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Original Article

Premature coronary artery disease and risk factors in India

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Summary

Background: The prevalence of CAD has progressively increased in India during latter half of the last century, particularly among the urban population. Indians also show higher incidence of hospitalisation, morbidity and mortality than other ethnic groups. In the Western population, incidence of CAD in the young is up to 5 % as compared to 12-16% in Indians.

Objectives: To see the frequency of different risk factors for coronary artery disease in young population age < 40 years.

Methods : The study was carried out on patients attending Cardiology OPD, MEDICINE OPD, CCU and Medicine wards in JNMCH, AMU Aligarh from dec 2010 to dec 2011.A total number of 40 patients, aged upto 40 years with clinical and ECG features suggestive of ischemic heart disease were evaluated in this study. This is an Observational study.

Results: Total of 40 patients were selected for study. In patients with young CAD smoking was seen 29 patients (72.5%). Low HDL was found in 15 patients (37.5%), raised LDL was seen in 33 patients (82.5%),hypertension in 21 patients (52.5%), impaired fasting glucose / DM in 8 patients (20%). 27 patients (67.5%) had a positive family history of CAD. 20 patients (50%) were overweight, had BMI >30, 20 patients (50%) had STEMI. In that, 18 patients had AWMI(45%) and only 2(5%) had IWMI. 2(5%) had new onset LBBB. 11(27.5%) had NSTEMI and 7(17.5%) had Unstable angina. On echocardiography, 29 patients (72.5%) had LV dysfunction.

Conclusion: The study shows that premature coronary artery disease in Indians is due to combination of thrombotic and atherosclerotic risk factors. Most common clinical presentation was in the form of STEMI and AWMI was the commonest. Males were commonly affected especially in the younger age group. Significantly, major risk factors like smoking, psychological stress, and hypertension were also evident among men as compared to women. Our study is important in fact that it generalizes the importance of smoking and dyslipidemia as primary targets for effective prevention of CAD in young Indians and stresses the need to look into newer risk factors i.e.Lp(a), low HDL, homocysteine, fibrinogen in young population and also to explore the possible association of drug addiction, infection and other miscellaneous factors which may be unique to the increasing problem of CAD in Indian subcontinent , specially in young. (Indian J Cardiol 2013,16:5-11)

Key words : LDL - low density lipoprotein, CAD - coronary artery disease, HDL - high density lipoprotein, DM - diabetes mellitus, Lpa - lipoprotein A, AMI - acute myocardial infarction, SVD - Single vessel disease, MVD-Multi vessel disease, STEMI- ST Elevated MI, NSTEMI - non ST elevated MI

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Introduction

The prevalence of CAD has progressively increased in India during latter half of the last century particularly among the urban population[1]. Premature CAD is defined as cardiac events occurring before the age of 45 in men and 55 in women . In its severe form, it is defined as CAD occurring below the age of 40 years. Cardiovascular disease is the leading cause of death in India accounting for 28% of mortality[2]

Risk of CAD in Indians is 3-4 times higher than White Americans ,6 times higher than Chinese ,and 20 times higher than Japanese [3,4],.

Indians are more prone as a community to CAD at a much younger age[5,6]. Indians also show higher incidence of hospitalization ,morbidity and mortality than other ethnic group[7] . In the Western population, incidence of CAD in the young is up to 5 % as compared to 12-16% in Indians[8,9] In some studies from India, percentage of patients below the age of 45 years suffering from acute MI is reported as high as 25-40%[10].The hospitalization rate for CAD at Christian Medical College Vellore , South India ,has increased from 4% of all cardiac admissions in 1960 to 33% in 1989[11]. In Singapore, mortality from CAD below 30 years of age is 10 times higher in Indian than Chinese population of the same age group[12] Young patients from other communities do not show extensive disease[13] whereas in young Indians there is often three vessel disease with poor prognosis[14] The post infarction period is also worse in Indians as compared to whites. This is reflected by three times higher rate of re-infarction and two times higher rate of mortality[15] The prevalence of CAD is two times higher than in rural India[16]. South Indians have higher prevalence The vulnerability of urban Indians to CAD is possibly related to different nutritional, environmental, and life style factors .The BMI in urban Indians as compared to rural Indians is 24 vs. 20 in males and 25 vs. 20 in females. Unfortunately, the on going urbanization of rural India is likely to narrow down these differences. Migration from rural to urban environment and migration from India to industrialized countries is another special risk factor for our people. Migration is usually associated with stress of seeking and maintaining the new job. Risk factor evaluation must start earlier.

High cholesterol level, the major modifiable risk factor for heart disease, has both environmental and genetic component. Premature CAD in the Indian population might be due to an unhealthy lifestyle alone or due to genetic factors in combination with an unhealthy life style. The genetic component has been largely ignored in india although it has the highest number of deaths due to heart disease. It would be interesting to determine what fraction of deaths due to CVD are due to genetic factors, specially family history. Many countries in the west have introduced MEDPED (make early diagnosis to prevent early death) programmes. An index case with family history is identified, and the responsible molecular mutation is determined. Then using a combination of cholesterol levels and mutation studies, the extended family members are screened. The programme has been highly successful in reducing mortality due to CVD in these subjects[17].

Role of genetics in CAD (thrifly gene hypothesis) requires detailed research in India.

Lp(a) : Independent risk factor .It is a genetic risk factor like LDL receptor gene, Apo B and PCSK9 promotes early atherosclerosis and thrombosis. 10 times more atherogenic than LDL-C[18]and stronger risk factor than DM for CAD in younger women .In Indians, both in India and abroad, levels of Lp-a are higher as compared to Whites in Great Britain suggesting a genetic propensity[19] .Lp-a levels above 30mg/dl are associated with 3 fold higher risk of CAD[20] . Increase of TG from 90mg/dl to 180mg/dl is associated with doubling the incidence of CAD .Indians worldwide demonstrate a triad of high TG with high LDL-C and low HDL. This triad combined with high levels of Lp-a constitutes the deadly lipid quartet[21,22].

Apolipoprotein-b: one third of Indian males, have higher levels of Apo-b associated with increased risk of CAD. LDL-cholestrol is of three phenotypes A,B,C. Of these type B have small and dense LDL constituting an important risk factor for CAD .A 75% prevalence of phenotype B is seen in asian Indians in contrast to 25% in Whites.

Plasminogen activator inhibitor (PAI-1) : high levels are reported in Indians in association with hyper-triglyceride and hyperinsulinemia. This combination promotes thrombosis by imparing fibrinolysis[23]. Insulin resistance syndrome: is an important risk factor for development of CAD in Indians[24]. Serum fibrinogen: increases blood viscosity and plays a key role in thrombosis.

Hyper-homocysteinaemia: homocysteine causes vascular damage by its deleterious effects on endothelial functions and its pro-thrombotic, pro-oxidant & mitogenic effects[25]. Infections & CAD : various infections, viral and bacteria have been Implicated. Amongst them C.pneumonia is considered as an important risk factor for CAD[26] and requires further studies to document relation between infection with CAD.

It is mandatory to have high index of suspicion of CAD in our population particularly, in those who present with atypical symptoms and strong family history. Evaluation of conventional risk factors must be done in men from the age of 30-years onwards and in women of post-menopausal age. In asymptomatic individuals with background of coronary risk factors, investigations including stress ECG, stress echo, must be routinely performed. In subjects with evidence of exercise induced reversible ischemia, coronary angiography must be routinely performed. In symptomatic individuals, mandatory coronary angiography must be done to delineate the culprit lesions for timely and appropriate intervention In the industrialized countries, there is a continuing decline of CAD during the last three decades. Between 1965- 1990, CAD mortality had decreased by 60% in Japan and Finland and by 50% in USA, Canada, France, and Australia due to early diagnosis and treatment[27].

Materials and Methods

The study was carried out on patients attending Cardiology OPD, MEDICINE OPD, CCU and Medicine wards in JNMCH AMU Aligarh from dec 2010 to dec 2011.A total number of 40 patients aged upto 40 years with clinical and ECG features suggestive of ischemic heart disease were evaluated in this study. This is an Observational study.

A detailed history and physical examination was carried out for every subject. The examination included a thorough general physical examination, assessment of vital parameters and systemic examination. The patient was thoroughly investigated for following parameters ECG, Echocardiography, Serum Lipid Profile, Plasma Glucose, Renal function test, Liver Function Test, Complete Haemogram, Urine (Routine & Microscopy) , Troponin , hsCRP, Homocysteine , Lp(a).

One was considered to be diabetic if his fasting and post prandial blood sugar was $\geq$ 126 mg/dl and/ or $\geq$ 200mg/dl respectively or patients were already on anti-diabetic treatment.

Dyslipidemia was defined when any of the lipid fraction was abnormal for example serum cholesterol $\geq$200mg/dl or HDL $\leq$35mg/dl and LDL $\geq$100mg/dl Or triglycerides >150mg/dl.

Newer risk factors (prothrombotics) were looked in some patients eg., Lp(a), homocysteine and fibrinogen of patient affected

Echocardiography was done in all patients to look for evidence of segmental wall motion abnormality, degree of MR(mitral regurgitation) and LV systolic & diastolic function.

Observation

Age :

Incidence of CAD increases with age . In our study 52.5% of patients were between the age group 35-40 years of age.

Table : 1

AGE	NO. OF PATIENTS	%
20-28	6	15%
29-34	13	32.5%
35-40	21	52.5%

Sex ::

Out of 40 cases in study 36 were males and 4 were females

Table : 2

SEX	No. of Patients	Percentage
Males	36	90%
Females	4	10%

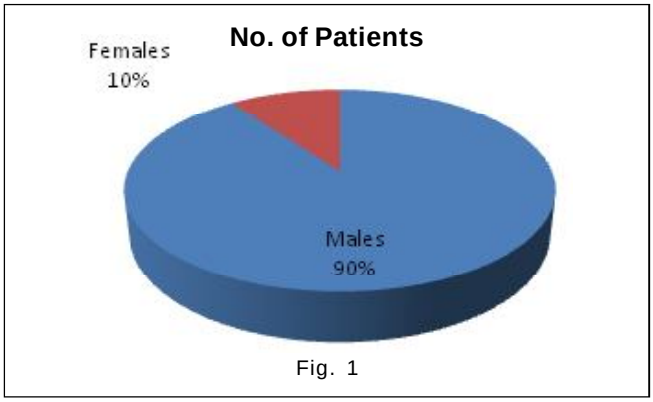

Fig. 1

Age : Sex ratio

It was observed that females present at higher age as compared to males and incidence in females increases as they approach towards menopause.

Table : 3

	MALES	FEMALES	% OF FEMALES
20-28	5	1	16% of females
29-34	13	0	0%females
35-40	18	3	14% of females

There were 4 females and 36 males out of the study group of 40 patients with CAD . Females were some what elder to their male counterpart. Mean age of females was 35.50 with standard deviation of 5.447

while mean age of males was 34.64 with standard deviation of 4.037. Most of the females were between the age group 35-40 years of age (75% of females). Youngest male was 27 years old , he was watchman by occupation and was heavy smoker and was also obese with sedentary life style .

FAMILY HISTORY : In our study of 40 patients, 27 patients (67.5%) had positive family history while 13 (32.5%) had negative family history.

SMOKING : Smokers are found to develop CAD more frequently than non smokers . In our study 72.5% of CAD patients were smokers(heavy smokers).

Out of 11 non smokers, 3 were females. Smoking was exclusively limited to males. Thus to conclude more effectively that 81% of males who develop CAD were smokers.

DIABETES MELLITUS : Out of 40 patients who developed CAD ,8 were having diabetes mellitus that is., 20% of patients had DM

LIPID PROFILE

Total cholesterol was measured for all cases. Lipid profile mainly LDL, HDL were measured. Out of the 40 myocardial infarction patients 67.5% were found to have dyslipidemia

Table: 4 Level of HDL Cholestrol in Cad Patients

HDL-Cholestrol level	No.of CAD patients
<20	1
21-25	5
26-30	4
31-35	5
36-40	13
41-45	5
46-50	3
51-55	2
56-60	1
>60	1

Table 5 : Level of LDL in Cad Patients

LEVEL OF LDL	No. Of Patients
<130mg%	7
130-160mg%	12
>160mg%	21

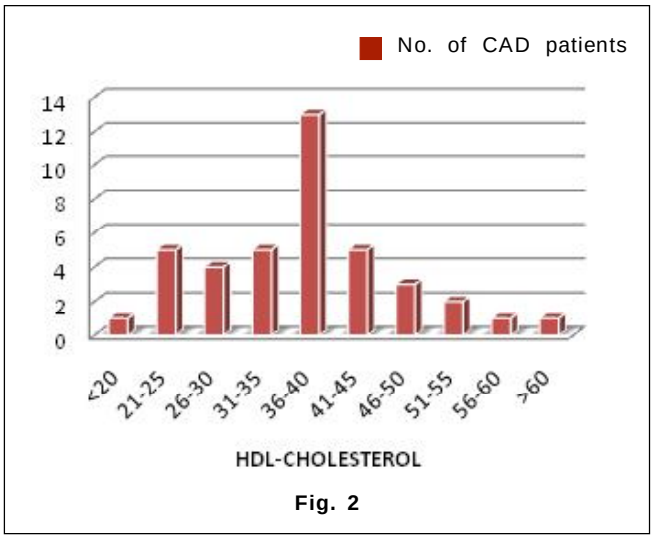

Fig. 2

It can be seen that the incidence of myocardial infarction increased with increasing levels of LDL Cholesterol.[1]

Level of triglycerides also follow the same pattern as LDL

HYPERTENSION : Blood pressure > 140 / 90 was taken as hypertension. 52.5% of cases with myocardial infarction were found to have a history of Hypertension or were newly diagnosed to have hypertension.

OBESITY : Obesity was calculated by taking body mass index and waist hip ratio. BMI < 25 consider as desirable. BMI of 25-30 was taken as overweight and >30 taken as obese.

Out of 40 patients admitted 20 i.e., 50% were having obesity.

Table 6 : BMI IN CAD PATIENTS

BMI	No. Of Patients	%
18.5 - 25	15	37.5%
25-30	5	12.5%
>30	20	50%

ECG Findings

Out of 40 patients taken in study, 20 patients had ST Elevation myocardial infarction. 18 patients had AWMI and only 2 patients had IWMI. Out of 18 patients who had anterior wall MI only 2 were females rest 16 were males.

2 pateints had LBBB and both were males. 1 of the patient had acute onset LBBB. He was a heavy smoker and alcoholic. He was thrombolysed in CCU. The other patient had LBBB and he presented to us

with a chronic stable angina. 11 patients had NSTEMI and 7 patients had USA

Table : 7

ECG FINDING	No. Of Patients
AWMI	18
IWMI	2
LBBB	2
NSTEMI	11
USA	7

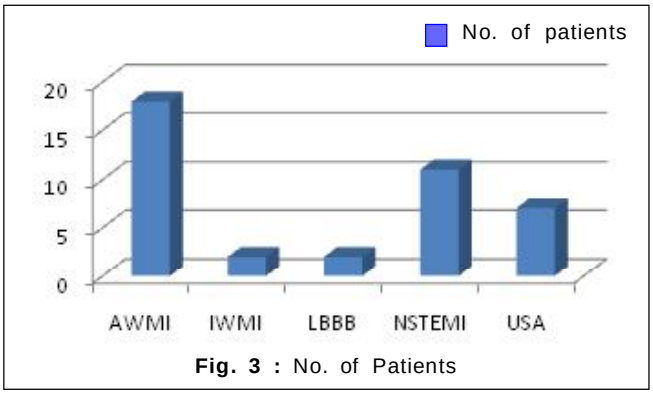

Fig. 3 : No. of Patients

LV DYSFUNCTION

Out of 40 patients admitted 29 had left ventricular dysfunction while 11 had normal left ventricular function.

Table 8 : LV Dysfunction in CAD

LV Dysfunction	No. Of Patients	%
Present	29	72.5%
Absent	11	27.5%

Homocysteine & Lp(a) :

Due to affordibility issue these two investigations could only be done in 7 subjects .All the 7 patients in whom these investigation was done were admitted in CCU and had AWMI . All these patients had history of smoking. Out of these 7 patients, 2 patients were having elevated levels of Lp(a). and homocysteine was not found to be elevated in any of these. Both the patients who had elevated levels of Lp(a) were having positive family history and were obese. Both of these patients were thrombolysed and mild LV dysfunction was there on echocardiography when done in follow up. 8 patients in follow up, came after coronary angiography and stenting. 3 patients had SVD 2 in LAD and 1 in LCx. 5 patients had MVD(multivessel disease) , 2 of them were advised CABG while 3 had undergone multivessel stenting.

Discussion

In this study of clinical spectrum and risk factors in the young CAD patients, the commonest symptom was chest pain and the commonest sign was hypertension. Risk factor analysis showed that smoking, hypercholesterolemia, positive family history, hypertension, obesity were frequently associated with young CAD patients. We are comparing the results of the study with the previous studies.

In our study,males were 90% and females were 10% (Male & Female ratio is 9:1). Significantly, major risk factors like smoking, psychosocial stress and hypertension were high among men as compared to women. In females, the risk of developing coronary artery disease started 10 years later than male. This is presumably due to hormonal factors. The most common age groups affected were between 37 to 40 years. This denotes increasing incidence of myocardial infarction in young age. The INTERHEART study also reported that younger age of onset of major risk factors explained the premature CAD in south Asians[28,31]. Similar observations have been made in other studies also i.e. Dwivedi et al. (4:1) in 2000[29,30].

In our study, 72.5% of the patients were smokers, all of them are males. The probable reason being the atherosclerotic process accelerated by enhanced oxidation of LDL-C and reduced the levels of HDL-C. Smoking impairs endothelium, increases inflammatory markers and fibrinogen, cause platelet aggregation and increases monocyte adhesion to endothelial cells. Previous case control studies in premature CAD from India reported smoking, hypertension and low HDL cholesterol as important risk factors[31]. Smoking is the commonest risk factor for CAD in young individuals and causes increase of 2-3 folds.In earlier studies too similar observations have been made i.e. Jeyachandran et al[32], in 1987 (53%), Gupta et al[33]., 1987, Bergstrand R et al[34]., Gower MC et al.[35], (89%). Dwivedi et al[30]., (61.42%) in relevance to smoking as a risk factor in CAD.

In our study, 67.5% of patients were found to have dyslipidemia. Dyslipidemia patients who are associated with obesity, insulin resistance also produces a prothrombotic state due to increased level of PAI - 1 and Fibrinogen. Similar observations have been made in other studies i.e. David JE et al in [36](68%) 1987.

In our study 67.5% of the patients were found to have positive family history. The genetic factors contribute to the risk of developing ischemic heart disease. The risk is estimated to be as high as 40%. Common deletion polymorphism of angiotensin converting enzyme (ACE) gene associated with increased level of ACE adds to the risk of coronary

artery heart disease. Genetic factor such as LDL receptor, factor V Leiden are also other genetic markers. In earlier studies too similar observation have been made i.e., Dwivedi et al[30]., (42.8%) in 2000.

In our study, 52.5% of the patients were found to have high blood pressure, the probable reason being the accelerated atherosclerosis, increased left ventricle wall stress, left ventricle tension and stroke work. Other reasons like left ventricular hypertrophy, abnormal coronary flow reserve and abnormal vasomotor response and micro vascular dysfunction also contribute. Similar observation have been found in other studies also i.e. Dwivedi et al[30]., (51.42%) in 2000.

In our study, 50% of patients were found to have obesity. Obesity is an important risk factor in the development of coronary heart disease. Obesity is associated with increase in blood volumes, cardiac output and left ventricular filling pressure. When the additional effects of hypertension and glucose tolerance are added, the adverse impact of obesity is even more evident. Obesity, especially central obesity is associated with an atherogenic lipid profile. Similar observations have been made in other studies also i.e. Dwivedi et al[30]., (35.71%) in 2000.

In our study, 20% of patients were found to have diabetes. The reason being it impairs endothelial and smooth muscle function and appears to increase leukocyte adhesion to vascular endothelium, a critical early step in atherogenesis. and also insulin resistance also produces a prothrombotic state due to increased level of PAI- 1 and fibrinogen. Similar observations have been made in other studies also i.e. Marty AK Das AK et al[37]., (18%), PK Biswas A38 (9.7%), Dwivedi et al30., (7.14%) in 2000.

In our study ,out of 40 patients 20 had STEMI. Out of these 20 patients who had STEMI 18 were having AWMI.2 patients were having IWMI . In remaining 20 patients 2 patients were having LBBB. And 11 patients had ST-T changes suggestive of iaschemia and out of these 11 patients 7 patients were having positive troponin test and were labeled as NSTEMI. 7 patients also had normal ECG and out of them 3 were positive for troponin test. Thus ,we had total of 10 NSTEMI patients. Similar results were seen in study done by I.WEINBERGER IN 1987 in Myocardial Infarction in Young Adults under 30 years: Risk factors & Clinical Course (Clin. Cardiol. 10 , 9-15 ; 1987).[30] Patients were studied in this group, out of 30 patients 15 had AWMI. Patients who had AWMI were having RWMA in LAD territory. Patients who had IWMI had RWMA in RCA & LCx territory . Patients who had LBBB were having mild global hypokinesia. Out of 40 patients 29 had LV dysfunction . Only 2 patients had severe LV dysfunction rest 27 patients had mild LV dysfunction.

8 patients presented after coronary angiography with /without revascularisation . 3 had SVD , 2 in LAD and 1 in LCx vessel. 5 patients had MVD , 3 undrgo multivessel stenting and in 2 CABG was done. The data suggest that malignant CAD <40 years is associated with TVD/ bad prognosis .

There were several limitations in this study. Firstly because of affordibility issues out of 40 patients in only 7 patients the two tests homocysteine and Lp-(a) could be performed . Only 2 patients were reported to have increased levels of Lp(a) and homocysteine and fibrinogen could not be found elevated in these patients . Since number of patients in which we could perform the test is not adequate enough therefore no final conclusion can be made. Secondly, measurement of risk factors in hospitalized patients are fraught with errors. BP values are unstable after acute coronary event, lipid levels quickly change. Thirdly, sample size was not adequate enough. Fourthly, many emerging risk factors (trigyceride remenant, lipid subtypes, C-reactive protein, insulin resistance) or genetic factors that have been implicated in premature CHD were not studied. And finally as the number of women in this study was small, the risk factors could not be generalized.

Conclusion

In conclusion the study shows that premature coronary artery disease in Indians is due to combination of thrombotic and atherosclerotic risk factors. Most common clinical presentation was in the form of STEMI and AWMI was the commonest.

Males were commonly affected especially in the younger age group. Significantly major risk factors like smoking, psychological stress, and hypertension were also evident among men as compared to women. These factors along with hormonal factors contribute the higher proportion of CAD in young males.

Our study is important in fact that it generalizes the importance of smoking and dyslipidemia as primary targets for effective prevention of CAD in young Indians. Although, these modifiable factors do not completely explain the burden of CAD in Indian subcontinent. Identification of newer emerging risk factors like prothrombotics (fibrinogen, Lp(a),PAI-1) is very important. Prevention and control of premature cardio vascular disease in India needs urgent control of these factors . improving life style with tobacco cessation, diet modulation with more fruits and vegetables and lower fat intake, and increased physical activity are critical, proper cooking practices avoiding reheating of oil(increases trans FA) Target oriented control of hypertension, lipid levels and glycemia is required. In our study family history of CAD is an important

risk factor contributing to CAD in young individuals. This is probably due to an inter play of both genetic and environmental factors. Thus screening of young healthy people and young CAD patients for dyslipidemia and other risk factors may help find people at high risk for early development of CAD and can help health care workers to take more aggressive approach to more effective primary and secondary preventive measures and therapeutic measures and need for research to identify unique risk factors which operate in Indian subcontinent.

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