

Newer perspectives of coronary artery disease in young

Amitesh Aggarwal, Saurabh Srivastava, M Velmurugan

Amitesh Aggarwal, M Velmurugan, Department of Medicine, University College of Medical Sciences and GTB Hospital, Delhi 110095, India

Saurabh Srivastava, Department of Medicine, School of Medical Sciences and Research, Sharda University, Noida 201308, India

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Correspondence to: Amitesh Aggarwal, MD, Associate Professor, Department of Medicine, University College of Medical Sciences and GTB Hospital, Dilshad Garden, Delhi 110095, India. dramitesh@gmail.com
Telephone: +91-11-22586262

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Abstract

Coronary artery disease (CAD) occurring in less than 45 years of age is termed as young CAD. Recent studies show a prevalence of 1.2% of CAD cases in this age group. Ethnic wise south Asians especially Indians are more vulnerable to have CAD in young age group with

a prevalence of 5% to 10%. Conventional risk factors such as smoking, diabetes, hypertension, obesity and family history seems to be as important as in older CAD subjects. But the prevalence of these risk factors seems to vary in younger subjects. By far the most commonly associated risk factor is smoking in young CAD. Several genes associated with lipoprotein metabolism are now found to be associated with young CAD like cholesterol ester transfer protein (*CETP*) gene, hepatic lipase gene, lipoprotein lipase gene, *apo A1* gene, *apo E* gene and *apo B*. Biomarkers such as lipoprotein (a), fibrinogen, D-dimer, serum Wnt, gamma glutamyl transferase, vitamin D2 and osteocalcin are seems to be associated with premature CAD in some newer studies. In general CAD in young has better prognosis than older subjects. In terms of prognosis two risk factors obesity and current smoking are associated with poorer outcomes. Angiographic studies shows predominance of single vessel disease in young CAD patients. Like CAD in older person primary and secondary prevention plays an important role in prevention of new and further coronary events.

Key words: Young; Coronary artery disease; Risk factors; Epidemiological trends; Prognosis

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Core tip: Coronary artery disease (CAD) in patients less than 45 years of age is termed young CAD. South Asians especially Indians are more vulnerable to have CAD in young age group. Although conventional risk factors, mainly smoking, are also important in young CAD but there are numerous other factors that are responsible for it. Several genes associated with lipoprotein metabolism are now found to be associated with young CAD. Gamma glutamyl transferase, vitamin D2 and osteocalcin seem to be associated with premature CAD in some studies. Angiographic studies shows predominance of single vessel disease in young CAD patients.

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INTRODUCTION

Coronary artery disease (CAD) occurring below the age of 45 years is termed as young CAD^[1]. However various studies had considered the age limit varying from 35 years to 55 years in the spectrum of young CAD^[2-10] (Table 1). This arena of cardiology has gained importance very recently due to increased prevalence in this age group over a last few decades, with varying risk factor profiles and difference in prognosis as well as longevity after an acute coronary episode. Recently, apart from the established biomarkers of CAD, many new markers, specifically associated with young CAD are discovered. The purpose of this review is to analyse the changing epidemiological trends, role of conventional and newer risk factors and prognosis of young CAD population.

TRENDS IN EPIDIMIOLOGICAL PROFILE

Coronary heart disease is the leading cause of morbidity and mortality, worldwide both in developing as well as developed countries, and is responsible for one third or more of all deaths in individuals greater than 35 years of age^[11,12]. World Health Organisation has projected that burden due to CAD is going to increase globally from 47 million disability adjusted life years (DALYs) in 1990 to about 82 million DALYs in 2020. Many studies have demonstrated that young CAD contributes to 2% to 6% of all acute coronary events^[13]. In the early 1980s, the Framingham study (FHS) reported a 10 year CAD incidence of 12.9 per 1000 in the age of 30 to 34 years and 5.2 per 1000 in the age group 35 to 44 years, in men and women respectively^[14].

Studies have shown an increased prevalence of CAD in the subjects with family history of premature CAD, than in general population (35% vs 14%)^[15]. The original as well as offspring cohort data of Framingham study, by National heart lung and blood institute (NHLBI's), from 1880 to 2003 revealed an annual incidence of cardiovascular disease of 3 per 1000 men between 35 to 44 years of age^[16]. Centre of disease control prevalence data for the year 2010 revealed that prevalence of CAD in the age group of 18 to 44 years, 45 to 64 years and more than 65 years was 1.2%, 7.1% and 19.8% respectively^[17]. Epidemiological data of United Kingdom published in the year 2000, reported a prevalence of 0.5% and 0.18% in men and women between 35 to 44 years respectively^[1]. The prevalence of occult CAD in 112 asymptomatic young individuals, less than 40 years of age, was found to be 11% (9 had

Table 1 Spectrum of terminology for young coronary artery disease

No.	Terminology	Age group studied	Ref.
1	Young CAD	Less than 45 yr	Ericsson <i>et al</i> ^[2]
2	Young CAD	Less than 40 yr	Konishi <i>et al</i> ^[3]
3	Young CAD	15-39 yr	Gupta <i>et al</i> ^[4]
4	Very young CAD	≤ 35 yr	Christus <i>et al</i> ^[5]
5	Premature CAD	Men ≤ 45 yr Female ≤ 55 yr	van Loon <i>et al</i> ^[6]
6	Premature CAD	Less than 60 yr	Genest <i>et al</i> ^[7]
7	Premature CAD	Less than 45 yr	Pineda <i>et al</i> ^[8]
8	Precocious CAD	2 case reports of familial CAD of 29 and 31 yr	Norum <i>et al</i> ^[9]
9	Early onset CAD	Less than 45 yr	Iribarren <i>et al</i> ^[10]

CAD: Coronary artery disease.

single vessel disease and 3 had double vessel disease) in a study done in Korea. The occult CAD in these individuals was defined by performing coronary CT angiography^[18].

The mean age of onset of CAD in Southeast Asians seems to be 53 years as compared to European figure of 63 years^[19]. South Asians especially Indians are at greater risk of developing CAD at a young age (5% to 10%) when compared to other ethnic groups (approximately 1% to 2%)^[20]. Reported prevalence of young CAD under the age of 40 years, in a study published from Indian subcontinent, in 1991 was 5% to 10%. This vulnerability of Indians to coronary events may be related to life style, environmental and genetic factors^[20].

The median age of presentation of CAD in young women is higher when compared to men. Singapore myocardial infarction registry of CAD in group less than 65 years showed that men have 4 times greater risk of CAD than women^[21]. In Asians 9.7% males and 4.4% females develop first episode of MI under 40 years of age^[20].

RISK FACTORS PROFILE

Conventional risk factors (Table 2)

Prevalence of conventional risk factors like diabetes, hypertension, smoking, dyslipidemia and obesity accounts for about 85% to 90% of premature CAD patients^[22]. Often young CAD patients have multiple coexisting risk factors contributing to the disease^[23]. The most common risk factor associated with young CAD seems to be smoking. The prevalence of smoking in younger individuals less than 45 years of age, with CAD, was reported to be 60% to 90% as compared to 24% to 56% in subjects greater than 45 years^[13,24]. Smoking in presence of additional risk factors like diabetes, hypertension and obesity predispose a young individual to increased risk of future acute coronary events^[25].

The prevalence of diabetes and hypertension seems to higher in young patients with CAD than without CAD. The prevalence of hypertension is 25% in young

Table 2 List of conventional and newer risk factors in young coronary artery disease discussed in the review

Conventional risk factors	Newer risk factors
Age	Polymorphisms in <i>CETP</i> gene
Sex	Hepatic lipase gene
Hypertension	Lipoprotein lipase gene
Diabetes mellitus	C-reactive protein gene
Dyslipidaemia	<i>Apo A1</i> gene
Obesity	<i>Apo B</i> gene
Smoking	<i>Apo E</i> gene
Family history of premature CAD	<i>HIF1A</i> gene
	Factor 5 leiden
	<i>MTHFR</i> gene
	Methionine synthase gene
	Cocaine use
	Lipoprotein-a, Fibrinogen and D-dimer
	Decreased serum Wnt
	Increased gamma glutamyl transferase
	Raised vitamin D2 and D3
	Decreased osteocalcin
	Hypothyroidism
	Systemic lupus erythematosus
	Rheumatoid arthritis
	HIV patients on HAART
	Homocysteinemia
	Kawasaki disease in childhood,
	Patent foramen ovale
	Spontaneous coronary artery dissection

CETP: Cholesterol ester transfer protein; HAART: Highly active anti retroviral therapy; *MTHFR*: Methylene tetrahydrofolate reductase; *HIF1A*: Hypoxia inducible factor 1 alpha.

CAD as compared to 13% without CAD. Similarly, the incidence of diabetes and pre diabetes is 14.3% and 7.6% in young CAD as compared to only 5.4% and 4.3% in patients without CAD respectively^[26]. However, prevalence of these risk factors is much higher in older individuals with CAD as compared to young CAD^[27-29]. Various studies have demonstrated a recent increase in the prevalence of hypertension [8.86% (2001-2002) to 27.7% (2009-2010)] and dysglycemia [7.6% (2001-2002) to 36.15% (2009-2010)] in young CAD^[30].

Although, dyslipidemia is an important risk factor for young CAD, there seems to be a little difference in prevalence of lipid abnormalities in younger and older patients. One study demonstrated a significantly increased level of LDL and total cholesterol in persons of CAD more than 55 years of age when compared with less than 55 years of age^[27]. Conversely in an another study there is high prevalence of lipid abnormalities in young CAD when compared to older CAD group^[28]. These differences in lipid parameters may due effect of dietary, genetic and environmental factors on lipid metabolism.

Obesity is a well established risk factor for CAD. There is little difference in the prevalence of obesity in young CAD when compared with older CAD patients^[28]. Sagittal abdominal diameter to skin fold ratio seems to be a good indicator in predicting premature CAD, even better than body mass index (BMI) and waist

circumference^[31].

Family history of premature CAD is an important risk factor for young CAD. It stresses the role of genes in the aetiology of young CAD. Studies have shown that person with a positive family history of premature CAD tend to have severe coronary atherosclerosis and is a very strong predictor of future acute coronary event^[32]. The atherosclerosis in coronary vessels, as revealed by increased plaque content is seen in individuals with a positive family history of premature CAD and increases the incidence of severe obstructive CAD^[32]. One study revealed around 64% of young CAD patients had a positive family history^[13].

The prevalence of conventional risk factors like hypertension (67%), dyslipidemia (67%), obesity (53%), smoking (42%), and diabetes (33%) is higher in women with a family history of CAD^[33].

Other risk factors

There are numerous risk factors found to be associated with CAD in younger people. Some of the newer risk factors are discussed in the review. Polymorphisms in cholesterol ester transfer protein (*CETP*) gene, hepatic lipase gene, lipoprotein lipase gene, C-reactive protein gene, *apo A1* gene, *apo E* gene, *apo B*, hypoxia inducible factor 1 alpha gene, factor 5 leiden, Methylene tetrahydrofolate reductase (*MTHFR*) gene and methionine synthase gene have been associated with premature CAD^[34-38].

Kuivenhoven *et al*^[39] found a significant association between variation at the CETP locus and angiographic progression of coronary atherosclerosis in men with CHD.

The ApoE4 allele has been associated with CAD in several populations. ApoE2/E2 homozygous individuals are at risk for type III hyperlipoproteinemia, which is associated with an increased risk for atherosclerosis^[40,41].

Homozygosity for the *MTHFR C677T* mutation has been associated with elevated levels of homocysteine, and homocysteine levels have been associated with CAD risk^[42,43].

Hepatic lipase (HL) is both a phospholipase and a triglyceride lipase and plays an important role in HDL metabolism and in the conversion of VLDL to LDL. Single nucleotide polymorphisms in the *HL* gene have been shown to associate with plasma lipid concentrations and increased CHD risk^[44].

Hypercholesterolemia is the most common and treatable cause of heart disease. Familial Hypercholesterolemia (FH) results from mutations in the LDL receptor, *ApoB*, *PCSK9*, and *ApoE* genes. FH is characterized by isolated elevation of plasma low-density lipoprotein cholesterol and is associated with high risk of premature cardiovascular disease^[45].

The prevalence of premature arcus senilis (16.1%), premature greying (34.9%) and premature balding (22.3%) have been found to be significantly increased in young CAD patients when compared to non CAD

subjects of same age^[26,46]. Thus young CAD patients are associated with premature ageing as depicted by these markers. The arcus senilis is also a marker of familial hypercholesterolemia which in turn is a risk factor for premature CAD.

Cocaine use is also considered as a risk factor for CAD, it is associated with a number of cardiovascular diseases, including myocardial infarction, heart failure, cardiomyopathies, arrhythmias, aortic dissection, and endocarditis^[47].

Young CAD patient shows an increased serum levels of lipoprotein-a, fibrinogen and D-dimer as compared to age matched controls^[8]. Decreased serum Wnt, increased gamma glutamyl transferase, raised vitamin D2 and D3 and decreased levels of osteocalcin are found to be associated with premature CAD^[48-50]. This association of CAD in young with high levels of vitamin D is in contradiction to the studies done in general population where deficiency of vitamin D is associated with adverse cardiovascular outcomes^[51-53].

Diseases such as hypothyroidism, systemic lupus erythematosus, rheumatoid arthritis, HIV patients on highly active anti retroviral therapy (HAART) (especially with protease inhibitors), homocysteinaemia, kawasaki disease in childhood, patent foramen ovale (causing paradoxical embolism) and various other conditions are found to associated with accelerated atherosclerosis^[54,55].

The mean age of presentation of spontaneous coronary artery dissection is 35-40 years, and is more common in females. The patients are divided into three groups: A peripartum, atherosclerotic and idiopathic group^[56]. Dissection occurs in tunica intima of coronary arteries, the blood penetrates and results in intramural hematoma in tunica media, resulting in restriction in the size of lumen, reduction of blood flow and myocardial infarction^[57].

PATHOPHYSIOLOGY OF CAD IN YOUNG

Conventional CAD accounts for about 80% of CAD in young adults. About 4% of heart attacks in young adults are due to congenital abnormalities of the coronary artery anatomy, about 5% due to blood clots that originate elsewhere and are carried to otherwise normal coronary arteries, and block the artery, in another 5%, various disorders of the blood clotting system increase the risk of clot formation. The remaining 6% of CAD in young adults is due to spasm or inflammation of the coronary arteries, radiation therapy for chest tumors, chest trauma, and abuse of cocaine, amphetamines, and other drugs. Coronary segments, with non-significant stenosis and non calcified plaque, shows positive remodeling that might be the cause of CAD in young individuals with normal coronary artery. Positive remodeling is related to plaque instability, suggesting it is more prone to rupture and erosion with subsequent coronary events. Lipid core plaques, in contrast to the severely calcified plaques, showed positive vascular remodeling, thus early plaques are more prone for

CAD^[58-60].

PROGNOSIS

Obesity and current smoking are the two important conventional risk factors associated with adverse outcomes in the form of increased mortality and future acute coronary events^[3]. Mortality of CAD in people of China, less than 40 years of age, was 13.81/100000 in 2006 which increased to 19.07/100000 in 2009^[61]. There is a widespread decrease in mortality due to CAD in older age group in the recent years but it not seen in CAD in younger age group^[62]. The possible explanation that is proposed is increase in prevalence of risk factors such as diabetes, obesity and hypertension in younger age groups^[62]. Mortality after an acute coronary event is two times higher in women than in men under 50 years of age^[63,64]. The cause of increased incidence of adverse event in women with premature CAD is still unknown.

In patient with acute coronary event both percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG) are associated with excellent immediate survival (mortality of 0.8% vs 1.4% for PCI and CABG respectively at 30 d) as well as long term survival outcomes at end of 5 years^[65]. But PCI seems to associated with lower rate of repeated acute coronary events and revascularisation procedures when compared to CABG at the end of 5 years (repeat myocardial infarction 89.9% vs 96.6% for PCI vs CABG)^[66]. Mortality outcomes at 30 d and 3 years after an ST segment elevation myocardial infarction in 3601 patients with and without family history of premature CAD were compared in Harmonizing outcomes with revascularization and stents in acute myocardial infarction (HORIZONS-AMI) trial, which did not show any significant association of family history of premature CAD with mortality outcomes^[67]. In patients with young CAD high C-reactive protein have been associated recurrence of future acute coronary event and raised fibrinogen levels seems to be associated with increased mortality^[6]. Persons with positive family history of premature CAD and coronary artery calcium scores greater than 80th percentiles benefit from treatment with statins for primary prevention of acute coronary events^[68].

Young CAD patients have higher rates of normal coronary vessels on angiography, mild luminal irregularities and increased prevalence of single vessel disease than older CAD patients^[24]. In recent study from Nepal of young CAD less than 45 years angiography revealed 7.6% had normal or non critical disease, 6.1% had triple vessel disease, 36.9% had double vessel disease and 53.8% had single vessel disease^[69].

Single vessel disease involving left anterior descending artery is much more common in young women when compared with young men with CAD^[70,71]. The prevalence of normal coronary arteries in patients with young CAD is about 8% to 22% as reported in various studies^[72-74] compared to 3% to 4% in general

CAD population^[75]. The cause of this high prevalence of normal angiography in young CAD patients is still unclear. The probable reason could be the natural extra luminal progression of disease in the initial stages, as the vessel wall compensates to maintain unrestricted luminal blood flow^[76]. An occlusive thrombus produced by the rupture of an angiographically “invisible” vulnerable plaque totally lysed after few hours or a long-lasting vasospasm leading to complete occlusion of a normal coronary artery or a combination of these two are the most likely mechanism of CAD in patient with normal coronaries^[77].

CONCLUSION

The overall prevalence of CAD including the subset of young CAD is on decreasing trend but mortality of CAD doesn't seem to be decreasing when comparing to older CAD patients. In addition to conventional risk factors numerous other risk factors and genes play an important role in the causation of the disease. The prognosis of CAD in younger people is better than older people. Current smoking and obesity have major impact in long term mortality and morbidity. Young CAD patients with an acute coronary event undergoing PCI and CABG have an excellent immediate and long term survival rates.

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