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Review Article

Coronary artery disease in Bangladesh: A review

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ABSTRACT

Coronary artery disease (CAD) is an increasingly important medical and public health problem, and is the leading cause of mortality in Bangladesh. Like other South Asians, Bangladeshis are unduly prone to develop CAD, which is often premature in onset, follows a rapidly progressive course and angiographically more severe. The underlying pathophysiology is poorly understood. Genetic predisposition, high prevalence of metabolic syndrome and conventional risk factors play important role. Lifestyle related factors, including poor dietary habits, excess saturated and trans fat, high salt intake, and low-level physical activity may be important as well. Some novel risk factors, including hypovitaminosis D, arsenic contamination in water and food-stuff, particulate matter air pollution may play unique role. At the advent of the new millennium, we know little about our real situation. Large scale epidemiological, genetic and clinical researches are needed to explore the different aspects of CAD in Bangladesh.

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1. Introduction

Coronary artery disease (CAD) is an important medical and public health issue because it is common and leading cause of death throughout the world. Bangladesh has been experiencing epidemiological transition from communicable disease to non-communicable disease (NCD). The overall mortality rate has decreased significantly over the last couple of decades. But deaths due to chronic diseases, specially the 'fatal four' i.e. cardiovascular disease (CVD), cancer, chronic respiratory disease and diabetes, are increasing in an alarming rate.¹ CAD is an important contributor to one of the four i.e. CVD. Of all South Asian countries, Bangladesh probably has the highest rates of CVD and yet is the least studied; in the global combat against CVD, Bangladesh is a country 'missing in action'.² Besides epidemiological transition, widespread environmental contaminants such as arsenic in groundwater

or particulate matter in air, or specific vulnerabilities in the genetic or metabolic make-up, may play important role in the etiopathogenesis of CAD in this population.

2. Rationality of the review

Data related to ischemic heart disease (IHD) in Bangladesh are often insufficient, suffer from statistical flaws and are not readily available. Many articles were published in national, non-indexed journals, which are not available online and difficult to procure. Recognizing these limitations, the present review has been planned to compile the available data on this important public health issue. This review will hopefully encourage future research and act as an important source of information.

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3. Methods

Data have been collected from the articles available from MEDLINE and BanglaJOL supported by the International Network for the Availability of Scientific Publications (INASP) up to the year 2012. Besides this, national journals which are not available online but recognized by the Bangladesh Medical and Dental Council have also been considered.

4. Epidemiology

The prevalence of CAD varies considerably by populations, may be up to 10 folds.³ South Asians are unduly prone to develop CAD.⁴ Most notable features of CAD in this population are the extreme prematurity and severity; 2–4-fold higher prevalence, incidence, hospitalization and mortality; 5–10 years earlier onset of first myocardial infarction (MI) and 5–10-fold higher rates of MI and death before the age of 40 years.⁴ The exact prevalence of CAD in Bangladesh is not known. Only a limited number of small-scale epidemiological studies are available. Probably the prevalence of IHD was first reported in 1976, which was 0.33%.⁵ More recent data indicates CAD prevalence between 1.85%⁶ and 3.4%⁷ in rural and 19.6% in an urban sample of working professionals.^{8,9} Despite marked disparity in values, there seems to be a rising prevalence of CAD in Bangladesh.

A recent study from rural Bangladesh demonstrated a dramatic increase in CVD from 1986 to 2006. The age-standardized CVD mortality rates increased by 30-fold (from 16 deaths per 100,000 to 483 deaths per 100,000) among males and 47-fold (from 7 deaths per 100,000 to 330 deaths per 100,000) in females.¹⁰ A nation-wide survey is needed to find out the current epidemiological aspects of CAD in the country.

5. Ethnicity and coronary artery disease in Bangladesh

Ethnicity has been suggested to play role in the undue susceptibility of South Asian population to CAD.^{11,12} CAD is premature in onset, clinically aggressive and angiographically extensive in South Asians.¹³ South Asian ethnicity was associated with increased morbidity and mortality after CABG,¹⁴ and in-stent restenosis but not mortality after PCI.¹⁵ Studies involving the immigrants in abroad have found that among the South Asians, Bangladeshis are even more prone to develop CAD, and are associated with higher morbidity and mortality related to CAD. Bangladeshis in New York, USA, had more extensive and severe heart disease with 53% having triple-vessel disease compared to 26% among whites.¹³

In UK, Bangladeshi men have 112% higher CAD mortality and 220% higher stroke mortality than Europeans.¹⁶ Also among the South Asians in UK, Bangladeshis have the highest prevalence of most of the CAD risk factors.^{17–19} Of all ethnic groups, they have the highest prevalence of smoking in men (57%),¹⁸ and diabetes (27%), the latter is 3–4 times more common in Bangladeshis than in Europeans.^{20,21} Shortness of

height is associated with a higher risk of heart attack and Bangladeshis are the shortest in UK.¹⁸

Bangladeshis appear to share with other South Asian populations the same susceptibility to CAD; however, the probability of existence of an even more prone ‘Bangladeshi ethnicity’ is not impossible. Complex interaction between genetic make-up and environmental factors may underlie this ‘Bangladeshi ethnicity’. Further research is needed to elucidate the role of ethnicity in the etiopathogenesis of CAD in Bangladeshi population.

6. Pathophysiology

The pathogenesis of CAD remains incompletely understood. Interplay between environmental and genetic factors likely contributes to the pathophysiology of CAD. The ‘classic’ risk factors such as hypertension, dyslipidemia, diabetes mellitus and smoking undoubtedly play vital role; in addition, some emerging risk factors and as-yet-unrecognized factors may be important. These factors in isolation, or in different combinations, in a genetically predisposed population, may explain the high prevalence of CAD in Bangladesh.

7. Genetic risk factors

From the genetic point of view, the increased susceptibility of South Asians to CAD may result from 3 mechanisms: 1) disease-related mutations specific to South Asian populations, 2) increased prevalence of susceptibility alleles and 3) adverse gene–environment interactions.²² First, there is little epidemiological or genetic evidence to support the existence of gene variants that are specific and exclusive to South Asians increasing their risk of CAD. Second, certain risk alleles may be more prevalent in South Asians compared to other ethnic groups, examples are polymorphisms involving genes regulating angiotensin-converting enzyme (ACE), apolipoprotein A (apoA), apolipoprotein B (apoB), apolipoprotein E (apoE), adipokine, homocysteine, plasminogen activator inhibitor-1, and fibrinogen.^{23–27} The third component, i.e. gene–environment interactions, ultimately determine the CAD risk; this is especially important where the frequency of disease associated alleles is similar in different ethnic groups but the exposure to the relevant environmental risk factor varies.

Susceptibility to CAD is claimed to be 40–60% inherited, but genetic risk factors predisposing to CAD are incompletely known.²⁸ Over the past few years, researchers have completed several genome-wide association studies (GWASs) to map underlying common susceptibility variants for CAD and its risk factors; collaboration between individual research groups has led to the formation of consortia to pool the results of GWASs using meta-analysis techniques.²⁹ The Coronary Artery Disease Genomewide Replication and Meta-analysis (CARDIOGRAM) consortium identified 13 loci newly associated with CAD in European descent.³⁰ On the other hand, the Coronary Artery Disease (CAD) Genetics Consortium performed a meta-analysis of 4 large genome-wide association studies of CAD, 2 of European ancestry (PROCARDIS and HPS)

and 2 of South Asian ancestry (PROMIS and LOLLIPOP) and found 5 new loci i.e. LIPA on 10q23, PDGFD on 11q22, ADAMTS7-MORF4L1 on 15q25, a gene rich locus on 7q22 and KIAA1462 on 10p11 for CAD, that have similar associations in Europeans and South Asians.³¹ Recently, 6 novel genetic loci have been identified in South Asians, which are associated with type 2 diabetes mellitus (DM), a major risk factor for CAD.³² However, many CAD genes are presently undiscovered, and it is likely that larger collaborative GWASs will map further common/low-penetrance variants and low-frequency or rare high-penetrance variants will also be identified in medical resequencing experiments.²⁹

The association between ACE gene polymorphism and blood pressure has been studied inadequately in Bangladeshi population.^{33,34} In 2002, Morshed et al found positive association between ACE insertion/deletion (I/D) polymorphism and hypertension in Bangladeshi population. Among the 3 ACE (insertion/deletion) I/D variants, the DD genotype was associated with the highest value of both mean systolic and mean diastolic blood pressure ($p < 0.05$) in men. In the overall population, blood pressure was highest in DD, intermediate in I/D, and the least in II subjects. Further research is needed to clarify the issue.

The frequencies of risk alleles of single-nucleotide polymorphisms (SNPs) mediating susceptibility to cardiovascular diseases differ among populations of varying geographic origin.³⁵ Elucidation of the genetic factors that predispose to CAD in South Asians is central to a fuller understanding of the epidemic and the nature of gene–environment interactions in the etiopathogenesis of CAD,²² and this is equally applicable to CAD in Bangladesh. Future research will hopefully identify novel genetic factors to further explain the undue susceptibility of South Asians, especially Bangladeshis, to CAD.

8. Environmental risk factors

8.1. Hypertension

In Bangladesh, approximately 20% of adult and 40–65% of elderly people suffer from hypertension; high incidence of metabolic syndrome, and lifestyle related factors like obesity, high salt intake and less physical activity may play important role in the pathophysiology of hypertension.³⁶

Bangladesh Non-communicable Disease (NCD) Risk Factor Survey 2010³⁷ was carried out by Bangladesh Society of Medicine in collaboration with Directorate General of Health Services and World Health Organization from November 2009 to April 2010 by using WHO STEPwise Surveillance approach in adults aged ≥ 25 years. According to the survey, prevalence of hypertension is 17.9% in general, 18.5% in men and 17.3% in women. Such a high prevalence of hypertension may contribute to the high prevalence of CAD in Bangladesh.

8.2. Diabetes mellitus

Exact prevalence of DM in Bangladesh is not known. According to the (NCD) Risk Factor Survey 2010³⁷ prevalence of self-reported or documented DM is 3.9% (men 4.3% and women 3.6%). The prevalence of DM in rural population was 7.2% in a

recent study.³⁸ Like in all other developed and developing countries, prevalence and incidence of type 2 DM is increasing in Bangladesh. In 2010, the International Diabetes Federation (IDF) estimated that 5.7 million (6.1%) and 6.7 million (7.1%) of people living in Bangladesh are suffering from DM and impaired glucose tolerance (IGT), respectively; by 2030, that number of diabetic population is expected to rise to 11.1 million.³⁹ This explosion in diabetes prevalence will place Bangladesh among the top seven countries in terms of the number of people living with diabetes in 2030.³⁹

8.3. Smoking and smokeless tobacco use

Tobacco consumption is quite common in Bangladesh: prevalence is 51.0% for any form, 26.2% for smoking and 31.7% for smokeless tobacco.³⁷

In a recently published study, betel quid chewing was found in 33.2% of rural.⁴⁰ Bangladesh is one of top 10 countries that make-up two-thirds of the world population of smokers.⁴¹ The association between smokeless tobacco use and CAD is inconclusive. In a recently published systematic review, 9 studies found no statistically significant positive association between the two, while 9 studies did find a positive association.⁴² A case–control study of non-smoking Bangladeshi adults aged 40–75 years conducted in 2010 found no statistically significant association between smokeless tobacco use in general and CAD among non-smoking adults.⁴³

8.4. Dyslipidemia

The excess burden of CAD among South Asians appears to be primarily due to dyslipidemia that is characterized by high levels of apoB, triglycerides (TG), and Lp(a); borderline high levels of low-density lipoprotein cholesterol (LDL-C); and low levels of high-density lipoprotein cholesterol (HDL-C) and apoA1.⁴⁴ An analysis from the INTERHEART Study⁴⁵ showed about 10 mg/dl lower mean LDL-C levels in Asians compared with non-Asians, a greater proportion of Asian had LDL-C ≤ 100 mg/dl, HDL-C levels were slightly lower among Asians compared with non-Asians. There was low HDL-C among South Asians in comparison to rest of Asia. Among South Asians, changes in apoA1 predicted risk better than HDL-C. ApoB/apoA1 showed the strongest association with the risk of acute myocardial infarction (AMI). Liberal use of saturated fats and trans fats, deep frying, reuse of cooking oil, and overcooking leading to destruction of folates may all contribute to dyslipidemia in this population.⁴⁶

Studies exclusively related to dyslipidemia are sparse in Bangladesh. In a study involving secretariat employees in Dhaka, abnormal fasting total cholesterol (TC), LDL-C, HDL-C and TG were found to be 17.3%, 48.5%, 75.6% and 48.5%, respectively.⁴⁷ A very recently published study⁴⁸ involving 51,353 predominantly urban persons over 2005–2011, demonstrated significantly higher mean serum levels of TC, LDL-C, TG, LDL to HDL ratio and TC to HDL ratio among younger adults aged 30–39 years compared to other age groups, regardless of sex. Probable explanation may include rapid urbanization with less physical activities, environmental pollution, climate change, and changes in dietary

habits, and also increasing access to day-to-day modern amenities leading to reduced physical activity and sedentary life styles, especially in younger adults. Another recent study⁴⁹ involving 3201 individuals found rising trend of dyslipidemia in sub-urban population; prevalence of dyslipidemia was 16.6% in general, 22.2% in males and 15.9% in females. Total cholesterol was high (>240 mg/dl) in 16.9%, LDL-C was high (>160 mg/dl) in 15.7%, HDL-C was low (<40 mg/dl) in 8.8%, and TG was high (>200 mg/dl) in 17.8% and very high (>350 mg/dl) in 2.0%. Women had significantly higher TC and LDL-C in comparison to men after the age of 40 years. Also fish cooked with mustard oil was found to have an apparent protective role. Contrary to the popular belief, dyslipidemia is common in rural people. In a study⁵⁰ conducted in 2001 involving rural population, high TC (≥ 240 mg/dl) was in 16.1%, high LDL-C (≥ 160 mg/dl) in 20.4%, low HDL-C (<40 mg/dl) in 66.4%, hypertriglyceridemia (≥ 200 mg/dl) in 15.0% and TC/HDL >5.5 in 32.7%. Here, less strict criteria were used to define dyslipidemia. So, the prevalence of dyslipidemia, especially low HDL-C, appears to be high even in rural population of Bangladesh. An interesting study to determine racial variation among Bangladeshi patients with type 2 DM demonstrated that the Bangalee patients have higher TG and lower atherogenic index compared with the Chakma patients, although no racial differences were found regarding TC, HDL-C and LDL-C.⁵¹ Despite considerable disparities in the prevalence of individual components of abnormal lipid profile, it is apparent that dyslipidemia is prevalent among the Bangladeshis in general. Studies are needed to determine the lipoprotein profile of the population for better understanding of the contribution of dyslipidemia to the etiopathogenesis of CAD.

8.5. Lifestyle related factors

As a result of socioeconomic transition, lifestyle, as well as, the dietary pattern is changing in Bangladesh. Increasing prevalence of obesity, tobacco use, high intake of processed foods and less physical activity accompany the transition. In general, 21.5% adults (male 21%, female 22%) have body-mass index (BMI) ≥ 25 kg/m²; increased waist circumference is alarming, especially in women (33.7%).³⁷

The prevalence of metabolic syndrome has been found to be 20.7%, 11.2% and 8.6% following modified Adult Treatment Panel III, International Diabetes Federation and World Health Organization definitions, respectively.⁵² In a recently published study, 19.5% of older persons in rural Bangladesh – 20.8% women, and 18.0% men – had metabolic syndrome.⁵³ The prevalence is higher in women.^{52,53}

Prevalence of obesity is increasing in children and adolescents in Bangladesh; it was 27.7% among affluent school children aged 6–9 years.⁵⁴ A recent study conducted among the obese children and adolescents attending the outpatient department of Bangladesh Institute of Research and Rehabilitation in Diabetes, Endocrine and Metabolic Disorders (BIRDEM), Dhaka, found the prevalence of metabolic syndrome to be 36.6%.⁵⁵

Sedentary life style may have association with CAD. In the Bangladesh NCD Risk Factor Survey 2010,³⁵ 27.0% of people

(10.5% men and 41.3% women) were found to have low-level of physical activity (<600 metabolic equivalent-minutes per week). Inadequate physical activity may contribute to obesity, especially in women. In a study⁵⁶ in Newcastle upon Tyne, UK, South Asians were found less physically active than the Europeans; 52% of Europeans did not meet current guidelines for participation in physical activity compared to 71% of Indians, 88% of Pakistanis and 87% of Bangladeshis. In general, level of physical activity inversely correlated with BMI, waist circumference, systolic blood pressure, blood glucose and blood insulin in all ethnic groups, but not with HDL-C level in blood. A systematic review suggested that low levels of physical activity among UK South Asians may contribute to their increased risk of diabetes and CAD.⁵⁷ Physical inactivity may contribute to the high incidence of CAD in Bangladesh.

Dietary pattern may play role in the etiopathogenesis of CAD. Nearly two-thirds of the typical daily diet of rural people consists of rice, some vegetables, a little amount of pulses and small quantities of fish if and when available, milk, milk products and meat are consumed only occasionally and in very small amounts.⁵⁸ Though over the years the consumption of rice and wheat has decreased, resulting in an overall decrease in cereal consumption from 59% to 41.33% as a percentage of monthly expenditure on major food items, still the proportion is quite high.⁵⁹ This may contribute to hypertriglyceridemia. On the other hand, use of liberal amount of cooking oil, fried vegetables and food preparations, extra salts added during preparation and pickles are important aspects of traditional Bangladeshi cuisine. Soybean oil, palm oil and mustard oil are the main edible oils. Vegetable oil, butter oil and ghee are also used. Deep-frying and reuse of cooking oil, the latter for financial constraint and ignorance, may lead to conversion of cis fat to trans fat. Food preparation methods result in significant nutrient loss; upto 40% of thiamine and niacin are lost during washing of rice before cooking, boiling rice and then discarding the water results in even more nutrient losses.⁶⁰ Chronic vitamin B complex deficiency may be associated with hyperhomocysteinemia. Traditional fast foods including Singara, Samucha, Puri, Pajju, and Paratha all are generally deeply fried. Commercially available packaged bakery and fast foods often do not contain any declaration of their fat content. With the social changes in recent years, Bangladesh is now experiencing a fast food culture, especially in urban areas. These commercial fast foods of western type, as well as, the traditional snacks were found to contain high amounts of cholesterol and saturated fatty acids, mainly derived from animal fats and palm oil.^{61,62} Research is needed to elucidate the role of these dietary issues in causation of atherosclerosis.

On an average, a Bangladeshi person consumes 126 g of fruit and vegetables daily,⁶⁰ which is far below the minimum daily consumption of 400 g of vegetables and fruit recommended by the Food and Agriculture Organization (FAO) and the World Health Organization (WHO).⁶³ In the Bangladesh NCD Risk Factor Survey 2010, consumption of inadequate fruit and/or vegetables (<5 servings per day) was found in 95.7% people.³⁷

High salt intake appears to be a significant problem with Bangladeshi population.

Average daily intake may be 15 g,⁶⁴ or even higher e.g. 21 g,⁶⁵ which far exceeds the recommendations by the WHO (sodium chloride < 5 g/day, sodium < 2 g/day)⁶⁶ or Dietary Guidelines for Americans 2010 (sodium < 2.3 g/day in general, and < 1.5 g/day for special groups).⁶⁷ Moreover, there is widespread misconception that, only raw salt is injurious to health, and it will no more be harmful after frying/roasting. High salt intake presumably contributes to hypertension, which is an established risk factor for CAD.

8.6. Hormonal contraceptives

Relationship between hormonal contraceptives and risk of CAD is a matter of ongoing debate. Existing observational data with earlier first- and second generation, higher-dosage formulations consistently demonstrate small but significantly elevated risks of MI and venous thromboembolism (VTE), while the newer-generation formulations currently in use indicate no increased MI risk, but a persistent increased risk of VTE.^{68,69} Hormonal contraceptives are the most widely used contraceptives in Bangladesh; overall contraceptive prevalence rate is 60.8%, hormonal contraceptive use rate is 39.2% (contraceptive pill 27.9%, injectable hormonal contraceptive 10.5% and implantable hormonal contraceptives 0.8%).⁷⁰ These steroid hormones may play some role in the increased prevalence of CAD in women in this population.

8.7. Infection

Role of infection as a risk factor for CAD is still inconclusive.⁷¹ Some of the most documented candidate infectious agents include *Chlamydia pneumoniae*, *Helicobacter pylori*, *Mycoplasma pneumoniae*, periodontal infections, cytomegalovirus, other Herpes viruses, human immunodeficiency virus, influenza virus,⁷² and even human papilloma virus.⁷³ Like many other developing countries, infections are likely to be common in Bangladesh; however, research relating the different infectious agents and CAD are almost lacking. A study carried out more than a decade ago found very high i.e. 92% seropositivity for *H. pylori* infection among healthy subjects.⁷⁴ 50–59% of the medical students were seropositive for *H. pylori* in a more recent study.⁷⁵ So, *H. pylori* appears to be prevalent in the country. C-reactive protein (CRP) in plasma is a marker of inflammation, one important cause of which is infection. Chronically raised CRP may be indicative of chronic infection leading to endothelial dysfunction and atherosclerosis. However, in a recent study, CRP has been found strongly associated with the metabolic syndrome but not with coronary atherosclerosis.⁷⁶ Several small studies involving Bangladeshi population have demonstrated higher CRP levels in stroke⁷⁷ and type 2 DM,⁷⁸ positive correlations between hs-CRP levels and severity of CAD,⁷⁹ and negative correlation between CRP and coronary collateral development.⁸⁰

8.8. Low-birthweight and childhood malnutrition

The developmental origin theory of CAD proposes that undernutrition in utero permanently changes body functions and metabolism leading to an increased risk of CAD in adult life; some studies suggest that birthweight is not a major risk factor for CVD but most of the recent studies are in favor of this

theory.^{81–83} Low birthweight (<2500 g) affects 36% of infants in Bangladesh, more than twice the 15% threshold that indicates a public health problem. Also, <1% of infants are born with very low birthweight (<1500 g).⁸⁴ There may be an association between the two public health problems i.e. low birthweight and CAD in this community. Undernutrition during childhood, adolescence, or young adulthood is related to CAD and stroke in adult life.^{85,86} Despite the progress achieved, malnutrition continues to be a serious problem with nearly half of the children being moderately underweight, one-third suffering from stunting and a large number of adolescents, girls in particular, being malnourished.⁸⁷ A recent analysis revealed that among the children under five years of age, 16% were severely stunted, 25% moderately stunted, 3% severely wasted and 14% were moderately wasted; furthermore, 11% of the children were severely underweight and 28% were moderately underweight.⁸⁸ Such a high prevalence of low birthweight childhood under-nutrition may facilitate development of CAD in adult in Bangladeshi population.

8.9. Homocysteine

Hyperhomocysteinemia has been found to be associated with increased risk of CVD, however, the role of vitamin supplementation in reducing this risk is a matter of ongoing debate.⁸⁹ Factors causing hyperhomocysteinemia include deficiencies of vitamin B₆, vitamin B₁₂, and folic acid; renal insufficiency; and genetic variants in enzymes responsible for homocysteine metabolism.⁹⁰

Lower serum folate and elevated serum homocysteine levels were found in Bangladeshis in comparison to the Whites in a study carried out in UK; interplay between genetic and dietary factors were postulated to be the explanation.⁹¹ In a study involving 1650 adults in Bangladesh, prevalence of hyperhomocysteinemia (men: >11.4 μmol/L; women: >10.4 μmol/L) was 63% among men and 26% among women; folate and cobalamin deficiency, smoking and betel nut use were the possible associations.⁹² Only few studies have been carried out in Bangladesh to look for the association between raised homocysteine and CAD.^{93,94} In a recent study carried out in Dhaka, plasma total homocysteine and Lp (a) were found elevated independently of the conventional risk factors of CAD in patients presenting with acute MI, and the levels came down with vitamin B complex and folate supplementation.⁹⁵ Another study demonstrated hyperhomocysteinemia in 61.9% of acute MI patients, and positive association between homocysteine level and extent of myocardial damage.⁹⁶ Plasma fasting homocysteine level was found to be significantly elevated in younger (<40 years) patients in comparison to the older (>40 years) counterparts with acute MI.⁹⁷ However, these studies were of small-scale and it is difficult to draw a firm conclusion from them. Also, studies are needed to define the role of genetic make-up in hyperhomocysteinemia, including genetic mutation in methylene tetrahydrofolate reductase (MTHFR) gene in Bangladeshi population.

8.10. Hypovitaminosis D

Role of vitamin D in cardiovascular health is of much interest at present. Experimental, as well as, some observational

studies suggest that vitamin D and its metabolites are integrally related to blood pressure and the rennin-angiotensin system. Vitamin D insufficiency affects almost 50% of the population worldwide. Few studies have been carried out to determine the prevalence of hypovitaminosis D in Bangladesh. High prevalence of suboptimal serum 25-hydroxycholecalciferol levels (<25 nmol/l) was described in lactating women of low socioeconomic status and those wearing Shari, a traditional ladies wear.⁹⁸ In another survey of women aged 18–60 years, serum 25-hydroxycholecalciferol levels were <40 nmol/l in 78% of university students and 83% of veiled women.⁹⁹ Betel nut chewing, which is prevalent in Bangladesh, has been reported to contribute to hypovitaminosis D by modulating the enzymes regulating circulating 1,25-dihydroxycholecalciferol concentration.¹⁰⁰ Positive correlation has been found between vitamin D deficiency and reduced level of apoA1 in Bangladeshi people in UK independent of glycemia and other dietary, anthropometric, and lifestyle related risk factors for type 2 DM and IHD. ApoA1 deficiency may in turn lead to low level of HDL, thereby increasing the risk of CAD.¹⁰¹ An association between vitamin D receptor polymorphisms and insulin secretory capacity has been described among Bangladeshi Asians in UK.¹⁰² Further research is needed to find out the association, if any, between vitamin D deficiency and CAD in Bangladesh.

8.11. Chronic arsenicosis

Arsenic contamination of groundwater in Bangladesh has been recognized as a massive public health hazard.^{103–105} An estimated 57 million people have been chronically exposed to groundwater with arsenic concentrations exceeding the WHO standard¹⁰⁶ and 85 million people at risk from arsenic in drinking water and in food crops.¹⁰⁷ Arsenic in irrigation water has been found to accumulate in soils, from where it is taken up by crops, thereby entering the food chain and contaminating crops, vegetables and fish.^{108,109} Although maximum uptake has been observed in some leafy vegetables and spices, arsenic uptake in rice constitutes the greatest source of exposure to the population from food.¹⁰⁹ Chronic arsenic exposure may facilitate systemic inflammation and vascular endothelial dysfunction, which may, in turn, increase the risk of CVD. The Health Effects of Arsenic Longitudinal Study in Bangladesh (2007–2008) has reported positive association between arsenic exposure from drinking water and plasma levels of markers of systemic inflammation and endothelial dysfunction.¹¹⁰ Previous studies in Bangladesh have found positive association between inorganic arsenic exposure from drinking water and risk of hypertension.^{111,112} Chronic arsenic exposure (>500 µg/L) in drinking water has been related to increased risks of CAD,^{113,114} and carotid atherosclerosis.¹¹⁵ Recently, a large prospective cohort study¹¹⁶ involving 11746 participants and 6.6 years of average follow up in Bangladesh has found positive association between long-term arsenic ingestion and increased cardiovascular mortality. The association was even worse among smokers. Further basic, as well as, clinical research is needed to better define the role of arsenicosis in the etiopathogenesis of CAD in Bangladeshi population.

8.12. Poor dental hygiene

Poor dental hygiene has been suggested to be associated with coronary atherosclerosis. Observational studies are in favor of this association though they do not support a causative relationship.¹¹⁷ On the other hand, periodontal interventions result in a reduction in systemic inflammation and endothelial dysfunction in short-term studies, but at present, there is no evidence that they prevent CAD or modify its outcomes.¹¹⁷ Despite lack of adequate data, poor dental hygiene is common¹¹⁸ and periodontitis seems to be prevalent in Bangladesh, especially in the adults and the economically weak population.¹¹⁹ The prevalence in Bangladesh has been found 18.5–42%.^{118,120,121} So, poor dental hygiene may play a significant role in the etiopathogenesis of CAD in this population. Further research is needed to find out the degree of association between these two public health problems.

8.13. Air pollution

In the recent years, air pollution has been suggested to contribute to cardiovascular illness. The overall evidence is consistent with a causal relationship between exposure to particulate matter <2.5 µm in diameter (PM_{2.5}) and cardiovascular morbidity and mortality.¹²² Air pollution is a significant problem, especially in the urban areas of Bangladesh. A study to evaluate the emissions and air quality in megacities found Dhaka to have the poorest air quality in respect of total suspended particles (TSP), sulfur dioxide (SO₂), and nitrogen dioxide (NO₂) among the megacities, and the pollutant levels were far beyond the WHO standard.¹²³ Air pollution in rural areas is less known. Indoor air pollution from the combustion of traditional biomass fuels is a significant public health problem predominantly for poor populations in many developing countries, including Bangladesh. 80% households in Bangladesh use biomass fuel such as wood, cow dung, dry leaves, crop residue, etc. Chronic exposure to the particulate matter in indoor air from combustion of traditional biomass fuels may be a contributor to the CAD in rural women who have the responsibility of cooking. A recently-published retrospective cohort study in a low-income rural area of Bangladesh demonstrated significantly increased respiratory and non-significantly increased cardiovascular mortality in association with household solid-fuel use.¹²⁴ Intensive research is needed to elucidate the role of air pollution in the aetiopathogenesis of CAD in Bangladeshi population.

8.14. Psychosocial factors

Psychosocial factors have repeatedly been shown to influence CHD risk in European white populations.¹²⁵ Factors such as depression¹²⁶ and chronic work stress¹²⁷ are independently associated with increased risk of heart disease, whereas social networks and support appear to be protective.¹²⁸ The association between psychological stress and atherosclerosis appears to be mediated mainly by altered immune reactions due to either activation or depression of the hypothalamic-pituitary-adrenal (HPA) regulatory feed-back mechanisms that influence both the vascular endothelium function and the recruitment of circulating monocytes and their conversion

to foam cells.¹²⁹ Mental illnesses are important but under-recognized public health problems in Bangladesh; awareness about mental illness and acceptance of treatment are very low due to social stigma and superstition.¹³⁰ Nation-wide survey on mental health in Bangladesh in 2003–2005 found the prevalence of mental disorders 16.05% in adult population.¹³¹ In other studies, the prevalence of mental disorders was 28% in urban areas¹³² and 16.5% in rural areas.¹³³ Prevalence of depression is 4.5%.¹³¹ No definite studies have been carried out in Bangladesh to find out the significance of psychosocial stress in the context of increased vulnerability to CAD in this population. However, in a study in UK,¹³⁴ South Asian men and women experienced greater chronic stress, in the form of financial strain, residential crowding, family conflict, social deprivation and discrimination, than the Europeans. They had larger social networks, but lower social support and greater depression and hostility. So, significant psychosocial adversity experienced by the South Asians compared with the Europeans was consistent with the heightened vulnerability to CAD observed in this population.

8.15. Hyperuricemia

Increased uric acid level in plasma has been considered as a risk factor for CAD. Studies relating to this issue are inadequate in Bangladesh. One study found hyperuricemia (>6 mg/dl) in 68.5% of CAD, however, no control subjects were included in this observational study.¹³⁵ Significant positive association was reported between serum uric acid level and the presence and severity of CAD in another study.¹³⁶

8.16. Food adulteration

Food adulteration is an important public health problem in Bangladesh.¹³⁷ Calcium carbide is widely used to artificially ripen fruits; calcium carbide is extremely hazardous because of contamination by traces of arsenic and phosphorus.¹³⁸ The chronic effect of such events is unlikely to be observed in short term, because the manifestation of the disease only occurs after long-term, low-level exposure. Research is needed to find out relationship, if any, between increased prevalence of CAD and food adulteration in this population.

9. Present status of cardiovascular care facilities

First integrated cardiovascular care started in this country with the formal establishment of National Institute of Cardiovascular Diseases (NICVD) in 3rd April 1981. In this institute, for the first time, percutaneous transluminal coronary angioplasty (PTCA) was done by foreign experts in 1987 and by Bangladeshi team in 1995, coronary stenting in 1997.^{139–141} First CABG was done in NICVD in 1985. Since then, cardiovascular care facilities have increased steadily, and at present, a good number of institutions in public, as well as, in private sector are rendering cardiovascular care throughout the country, though they are more concentrated in the capital city. Almost all sorts of coronary interventions and bypass surgery are being done at a relatively low cost. In the recent

years, primary percutaneous coronary intervention (PCI) is being performed in Government,¹⁴² as well as, in private¹⁴³ centers. Facilities for post-graduation in cardiology have increased in recent years. Research works are being done regularly as a prerequisite for post-graduate courses, and also independent of this.

Bangladesh is double-burdened with communicable and non-communicable diseases. In the context of socioeconomic transition, the communicable diseases are coming under control, whereas the non-communicable diseases and their risk factors are rising. The Health, Nutrition and Population Sector Programme (HNPS) is now in operation that responds to the increasing need for prevention and management of NCDs. Government has formulated National Non-communicable Disease Strategy and plan of action.

10. Ongoing research

The Bangladesh Risk of Acute Vascular Events (BRAVE) study,² is going on to find out the risk factors, conventional and unconventional, to explain the undue predisposition of the people of Bangladesh to CAD and to build the first epidemiological resource in Bangladesh. The study is the joint collaboration of Cambridge University of UK, International Centre for Diarrhoeal Disease Research, Bangladesh (ICDDR) and NICVD in Dhaka, Bangladesh. The initial results of BRAVE study have identified several environmental contaminants (e.g. arsenic in the blood) and nutritional elements (e.g. zinc deficiency) as important drivers for heart attacks in this population. An ongoing study at BIRDEM using the VerifyNow P2Y12 assay has found clopidogrel resistance in 46.7%, and prasugrel resistance in 7% of non ST-elevation acute coronary syndrome (ACS) patients undergoing PCI.¹⁴⁴ Such highly prevalent clopidogrel resistance may be related to the recurrence of ACS and occurrence of stent thrombosis and in-stent restenosis after PCI in this population.

11. Future directions

Data related to different aspects of CAD in Bangladesh are inadequate. Large, preferably, nation-wide epidemiological and clinical studies should be carried out to gain reliable information on this important public health issue.

Cardiovascular disease prevention should be integrated with primary health care.

Cardiovascular health promotion should be part of the national media strategy and the health education curriculum. The public health approach should target population-wide lifestyle intervention, screening for high blood pressure, DM and dyslipidemia. Healthy life styles including consumption of heart-healthy diets, avoidance to smoking and smokeless tobacco, moderation of salt intake and increased physical activity, should be promoted. Limitations can be placed on the concentrations of salt, sugar, trans-fats and saturated fats in manufactured food products. Food labeling should also be introduced to facilitate informed choice by consumers. Food adulteration should be dealt with rigorously. Provision of safe,

arsenic-free water and food should be ensured. Necessary legislative and administrative steps should be taken to reduce air pollution. Policy change should address urban planning, transport and preservation of environment. Special attention should be given to stop malnutrition and under-nutrition in fetal and neonatal life through nutrition programs. Public awareness should be created to avoid childhood obesity. If indicated by further research, vitamin D deficiency should be avoided by fortification of food. Intensive research, may be in collaboration with international organizations, should be undertaken to explore the still-undiscovered risk factors unique to this nation, which are responsible for the high prevalence of CAD in Bangladesh.

12. Conclusion

CAD is highly prevalent in Bangladesh. At the advent of the new millennium, we are really unclear about the real situation. Along with the classical risk factors, genetic make-up and environmental factors unique to our population may exist. We have no more time to lose. Large-scale, preferably, nation-wide survey and clinical research should be conducted to determine the different aspects of CAD in Bangladesh. The information available thereby, would help to formulate national policy to combat the deadly epidemic more efficiently in future.

Conflicts of interest

All authors have none to declare.

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