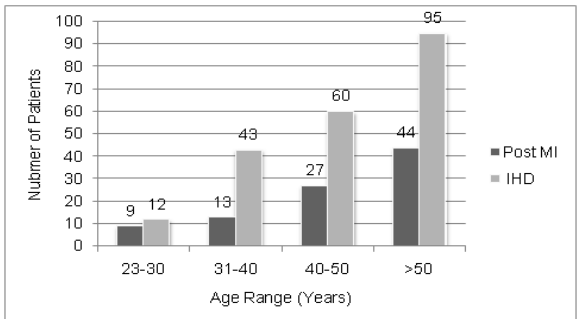

Fig :- 1a Agewise distribution of the male patients of different categories of coronary artery disease (MI-93, IHD-210) included in the study.

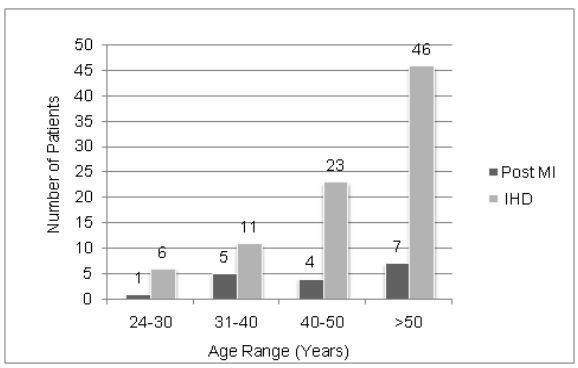

Fig :- 1b Agewise distribution of the female patients of different categories of coronary artery disease (MI-17, IHD-86) included in the study.

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