A retrospective case-control study of modifiable risk factors and cutaneous markers in Indian patients with young coronary artery disease

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DECLARATIONS

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Summary

Objective Indians have the highest risk rates for coronary artery disease (CAD) among all ethnic groups. There is a paucity of data on the risk factors and clinical markers associated with premature CAD. We aimed to determine whether young CAD is due to preventable lifestyle-related factors and cutaneous clinical markers are useful in identifying at-risk patients.

Design Single-centre retrospective study.

Setting Tertiary care center.

Participants A total of 292 patients (age ≤40 years) who presented with acute CAD between January 2005 and June 2009 and 92 age, and gender-matched controls.

Major outcome measures Details of smoking, family history of premature CAD, waist size, blood sugar and lipid profile. Clinical evidence of arcus juvenilis, premature greying of hair and premature baldness sought.

Results Dyslipidaemia (91%), smoking (74.3%), low high-density lipoprotein cholesterol (HDL-C) (68.9%), central obesity (47.7%) and greying of hair (34.9%) were the most commonly associated factors. Compared with male patients, females had greater prevalence of dyslipidaemia, low HDL-C, central obesity, hypertension, diabetes and family history of premature CAD. The presence of cutaneous markers was significantly associated with premature CAD.

Conclusions CAD in young Indian people is multifactorial; dyslipidaemia, low HDL-C, smoking, hypertension, central obesity and family history of premature CAD are the most common risk factors. Smoking in men and central obesity in women are the most prevalent factors. Clinicians should be highly suspicious of patients with presence of cutaneous markers, and they should be followed intensively for lifestyle modifications.

Contributorship
All of the authors contributed in the design and concept of study, collection of data, manuscript preparation and review of literature

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Introduction

Coronary artery disease (CAD) is a leading cause of morbidity and mortality in both developing and developed countries. Approximately, one-sixth of the world's population lives in India. CAD is the most common cause of mortality in India.[1] The South Asian population, especially that of the Indian subcontinent, is believed to have a higher risk and prevalence of CAD as compared with other ethnic groups.[2] India has 29.8 million symptomatic patients with CAD, 19.3 million diabetics and 118 million hypertensive individuals, who are at risk of developing metabolic syndrome, thus potentiating the risk for CAD.[3–5] CAD in the Indian subcontinent has been reported to manifest almost a decade earlier than in the West.[5] Moreover, deaths related to CAD occur 5–10 years earlier in the Indian subcontinent than in Western countries.[6]

The association of smoking, dyslipidaemia, hypertension, diabetes, central obesity and a positive family history with CAD is well established, and recent studies have also associated these risk factors with premature CAD.[7–10] More recently, various reports have indicated the potential association of different cutaneous markers with premature CAD so that the population at risk can be identified early.[11–14] However, well-defined studies analysing such an association in India are lacking. This retrospective case-control study was done to establish the association of the above mentioned modifiable risk factors and identify the association of cutaneous markers like premature greying of hair, premature baldness and arcus juvenilis and further analyse the pattern of distribution of these risk factors in both males and females with premature CAD in India.

Methods

The present retrospective case-control study was conducted at the Guru Teg Bahadur Hospital, a 1200-bed teaching hospital in New Delhi. Ethical approval for the study was obtained from the Institutional Ethical Review Committee. The case records of all patients presenting acutely with premature CAD (age ≤40 years) and hospitalized to the coronary care unit of our hospital between January 2005 and June 2009 were analysed retrospectively. In order to obtain an adequate control population, records were searched for age and gender-matched patients who presented to hospital with non-cardiac complaints during the same time period. Data was obtained and selected for all patients who presented to outpatient clinics with acute conditions like viral rhinitis, sore throat, diarrhea, etc. All patients with a previous history of CAD and those who were admitted during acute presentation were excluded to remove elements of confounding bias. After very carefully reviewing all the available data, 92 patients were selected as controls.

Records of all subjects less than 40 years of age presenting with acute coronary syndrome were included for analysis. The diagnosis of acute coronary syndrome was made on the basis of symptoms, electrocardiogram (ECG) abnormalities, cardiac injury enzymes and/or echocardiography as described by Luepker *et al*.[15] The case sheets were scrutinized for historical features, smoking and family history of premature CAD. Records were screened for presence or absence of arcus juvenilis, premature greying of hair and premature balding. Incomplete case records (with missing data on smoking history, family history of CAD, diabetes mellitus, hypertension, premature arcus, balding or greying of hair), subjects who presented as brought dead to the hospital or those who had unexplained deaths were excluded from the study.

Waist size, fasting and postprandial blood sugar, fasting lipid profile (total cholesterol, high-density lipoprotein cholesterol [HDL-C], low-density lipoprotein cholesterol [LDL-C] and triglycerides) and measurement of carotid intima media thickness (CIMT) was also noted. Smoking was defined as use of bidi (bidis are small, hand-rolled cigarettes wrapped in a piece of local tobacco leaf), cigarette or oral tobacco. Consumption of 1 g of oral tobacco was taken as equivalent to smoking one cigarette. The grading of smoking was assessed by calculating the smoking index (SI), which was based on the number of cigarettes/day multiplied by total duration in years of active smoking. The guidelines used for diagnosis of dyslipidaemia, hypertension, diabetes mellitus, obesity, premature greying of hair and baldness in this study have been described elsewhere.[4]

The intima media thickness (IMT) of the carotid artery, determined by a high-resolution B mode USG System having an electronic linear, high-frequency broadband transducer for superficial scanning with a mid-frequency of 7.5 MHz, was measured at three areas along the vessel wall including (1) the posterior aspect of the common carotid artery, (2) common carotid artery bifurcation and (3) anterior wall of internal carotid artery. IMT measurements were quantified as the average of arterial wall thickness (excluding segments involved with plaque) as per protocol followed by the trained physician who had done the measurements. Note was also made of the presence of any plaque.

Statistical analysis was done using SPSS v.17 (SPSS South Asia, New Delhi, India). Continuous variables were expressed as mean ± standard deviation (SD) and percentage was calculated for categorical variables. Comparison of continuous and categorical variables was done in both male and female groups using unpaired two-tailed *t*-test and chi-squared test and any statistically significant difference was noted. Odds ratio (OR) was calculated for risk factors with discrete variables. For the purpose of the study, P value < 0.05 was considered statistically significant.

Results

A total of 292 young patients (age ≤40 year) of acute coronary syndromes were admitted to our hospital during the study period from January 2005 to June 2009. Mean age of patients was 36.3 ± 4.1 years with 261 (89.4%) being men and 31 (10.6%) being women. Ninety-two controls were selected from the same time period with mean age of 35.6 ± 3.26 years with 81 (88.0%) being men and 11 (12%) being women. There was no significant difference between the case and control groups with regard to age and gender ($P > 0.05$). ST elevation myocardial infarction was seen in 79.4% patients in CAD group with anterior wall involvement as the most common ECG diagnosis (48.6%). Risk factor profile of young CAD patients is shown in Table 1. Dyslipidaemia, smoking, low HDL-C and central obesity were the most commonly associated risk factors in young CAD patients. Smoking (OR, 17.6; 95% confidence interval [CI], 9.2–33.4; $P < 0.0001$), hypertriglyceridaemia (OR, 2.58; 95% CI, 1.43–4.66; $P = 0.0021$), hypertension (OR, 2.2; 95% CI, 1.14–4.31; $P = 0.0235$) and central obesity (OR, 1.91; 95% CI, 1.13–3.22; $P = 0.0217$) were more significantly associated with the patient group as compared with the control group. The presence of cutaneous markers namely arcus juvenilis (OR, 17.46; 95% CI, 2.37–128.39; $P = 0.0003$), premature balding (OR, 12.89; 95% CI, 3.09–53.74; $P < 0.0001$) and premature greying of hair (OR, 3.95; 95% CI, 2.01–7.76; $P < 0.0001$) were also found to be more significantly associated with young CAD patients as compared with controls. Mean CIMT was found to be 0.62 ± 0.12 mm. In all, 11.7% of patients had a CIMT value of more than 0.80 mm and 9.9% had presence of plaque in carotids.

Subgroup analysis of CAD patients showed 261 men with a mean age of 36.1 ± 4.1 years and 31 women with a mean age of 37.1 ± 3.6 years. Risk factor profile and comparison of young CAD male and female patients is shown in Table 2. As compared with women, men were more likely to be smokers, have increased total cholesterol, LDL-C, triglycerides, CIMT, premature arcus and greying of hair. Dyslipidaemia, low HDL-C, central obesity, hypertension, diabetes and family history of premature CAD were more commonly associated with female gender. However, only the difference in smoking (more in men) and hypertension and central obesity (more in women) were statistically significant.

A majority of patients had between four and five concurrent risk factors among those studied, including smoking, family history of premature disease, hypertension, dysglycaemia, central obesity, increased LDL-C, increased triglycerides and low HDL-C (Figure 1).

Discussion

In this retrospective study, we found a statistically significant association of smoking, hypertension, hypertriglyceridaemia and central obesity in Indian patients with premature CAD as compared with controls; smoking was more predominantly associated with men and hypertension and central obesity were more commonly associated with women. Among cutaneous markers the patients had a significantly higher occurrence of

Table 1
Profile of risk factors in young CAD patients and young control population

	CAD group (n = *292)*	*Control group* (n = *92)*	P *value*	*OR (95% CI)*
Age (years ±SD)	36.3 ± 4.11	35.6 ± 3.26	0.1737	
Smokers*	217 (74.3)	13 (14.1)	<0.0001	17.6 (9.2–33.4)
Smoking index*	Range 0–1500 Median 120 IQ range 300	Range 0–600 Median 0 IQ range 0	<0.0001	
Hypertension*	73 (25.0)	12 (13.0)	0.0235	2.2 (1.14–4.31)
Family history of premature CAD	88 (30.1)	25 (27.1)	0.6799	1.16 (0.69–1.95)
Diabetes mellitus	43 (14.7)	7 (7.6)	0.1115	2.10 (0.91–4.84)
Prediabetes	16 (5.4)	4 (4.3)	0.8753	1.28 (0.42–3.92)
Central obesity*	113/236 (47.7)	27/83 (32.5)	0.0217	1.91 (1.13–3.22)
Premature arcus*	47 (16.1)	1 (1.1)	0.0003	17.46 (2.37–128.39)
Premature balding*	65 (22.3)	2 (2.2)	<0.0001	12.89 (3.09–53.74)
Premature greying*	102 (34.9)	11 (11.9)	<0.0001	3.95 (2.01–7.76)
Dyslipidaemia	172/189 (91.0)	73/83 (87.9)	0.5787	1.39 (0.61–3.17)
High total cholesterol	36/189 (19.0)	17/83 (20.5)	0.9134	0.91 (0.48–1.74)
Low HDL-C	122/177 (68.9)	47/79 (59.5)	0.1838	1.51 (0.97–2.62)
High triglycerides*	81/185 (43.8)	19/82 (23.2)	0.0021	2.58 (1.43–4.66)
High LDL-C	73/ 173 (42.2)	28/80 (35.0)	0.3427	1.36 (0.78–2.35)
Mean carotid intima media thickness (mm)*	(*n* = 111) 0.62 ± 0.12	(*n* = 74) 0.54 ± 0.08	<0.0001	–
Increased CIMT (>0.80 mm)*	11 (9.9)	1(1.1)	0.3447	3.56 (0.46–27.97)
Plaque*	13/111 (11.7)	0/74 (0.0)	0.0058	–

IQ, interquartile
Figures in parentheses denote percentages
*$P < 0.05$

arcus juvenilis, premature greying of hair and premature baldness.

CAD has been known to be a disease in which multiple factors like smoking, dyslipidaemia, hypertension, diabetes, central obesity and hereditary factors play a major role. Smoking has been shown to be a major dominant modifiable risk factor associated with young CAD.[8,10] It has been observed that health awareness campaigns in the developed world have resulted in a decline in smoking and it has become socially less acceptable than it was a decade ago.[16] In contrast, developing countries like China and India are witnessing an increase in the incidence of smoking, especially among adolescents and a rise in the use of smokeless tobacco.[17] We noted a high incidence (74.3%) of smoking in our study subjects, with a stronger association with men. Similar findings have been reported by Achari and Thakur.[7] The results indicate that greater efforts are needed to control smoking among the young.

The importance of dyslipidaemia in the pathogenesis of CAD is well known. Elevated levels of cholesterol, LDL-C and triglycerides have been found in young Indian subjects with CAD and been postulated to be of particular importance even in the younger variant of the disease.[7–10] In a study done between 1998 and 2002 in a North Indian population, Goel *et al.*[9] showed that CAD occurs at much lower levels of total cholesterol and LDL-C than other populations, and high triglyceride and low HDL levels are more of a universal phenomenon in this population. Our study revealed a high prevalence of dyslipidaemia (91%), especially low HDL-C (68.9%), in our study population and significantly higher triglyceridaemia in the patient population. It can be postulated that metabolic profile of patients have deteriorated over time and a possible explanation could be degradation of lifestyle habits with greater consumption of junk foods by the young population.

Table 2
Comparative risk factors profile of young male and female CAD patients

	Males (n = *261)*	*Females* (n = *31)*	P *value*	*OR (95% CI)*
Age (years ±SD)	36.1 ± 4.1	37.1 ± 3.6	0.1572	
Smokers*	211 (80.8)	5 (16.1)	<0.0001	21.94 (8.03–59.98)
Smoking index*	Range 0–1500 Median 140 IQ range 284	Range 0–112 Median 0 IQ range 0	<0.0001	
Hypertension*	59 (22.6)	14 (45.1)	0.0116	0.35 (0.17–0.76)
Family history of premature CAD	76 (29.1)	12 (38.7)	0.3717	0.65 (0.30–1.41)
Diabetes mellitus	35 (13.4)	8 (25.8)	0.1156	0.45 (0.18–1.07)
Prediabetes	14 (5.3)	2 (6.4)	0.8014	0.82 (0.18–3.80)
Central obesity*	91/ 210 (43.33)	22/26 (84.61)	0.0002	0.14 (0.05–0.42)
Premature arcus	44 (16.8)	4 (12.9)	0.7600	1.37 (0.46–4.11)
Premature greying	95 (36.3)	8 (25.8)	0.3330	1.65 (0.71–3.82)
Dyslipidaemia	159 /170 (93.5)	19/19 (100)	0.9681	–
High total cholesterol	35/170 (20.5)	1/ 21(4.7)	0.1460	5.19 (0.67–39.98)
Low HDL-C	113/159 (71.0)	17/ 18 (94.4)	0.0648	0.14 (0.01–1.12)
High triglycerides	72/164 (43.9)	9/21 (42.8)	0.9276	1.04 (0.42–2.61)
High LDL-C	67/155 (43.2)	6/ 18 (33.3)	0.5807	1.52 (0.54–4.27)
Mean carotid intima media thickness (mm)	0.62 ± 0.14	0.59 ± 0.06	0.1829	–
Increased CIMT (≥0.80 mm)	11/96 (11.4)	0/15 (0.0)	0.3593	–
Plaque	13/96 (13.5)	0/15 (0.0)	0.2779	–

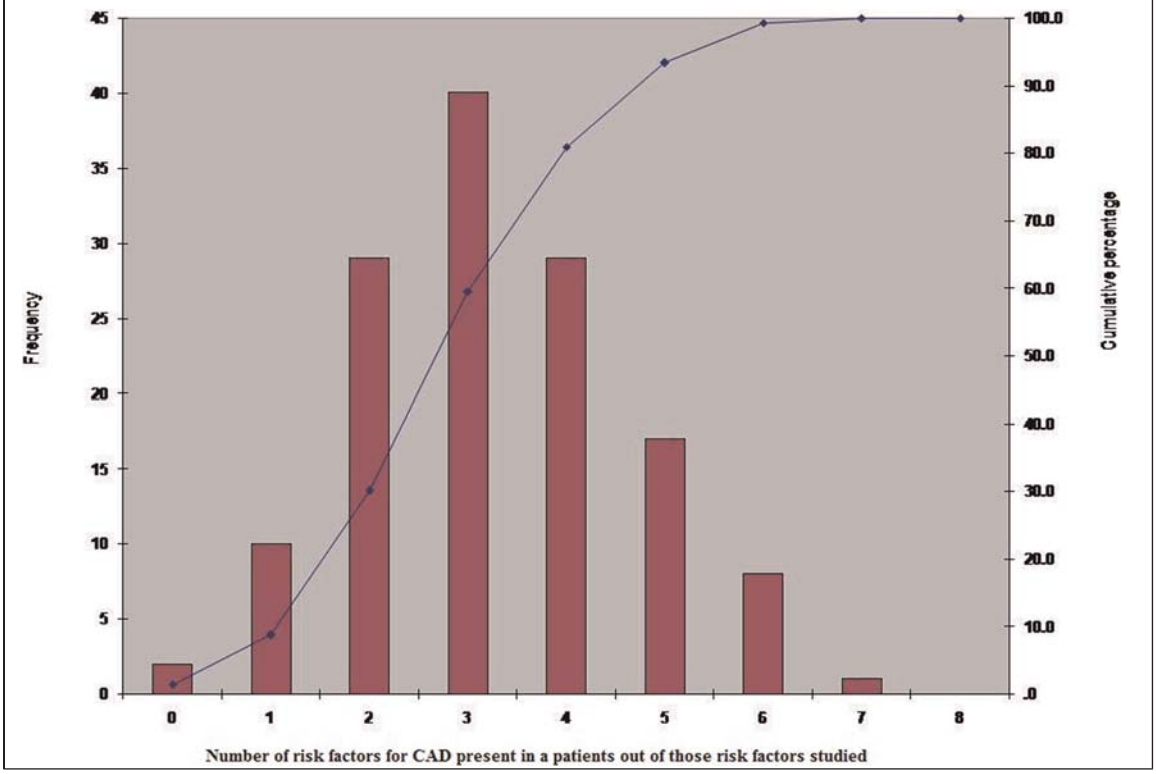
IQ, interquartile
Figures in parentheses denote percentages
*$P < 0.05$

Enas *et al.*[18] showed that Indian emigrants to Western states have a high prevalence of dyslipidaemia and insulin resistance, thereby increasing risk of CAD. A modest increase in body fat with central distribution has been shown to increase the risk of CAD.[19] We found that a high prevalence (80.7%) and a statistical significant association (OR, 1.91; 95% CI, 1.13–3.22; $P = 0.0217$) of central obesity in patients with premature CAD (80.7%).

Jain *et al.*[20] showed that a family history of premature CAD in first-degree relatives is associated with development of CAD. Gambhir *et al.*[21] further showed that low-molecular-weight isoforms of lipoprotein (a) were prevalent in Indian subjects with a positive family history of premature CAD. Interleukin-6 gene polymorphisms have also been described to be important genetic factors in premature CAD, and in the regulation of key atherogenic markers in Asian Indian families.[22] We found that a positive family history was present in 30.1% of our subjects. The family history not only indicates the genetic predisposition to disease but may also represent the sum total of the interaction of the individual with his environment, expressed in several ways including diabetes, thrombotic disorders, as well as a behavioural predilection to smoking. However, since it was a retrospective study, we could not assess association of low-molecular-weight isoforms of lipoprotein (a) due to the unavailability of data. Prevalence of an increasing number of risk factors in patients with premature CAD is also crucial since it has been shown that as the number of cardiovascular risk factors increases, so does the severity of asymptomatic coronary and aortic atherosclerosis in young people.[23]

There has been increased interest regarding the usefulness of cutaneous markers in identifying people at high risk for CAD.[12–14,24–26] We analysed the association of arcus juvenilis, premature greying of hair and premature baldness in this study and found a statistically significant association between these cutaneous markers and the presence of young CAD. Recent studies

Figure 1
Distribution of the subjects by the number of conventional risk factors present among them ($n = 136$). Risk factors included are smoking, family history of premature CAD, hypertension, dysglycemia, central obesity, increased LDL-C, increased triglycerides and low HDL-C.



in Singapore by Wu *et al.*[13] and Ang *et al.*[24] have demonstrated a significant association of arcus with cardiovascular risk factors. Our study highlights the importance of this marker in young CAD patients as well. Premature greying of hair has been shown to predispose one for CAD, and Pomerantz[27] showed that premature greying of hair occurs in patients with CAD under 35 years of age. Trueb[28] suggested that scalp ageing is subject to intrinsic and extrinsic factors including ultraviolet radiation and smoking. Usefulness of baldness as a marker of underlying CAD is still controversial. Recently, Mansouri *et al.*[14] reported a significant association of androgenetic alopecia with CAD in women under the age of 55. We also reported a significant association of premature greying of hair and baldness in patients with premature CAD.

CIMT has been proposed to identify preclinical disease and it has been shown that a 0.1-mm increase in thickness augments the likelihood of acute myocardial infarction by 11%.[29] Ward *et al.*[30] showed that an increase in CIMT by 0.80 mm correlated with an enhanced risk of carotid atherosclerosis. We found that 11.7% of our study subjects had CIMT value more than 0.80 mm and 9.9% showed plaques. Measurement of CIMT could be used as a reliable non-invasive tool for early detection of CAD. Further prospective studies in the Indian population may be needed to establish its use.

The importance of the study lies in the fact that our study brings out the distinct association of smoking in a large subgroup of obese young men and women suffering from CAD. This paper serves as a guide for policy-makers to

help focus them on potential targets to develop strategies to prevent premature CAD. Our study highlights smoking, hypertension, central obesity and dyslipidaemia as potential targets. Also, we postulate that the presence of cutaneous clinical markers like arcus senilis, premature greying and baldness can be used as preliminary evidence by clinicians for classifying patients at risk for premature CAD and that these patients should then be monitored intensively for control of other modifiable risk factors. A large multicentre prospective study can help further substantiate our hypothesis and help devise a scoring system specific for Indian patients at higher risk for young CAD. As Figure 1 shows most of the patients had more than two risk factors, patients need to be managed intensively for control of multiple risk factors.

Our study has a few limitations. While it would have been desirable to determine the effect of serum homocysteine levels, lipoprotein (a), small LDL-C, C-reactive protein, psychological factors like stress, diet and lifestyle in the study subjects, it was not economically or logistically feasible for our study group. Since it was a retrospective study, many patient's data had to be excluded due to the insufficiency of this data. Thus, the study sample may not be a true representation of the population of young CAD patients at large. Also, we could not get too many controls for more efficient comparison since we choose only patients who presented to outpatient clinics.

The rise in prevalence of premature CAD is a reality that is becoming increasingly evident in India. While men are still predominantly affected, young women may no longer be considered immune to its occurrence. Premature CAD in India is of a multifactorial causation and dyslipidaemia, low HDL-C, smoking, central obesity and family history of premature CAD play a crucial role in its development. While smoking in men and central obesity in women are prevalent modifiable associated factors, premature greying of hair may indicate an underlying CAD.

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