Review Article

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Vascular Disease in Young Indians (20-40 years): Role of Ischemic Heart Disease

Internal Medicine Section

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ABSTRACT

Coronary Artery Disease (CAD) occurs at a younger age in Indians with over 50% of Cardiovascular Disease (CVD) mortality occurring in individuals aged less than 50 years. Although several risk factors have been suggested; smoking, dyslipidemia and hypertension are major risk factors in the young. In this review, we have pooled the current evidence on Ischemic Heart Disease (IHD) in young (20-40 years) and provided an opinion for the effective management of IHD in young Indians.

Keywords: Coronary artery disease, Management, Risk factors

INTRODUCTION

Coronary Artery Disease (CAD) occurs at a younger age in Indians [1-4], with over 50% of CAD mortality occurring in individuals aged less than 50 years, and one-fourth of all acute Myocardial Infarctions (MIs) are reported in patients below 40 years [3]. Projection suggests that by 2015, 62 million Indians will have CAD of which 23 million are expected to be below 40 years [5].

Differing pattern of dyslipidemia combined in inherent insulin resistance and contribution from varying lifestyle makes Indians more vulnerable to CAD at a younger age [4]. Although several risk factors have been suggested; smoking and other forms of tobacco, dyslipidemia and hypertension are major risk factors in the young [6,7]. Clinical presentation of CAD in young Indians may vary from multiple vessel disease without any clues offered from risk factors to extensive ischemia in an asymptomatic individual [8]. Occurrence of CAD in absence of any conventional risk factors at a young age makes it difficult to understand the aetiopathogenesis [9-11]. A dilemma may exist among clinicians as to adopting specific management strategies in young CAD patient. Appropriate selection of medical and/or interventional strategies to improve morbidity and mortality outcome may be difficult; however, effective risk stratification is necessary to improve outcomes [12-14].

In pursuit of such enormous premature CVD burden, we pool current evidence on IHD in young (20-40 years) and provide an opinion for the effective management of IHD in young Indians.

Epidemiology in India

Increasing rates of CAD in India in last three decades sends an alarm to look for the factors responsible for its increasing prevalence. In Asian Indians, risk of CAD is 3-4 times higher than Americans, 6 times higher than Chinese and 20 times higher than Japanese [15-17]. In the Framingham Heart Study, the incidence of an MI over a 10-year follow-up was 12.9/1000 in men 30 to 34-year-old and 5.2/1000 in women 35 to 44-year-old [18]. In a multinational study, Awad et al.,, observed prevalence of 23% in young adults (<55 years) how were hospitalized for Acute Coronary Syndrome (CAD) [19]. Prevalence data among young Indians is limited. In young patients increasing rates of CAD prevalence in adults have been reported previously [20]. Investigations in 1990s reported CAD prevalence of around 12-16% in the Youth/Young-population [21]. Prevalence of acute MI as high as 25 to 40% has also been reported in the young [22]. Analysis of INTERHEART data in South Asians revealed acute MI prevalence of 11.7% (n=55/470) in India in patients aged below 40 years [23]. In 25 748 ACS patients from Kerala state; Mohanan et al., observed ACS prevalence of 22.2%, 57.2% and 20.6% in age group of < 50 years, 51 to 70 years and > 70 years respectively. Further they found similar prevalence of three ACS types (22.4% for ST-elevation myocardial infarction {STEMI}, 22.2% for Non-St Elevation MI {NSTEMI} and 22.0% for Unstable Angina {UA}) in patients below 50 years [24]. We need a detailed, large pan India prospective study to estimate the prevalence of CAD in young Indians, both male and female.

Gender Differences

In general population, prevalence of CAD especially MI is more common in males than in females. In a small observational study in young Indians, Aggarwal et al., found CAD prevalence of 94.94% (n=75/79) and 86.75% (n=72/83) in periods 2001-2002 and 2009-2010 respectively [25]. Other reports also suggest a higher CAD prevalence in young Indian males than females [26]. Bhardwaj et al., also reported acute MI almost exclusively in young males (n=123/124) [6].

Aetio-pathogenesis

Risk factors for CAD: Smoking, Apolipoprotein B/Apolipoprotein A1 (ApoB/ApoA1 ratio), hypertension, diabetes, abdominal obesity, psychological factors, poor daily consumption of fruits and vegetables, regular alcohol consumption, and absence of regular physical activity are risk factors for CAD validated by INTERHEART study and these account for 90% population attributable risk [27]. Presence of these factors in the young also predisposes them to CAD. Kerala ACS registry reported hypertension (48.4%), diabetes (37.6%), and smoking (34.4%) in patients who had ACS [24]. Many investigators reported similar risk factor profile even in the young as observed by INTERHEART study [9,26]. Ghosh et al., compared the risk factors amongst different groups. They observed increasing prevalence of risk factors with increasing age signifying prevention of risk factors in early age to prevent future complications [28].

Though difficult to quantify, stress, adverse childhood experiences and psychological behavior also play an important role in the development of CAD. Essentially, INTERHEART study found odd ratio of 2.67 for psychological factors in the causation of CAD in the general population, with population attributable risk as high as 32.5% [27].

Pathogenesis

Pathophysiologically, young CAD can be classified in to four major mechanisms namely atheromatous, non-atheromatous, hypercoagulable states and associated with substance misuse [12].

Atheromatous CAD is common in young and previous investigations provide agreement for this mechanism [29-31]. Close look at risk factors in young also validate atheromatous CAD aetiology. A high degree cigarette smoking was found in young atheromatous CAD [32-34]. Characteristic dyslipidemia with high prevalence low High-Density Lipoprotein Cholesterol (HDL-C) and high triglycerides can also promote atherosclerotic CAD [35].

Apart from conventional risk factors, other factors like increased levels of Lipoprotein-a (LP-a), hyperhomocysteinemia, have also been investigated [36,37]. A prospective study in north-Indian adult population identified significantly higher levels of LP-a in patients with ACS than controls [38]. In patients below 40 years, Gambhir et al., reported LP-a as independent risk factor for CAD. In their small sample evaluation of young CAD (n=50) compared to age matched controls (n=50), significantly higher levels of Lp-a (35.0±32.4mg/dL vs. 20.3±17.0mg/dL, p<0.002, respectively) were found [39]. Hyperhomocysteinemia is associated with vascular diseases including CAD [37]. Significant association of increased homocysteine levels with CAD in the young (<45 or <55 years) has been reported in many studies including investigations from India [40-43].

Non-atheromatous CAD is may be majorly associated with congenital anomalies of coronary arteries that manifest in young age [44]. Myocardial bridging causing direct coronary compression or augmentation of existing coronary atherosclerotic lesion may also affect young and present with ischemia [45,46]. Spontaneous coronary dissection can also manifest as ACS in young. In young females (31-50 years) with ACS (n=77) who underwent coronary angiography, Saw et al., reported different aetiologies like Spontaneous Coronary Artery Dissection (SCAD), coronary fibromuscular dysplasia, coronary vasculitis and coronary ectasia [47]. Paradoxical coronary embolism can also be a cause of ischemic disease in non-atheromatous coronaries [48]. Coronary artery aneurysm, MI resulting from septic vegetations from infected aortic valve also has been reported [12]. In our view, non-atheromatous CAD is not an uncommon entity and clinician should have high index suspicion in young individuals for this aetiology.

Evidence related to hypercoagulable states like antiphospholipid syndrome, nephrotic syndrome, factor V Leiden mutation, etc., suggests possibility of ACS or MI in young [12]. Acute MI can be the presentation of antiphospholipid syndrome associated with disease like systemic lupus erythematosus [49]. Long term use of contraceptive pills poses risk of MI [50,51]. Compared to noncurrent Oral Contraceptive (OC) pill users, Peragallo et al., in a meta-analysis observed significantly increased risk of venous thromboembolism (odds ration {OR} 2.97) and ischemic stroke (OR 1.90) but not that of MI (OR 1.34) or hemorrhagic stroke (OR 1.03) in patients with current use of OC pills [52]. This aetiopathogenic mechanism should be explored in unexplained young CAD cases.

Being young at age, this population is often involved in illicit drug abuse. Cocaine use association with MI has previously been reported. Increased sympathetic activity, coronary arterial spasm and increased coagulability are proposed mechanism for MI [53-55]. Enquiry into recreational drugs use should be done in all young ACS cases.

Issues in females

Epidemiological data suggests that CAD is relatively infrequent in women. High mortality in CAD is attributed to failure to recognize ACS in young women. Hormonal protection possibly prolongs development of atherosclerosis in women. Impaired coronary microcirculation, coronary spasm, coronary dissection and endothelial rupture culminating in to thrombosis are more frequent in women [56]. Apart from classical risk factors, psychosocial factors are especially important in Indian women. Literature suggests that young women have worse outcomes when compared to men and may have more iatrogenic complications [56,57].

Investigations

All individuals should be investigated for risk factor profile including diabetic profile [fasting and postprandial blood glucose, glycosylated hemoglobin (HbA1c)], lipid profile (LDL-C, HDL-C, total cholesterol, triglyceride levels, non-HDL-C cholesterol, serum lipoprotein-a), and serum homocysteine. Some of the investigations are to be performed in selected cases based on clinical suspicion including protein C, protein S, antiphospholipid antibodies, and urine screen for cocaine.

For definitive diagnosis of CAD, investigations like Electro-cardiogram (ECG), cardiac troponin and coronary angiography are must. Specialized investigations are necessary in selected individual cases.

Electrocardiogram (ECG)

Immediate assessment of patient with suspected ACS should be done with a 12-lead ECG. Based on changes in ST-segment and T wave, clinical diagnosis of ACS can be differentiated. In case of no changes on ECG and physician has strong suspicion of ACS, repeat ECG can be taken after an interval. It is to be remembered that a normal ECG doesn't rule out ACS or changes in ST-T segment do not always suggest MI [58-60].

Cardiac troponin

Undoubtedly cardiac specific troponin and High-Sensitivity Troponin are diagnostic biomarkers for acute MI [59].

Exercise stress test

A suspected CAD can be ascertained with exercise stress test. After multivariate analysis, Uthamalingam et al., observed that stress induced ST-segment elevation in lead aVR was strongest predictor of left main coronary artery or ostial left anterior descending artery stenosis [61].

Echocardiography (ECHO)

Wall motion abnormalities diagnosed on transthoracic ECHO may suggest possible IHD. Some investigations using stress ECHO with exercise or pharmacotherapy suggest a greater sensitivity and specificity. It can be used as a screening test to select individuals [62].

Coronary angiography

Angiographic visualization of coronaries provides essentials of coronaries in order to optimize the treatment strategy. It is also a tool to distinguish between the atheromatous and non-atheromatous coronary involvement in young [63]. Uddin et al., compared angiographic profile of young (< 40 years, n=50) to the older population. The important observations for young were more family history of premature CAD, normal coronaries or single vessel disease, less extensive coronary atherosclerosis and lesser number of inoperable vessels [64]. In another study of young adults (<40 years, n=239), investigators observed angiographically normal coronaries in 16.9% and 37.2% of STEMI and CAD patients respectively [65]. In case of suspected acute MI without ST elevation, coronary angiography is advised for persistent or recurrent ischemia with or without ECG changes and also in presence of shock, severe pulmonary congestion or continuing hypotension [66]. Coronary angiography provides key details of coronary vasculature and helps differentiate atheromatous and non-atheromatous and can provides prognosis of CAD based on disease involvement.

Coronary Computed Tomography (CT) Angiography (CTA)

In selected individuals CTA can be helpful in determining the aetiology of CAD and delineating the coronary atherosclerosis. Kim et al., interestingly observed that individuals classified as low-risk (n=2133) by NCEP guidelines actually had atherosclerotic plaques (11.4%), significant stenosis (1.3%) significant stenosis

due to non-calcified plaques (0.8%), on assessment by cardiac CTA. Excepting one patient, all patients who had non-calcific stenosis were young. This suggests prognostic role of CTA in otherwise low risk patients [67]. In a prospective study of young (<45 years, n=1635), Otaki et al., observed a stronger correlation between number of risk factors, and extent and severity of CAD. After adjustments for sex and risk factors, they reported family history of CAD being the strongest predictor of obstructive CAD (≥50% stenosis) (OR = 2.71) [68]. In selected individuals CTA is must where suspicion of either congenital anomalies of coronaries or spontaneous coronary dissection is high and patient has CAD. Retrospective evaluation by Ma et al revealed 13.6% patients having one or more myocardial bridge and mural coronary artery by 256-slice CTA. LAD was commonly involved (60.41%) and over one-third of mural coronaries had more than 50% stenosis in systole phase [69].

Management

Medical

Optimal medical management of young CAD is essential to reduce recurrent CAD and mortality.

A large observational study in young individuals with ACS found significant reduction in atrial fibrillation, stroke, and major bleeding episode over the study period (1999-2007). Also, in-hospital mortality and 30-day adjusted mortality reduced by more than 30% in this population. Investigators attribute it to the aggressive management [19]. This medical management of CAD starts with risk factor reduction, lifestyle therapy incorporating dietary and exercise measures remains central to management of young IHD [70,71]. Control of blood pressure, lipids and sugars with recommended treatments should be aggressively followed. High-intensity statin treatment should be instituted. Treating non-conventional risk factors should be taken in to consideration based on overall CV risk. LP-a was found to be associated with increased residual risk in the AIM-HIGH Trial (Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglyceride and Impact on Global Health Outcomes Trial). But simvastatin in combination with extended-release niacin could not improve CV outcomes regardless of significant reduction in LP-a at 1 year [72]. Decision in such cases should be on clinical judgment and patient preferences. Drug therapy prescribed to young remains the same as is recommended in guidelines [58,59].

Interventional

Cole et al., in a fifteen years follow-up of young individuals with angiographically documented CAD identified single, double and triple vessel disease in 60.6%, 24.5%, 12.8% of women (n=94) and 55.8%, 27.2%, 14.8% of men respectively [73]. Depending on pathogenesis of CAD, interventional modality is directed in an individual.

Atherosclerotic obstructive CAD

Major therapeutic options for obstructive CAD in young include cardiac catheterization, Percutaneous Coronary Intervention (PCI) or Coronary Artery Bypass Grafting (CABG). Awad et al., reported data of young adults with CAD and use of hospital therapies for management at three different time-periods of hospitalization. They observed declining trend in use of thrombolysis and CABG whereas increasing use of PCI (P for trend < 0.05) [19]. This is possibly also true for Indian setting. A limited accessibility to PCI facility in India is a major challenge for timely intervention with PCI. Thrombolysis following STEMI, remains a major modality of intervention in India. Vaidya et al., studied young adults with STEMI and identified that 78.7% were thrombolysed in a government hospital set up whereas 38.7% were referred to higher centre for further intervention [74]. In a small study comparing tenecteplase (n=14) and streptokinase (n=10), Dhoot et al., observed higher rate of recanalization with tenecteplase (86%) compared to streptokinase (50%) [75], and though more expensive, should be the agent of choice.

PCI should be the choice for young patients where feasible. Ergelen et al., observed favorable short term and intermediate outcome in young (<45 years, n=465) than old (n=1959). Also, PCI was safe, more feasible and an effective modality for young than old [76]. Similarly Chua et al., observed better outcomes in younger patients without significant differences in repeated PCI or reinfarction compared to older adults [77]. With use of drug eluting stents with PCI, and use of better antiplatelet agents, we expect higher success rates with better long-term outcomes. However, long-term prospective studies are warranted to establish this hypothesis.

CABG is an option for more severe involvement of coronaries especially for complex triple vessel disease or with impaired left ventricular dysfunction specially when associated with diabetes. Christus et al., observed that CABG was needed in 13.5% of young adults below 35 years of Asian ethnicity. Most patients were managed medically (54.5%) and PCI with stenting was performed in 32% of patients [78]. CABG also has better success rate with preference of arterial than venous grafts [79].

Lone Aspiration Thrombectomy (LAT) is also another intervention in young adults with STEMI. Jamil et al., reported outcome of 10 patients who underwent LAT without stenting for STEMI. Nine patients at one month had no major CV events. Also, five patients at 2 months and three patients at 2 years had no major adverse consequences [13]. It can be alternative option in select individuals. The reason for this is that often in the young the underlying lesion is non-significant, with plaque rupture and thrombotic occlusion being the main reason for the STEMI. However, long-term, large scale, comparator studies are warranted.

The Coronary aRterydiseAse in young adults (CRAGS) study in adults below 50 years who underwent PCI suggests that disease progressed in 13.5% of the patients who required repeat revascularization. Hypertension, diabetes and multivessel disease were independent predictors of disease progression. Investigators identified need for effective use of currently available therapies for secondary prevention in young adults [80].

Non-obstructive CAD

It is more common in young adults than the elderly, and has lower 30-day and six months mortality as well as lower MI rates as compared to obstructive CAD [81]. Revascularization in such case should be decided on individual basis. Patients who have high-ischemic risk as identified by risk factor investigations, revascularization may be offered. Antiplatelet agents may be advised to reduce future coronary events. Patients who are not amenable to revascularization tend to have higher mortality and outcome may vary depending on various factors including age [82]. Optimal medical management of such individuals should be done. Regular follow-up for disease progression are mandated.

CAD associated with other causes

Aetio-pathophysiological causes like hypercoagulable states, illicit drug use, etc. need to be looked into while evaluating CAD in young. Undiagnosed familial hypercholesterolemia may sometimes present as acute MI. Clues from detail patient's family history and clinical examination should be evaluated to make an early diagnosis and to reduce morbidity and mortality in young CAD.

CONCLUSION

- Indians have higher risk of CAD at young age compared to other populations.
- Risk factor profile remains similar to those of old adults such as dyslipidemia, tobacco, diabetes, and hypertension but conditions like hyperhomocysteinemia, hypercoagulable states, and cocaine use, etc. are specific to younger population and should be evaluated in CAD cases.
- CAD in the young is increasing in prevalence in India due to changing lifestyle.

- Family history of premature CAD is one of the strongest risk factor in young individuals.
- Obstructive as well as non-obstructive pathologies prevail in young individuals.
- Search for causes like coronary dissection, myocardial bridging, coronary anomalies, aorto-arteritis etc., is necessary in cases where causes remain unidentified.
- Investigations like exercise stress testing, stress echocardiography, coronary angiography can help identify young individuals at higher risk of CAD.
- Risk factor prevention is essential to prevent CAD in young.
- Optimal medical management can be helpful in non-obstructive CAD.
- For obstructive CAD, PCI with stenting should be preferred if available and affordable.
- Thrombolysis still remains one of the major therapeutic approaches even for the young CAD due to ease of availability. Preference to newer fibrinolytics like reteplase, or tenecteplase should be given if available and affordable.
- For complex coronary lesions, multivessel disease or with LV dysfunction, especially when associated with diabetes CABG can be a method of choice. Preference to total arterial grafting should be given.
- Lone aspiration thrombectomy is another approach, when underlying lesion is insignificant and occlusion is predominantly due to a large thrombus. In absence of strong clinical evidence, it should be reserved for selected patients where it would be safe to leave them unstented.
- Optimal secondary prevention medications and strict adherence to life style changes should be ensured to reduce future coronary events.

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