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Review Article

RISK FACTORS OF CARDIOVASCULAR DISEASE (CVD) - A CRITICAL SCIENTIFIC REVIEW

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ABSTRACT

Cardiovascular Diseases (CVDs) are taking the biggest toll on human health since the last few decades. Around the middle of the 20th century, morbidity and mortality due to CVDs began to increase exponentially due to drastic change in lifestyle and rapid urbanization. At that point of time a very little was known about its causes or risk factors. Identification of risk factors is crucial in planning the treatment and prevention strategies for any disease. Profound research works have been conducted worldwide to identify risk factors of CVDs. Conventional risk factors like obesity, smoking, hypertension, diabetes, dyslipidemia, physical inactivity etc are already given due importance in risk prediction, prevention and management of CVDs. The risk assessment tools available at present are mainly based on these conventional risk factors. Even after adjusting the conventional risk factors, CVD related morbidity and mortality are still growing. Moreover CVDs are now reported at an early age. Hence there is also a need to identify novel risk factors which can be helpful in predicting and identifying CVDs earlier. The future of CVD risk assessment is an integration of both traditional as well as emerging risk factors for better prediction, diagnosis and planning therapeutic and preventive interventions of CVDs.

INTRODUCTION

With rapidly changing lifestyle over past few decades, many non-communicable diseases (NCDs) have emerged as global challenge. Cardiovascular diseases (CVDs) take a lion's share in all NCDs and they are the number one cause of death globally. As per the recent reports of WHO, 17.9 million people die each year from CVDs which is 31% of all deaths worldwide. 85% of all CVD deaths are due to heart attacks and strokes. More than 75% deaths occur in middle income countries like India[1]. CVDs include a basket of diseases out of which 10 diseases have been identified as most common cause of CVD related death. These are ischemic heart disease (IHD), Stroke (ischemic, haemorrhagic and other stroke), atrial fibrillation, peripheral arterial disease (PAD), aortic aneurysm, cardiomyopathy and myocarditis, hypertensive heart disease, endocarditis, rheumatic heart disease (RHD), and a category for other CVD conditions[2].

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Keeping in view these important causes, risk factors have been identified by various researchers accordingly. The concept of "risk factors" in coronary heart disease (CHD) was first given by the Framingham heart study (FHS), way back in 1957. In past few decades the field of cardiology has made milestone progress in terms of risk assessment, diagnosis, prevention and treatment of CVDs. Various validated CVD risk assessment tools have been designed for use of clinicians. The Seven Countries Study (SCS) is the first major study to investigate diet and lifestyle along with other risk factors for cardiovascular disease[3]. The Framingham Heart Study (FHS) has also made significant contribution in identifying various risk factors of CVDs[4]. Many other cumulative researches have been done to list out potential risk factors of CVDs. The risk factors have been categorised into two parts. Modifiable risk factors are those where an intervention is possible to modify the risk and non-modifiable risk factors where such an option is not available. Obesity, smoking etc have been proved beyond doubt as risk factors for CVDs. Hence these are regarded as existing risk factors. New and

contemporary researches have also found some other risk factors like Coronary Artery Calcium score (CAC), Carotid Intima-Media Thickness (CIMT) etc which are regarded as emerging risk factors[5]. This review work will cover both existing and emerging risk factors in Indian scenario.

MATERIALS AND METHODS

Search Strategy

Electronic database like Google Scholar, PubMed, and Cochrane have been used for search work. These databases have been searched with key words "cardiovascular disease risk factors". Research papers relevant to Indian population and published in the last 20 years (2000-2019) were shortlisted and included in the review work. Abstracts, conference proceedings, reports of consultative committees and text books have also been referred and retrieved as required.

Review Strategy

Once short listing of the relevant research papers was finished, a comprehensive list of risk factors for CVDs was prepared from those papers. Then they were segregated in to two categories. The first category was existing or conventional risk factors containing 9 (nine) items and the second category was emerging risk factors containing 8 (eight) items. Each risk factor was analysed with special reference and applicability to Indian population.

Existing or Conventional Risk Factors

Conventional risk factors can be further divided into two categories i.e. modifiable and non-modifiable risk factors

Modifiable Risk Factors

Dyslipidemia

Dyslipidemia means abnormal amount of lipids (triglyceride & cholesterol) in the blood. A typical dyslipidemia will have low HDL, elevated LDL and/or elevated VLDL with or without elevated TG. Dyslipidemia, particularly an elevated LDL is strongly associated with increased CVDs. The land mark evidence regarding this was published in The Journal of the American Medical Association (JAMA), way back in 1984 as a result of The Lipid Research Clinics Coronary Primary Prevention Trial[6]. Since then the link of hyperlipidemia and CVD risk has gone through many controversies. It took decades for the scientific community as well as clinicians to reach a universal consensus on the matter. Researchers have proven this beyond doubt that dyslipidemia plays a crucial role in atherosclerosis. Several clinical trials have proved that effective management of dylipidemia can reduce CVD risk. Statins are the main stay of treatment of dyslipidemia. A very important study published in 2015 proved that Statin therapy was associated with a lower risk of all-cause mortality in patients with non-obstructive CAD documented by coronary computed tomography angiography (CCTA), regardless of combined clinical risk factors[7]. This study indirectly proved the strong association of dyslipidemia and CVD risk. Many land mark review work have been published after reviewing most of the important research works on the association between hyperlipidemia and CVD risk, have firmly concluded that there is a solid link between elevated cholesterol (especially LDL-Cholesterol) and CVD. The risk is modifiable and Statin therapy has become standard medical practice for management of dyslipidemia which in turn can reduce mortality in CVDs[8].

Obesity

Obesity has been accepted as a modifiable risk factor of CVDs.

However, there are controversies regarding the link of generalized obesity and CVD risk. But the link between central or abdominal obesity and increased CVD risk has been proved with solid evidence from multiple research findings[9,10]. Abdominal obesity has multiple pathophysiological effects on the human body. These are visceral adiposity, insulin resistance, dyslipidemia, increased inflammatory response, increased level of acute phase reactants like CRP, atherosclerosis, prothrombotic state etc which are potentially harmful for the cardiovascular system[11]. Adiponectin level becomes considerably lower in obesity which may result in impaired fibrinolysis and endothelial dysfunction which in turn increase CVD risk[12]. On the other hand many clinical trials have suggested that effective weight management can reduce CVD risk and mortality in CVDs[13]. Moreover the onset of CVDs in early age group in Indians and south Asians can be attributed to early onset of central obesity in these populations.

Tobacco Abuse

Smoking has long been identified as a modifiable or preventable risk factor for CVDs. Both smoking and second hand smoke exposure are equally responsible for causing CVDs [14,15]. Smoking alone is responsible for alarming 10% of all CVDs. 87% of the estimated 430,000 worldwide adult deaths caused by second hand smoke in 2004 were due to ischaemic heart disease[16]. But use of tobacco is multi dimensional. In countries like India and Bangladesh, smokeless tobacco is used more frequently in the form Gutkha, Paan masala etc rather than smoking. Initially it was believed that smoking of tobacco causes CVDs and smokeless tobacco is more attributable to cause cancer. But of late it was also proved that use of tobacco in any form whether smoke or smokeless is strongly associated with CVDs[17]. A meta-analysis estimated that smokeless tobacco users are at 1.13 times more risk of experiencing a fatal myocardial

infarction and 1.40 times more risk of experiencing a fatal stroke[18].

Tobacco and cigarette smoke contains approximately 4000 chemicals which are further processed and modified by human body. These chemicals adversely affect human organ system in multiple ways. In the cardiovascular system, the devastating effect of tobacco is multi-factorial. It results in dyslipidemia. It increases levels and oxidation of proatherogenic lipids and decreases level of HDL. Endothelial dysfunction, a pro-coagulatory state, and initiation of inflammatory cascade are some of the other important pathological consequence of smoking[19]. All together these factors contribute to CVD progression and fatal outcome.

Hypertension

Hypertension or high BP is one of the important and modifiable risk factors of CVDs. It is more commonly encountered in comparison to other modifiable risk factors like Diabetes, smoking, dyslipidemia, obesity etc. Hypertension negatively affects the cardiovascular system in multiple ways like Left ventricular hypertrophy (LVH), damaged and narrow arteries, compromised vascular elasticity, aneurysms, dilated cardiac chambers, enlarged size of the heart (cardiomegally), weakened cardiac muscles (cardiomyopathy) etc. All these can ultimately lead to cardiac failure.

Hypertension alone accounts for an estimated 54% of all strokes and 47% of all ischemic heart disease events globally[20]. Uncontrolled hypertension increases the risk for a variety of cardiovascular diseases like stroke, coronary artery disease (CAD), congestive cardiac failure (CCF), atrial fibrillation (AF), and peripheral vascular disease (PAD) [21,22]. Systolic blood pressure (SBP) is a better indicator of cardiac events than diastolic blood pressure (DBP) after the age of 50 years [23]. In the elderly population pulse pressure has an additional prognostic value apart from these two [24]. This is also proven that with an elevated systolic and a normal or low diastolic BP (isolated systolic hypertension) the risk of CVDs increase proportionately [25].

Diabetes mellitus

Diabetes is also an important risk factor for CVDs. The American Heart Association (AHA) considers diabetes to be one of the seven major modifiable risk factors for CVDs. It can affect almost all vital organs of the body if left uncontrolled and cardiovascular system is no exception. The global diabetes prevalence in 2019 is estimated to be 9.3% (463 million people worldwide). This is predicted to rise up to 10.2% (578 million people worldwide) by 2030 and 10.9% (700 million people worldwide) by 2045. Ironically almost 50 % (one in every two diabetes patients) don't even know that they have the disease [26]. This unawareness leaves their blood sugar uncontrolled further leading to complications including CVDs. Adults having diabetes are two to four times more likely to die from heart disease than adults without having diabetes. The statistics given by AHA is quite alarming in this regard which says at least 68 percent of people of age 65 or older with diabetes die from some form of heart disease and 16 percent die out of stroke [27].

Moreover the pathogenesis of Diabetes related CVD is complex and multi factorial which need profound understanding. Clinically up to 97% of patients with diabetes are dyslipidemic which is highly associated with atherosclerosis. The characteristic dyslipidemia (High LDL, Low HDL and high Triglyceride) and the peculiar small and dense LDL particle size are proved to be more atherogenic [28]. Diabetes damages both microvasculature & macrovasculature of the body. Insulin resistance is strongly associated with hypertension and weight gain leading to obesity [29]. Diabetes is a state of chronic inflammation which increases cardiovascular risk [30]. Diabetics are exposed to higher levels of oxidative stress which plays a crucial role in the pathogenesis od CVDs as a complication of diabetes [31]. Diabetes is also related to a hyper-coagulable state [32]. All these factors act synergistically to increase CVD risk in Diabetics.

Physical Inactivity

Physical activity is defined as any bodily movement produced by skeletal muscles that require energy expenditure [33]. With a rapid change in life style, working culture, leisure and recreational activities since last few decades, the level of physical activity has been significantly reduced. In general "exercise" and "physical activity" are being interchangeably used. But this is not right. Rather exercise is a planned, structured, repetitive, and purposeful activity for the improvement or maintenance of one or more components of physical fitness. Hence "physical activity" is a broad term which includes exercise as well as other activities which involve bodily movement and are done as part of playing, working, active transportation, house chores and recreational activities [33]. The benefits of regular and adequate physical activity have been proven beyond doubt. It includes energy balance, weight control, improved elevated BP, balanced lipid levels, improved endothelial function, enhanced cardio respiratory fitness, improved muscular endurance, improved insulin sensitivity, improved metabolic fitness and so on.

On the other hand physical inactivity is estimated to be the main cause for approximately 21-25% of breast and colon cancers, 27% of diabetes and approximately 30% of ischaemic heart disease burden [33].

The inverse relation between physical activity and incidence of CAD was proved by Morris et al in his "London transportation study" almost 70 years back. In this study conducted during 1950, on the drivers and conductors of double-decker buses of London, Morris and Crawford proved that the sedentary bus drivers with limited physical activity had almost double the incidence of CAD in comparison to their counterpart conductors who had to continuously move up and down for ticketing [34]. This study laid the foundation of the positive link between physical inactivity and CAD. Since then many published evidences further justified it.

Another study conducted on college alumni without history of CVD and 16 years follow up, proved that there was a 39% reduction in cardiovascular morbidity and a 24% reduction in cardiovascular mortality in subjects with exercise energy expenditures of more than 2,000 kcal per week [35].

A sedentary life style arising out of low physical activity is strongly and independently associated with significant increase in CVD risk. The exact patho-physiology how physical inactivity results in increased risk of CVD is not clearly understood. But most probably it may be due to the deprivation of the benefits, the body or cardiovascular system in particular, gets out of optimum physical activity which has been discussed earlier[36]. However the risk is modifiable with increase in physical activity and regular exercise.

Unhealthy Diet

The association of different dietary components and CVD risk is a very complex topic. Often an unhealthy diet is associated with unhealthy life style, physical inactivity, smoking and alcohol abuse. A clear differentiation of healthy and unhealthy diet is also is also very difficult task. So far food is considered the world population is very much diversified. There exists a lot of variation within and in between populations in dietary pattern, food quantity, eating habits, selection of food items like vegetarian, non-vegetarian, mixed etc. Food preparation, food processing, food packaging, food storage etc are also important in their healthy and unhealthy effects on the body. For example, a very healthy vegetable when cooked or processed in an unhealthy manner, no more remains healthy. Moreover any particular food or diet plan which is considered to be healthy for one population may not be exactly suitable for another population. Hence having a clear cut dietary guideline for CVD risk reduction is also a herculean task. However many components of food like transfats, refined sugar, low fibre content, very low or excessive dietary sodium, toxic additives in processed foods etc are linked to CVD as well risk of many other conditions like diabetes, dyslipidemia and obesity.

A population based case–control study, using biomarkers; revealed that dietary intake of total trans-fatty acids is associated with modest increase and trans isomers of linoleic acid with a larger increase in the risk of primary cardiac arrest [37].

A large prospective cohort study done in Denmark on the impact of replacing saturated fats with high-Glycaemic Index carbohydrates found that when high- Glycaemic Index carbohydrates replaced saturated fat, myocardial infarction (MI) risk increased by 33% [38]. A meta-analysis study published in 2012 found that increased Glycaemic Load is associated with a 27% increase in coronary heart disease (CHD) and myocardial infarction (MI) risk [39].

Dietary fibre is a type of complex carbohydrate containing polysaccharides and lignin that cannot be digested by human and other vertebrates. Intake of low fibre content diet is directly linked to dyslipidemia and hence increased CVD risk whereas adequate dietary fibre reduces the risk of CVD and diabetes [40].

Salt (NaCl) is the main source of dietary sodium. Excessive dietary sodium is directly associated with hypertension and CVDs. A state of the art review article published in 2014 proved that as compared With usual Sodium intake, both low- and excessive Sodium diets are associated with increased mortality [41]. Higher sodium intake (>5 grams/day) is directly associated with increased risk of CVD events in those patients with hypertension [42].

Non-modifiable Risk Factors

Age & Sex

These two are independent and non-modifiable risk factors. Almost every CVD risk assessment tool considers these two as fundamental factors for risk prediction. Apart from predicting the CVD risk on their own merit, these two factors also provide an insight to the intensity and duration of exposure to other risk factors.

According to a cohort study from Finland, consisting of 14 786 men and women within the baseline age 25 to 64 years, in both sexes, the risk of CHD increased markedly with age. Men are at higher risk of CVD as compared to women of their age. In this study it was found that CHD incidence among men was almost 3 fold and mortality rate was almost 5 fold greater than in women [43]. The role of other major risk factors in development of CVD was fairly similar in both the sexes.

Family History

In health sciences, a family history is a record of health information about a person and his or her close relatives. A complete family history includes information from three generations of relatives, including children, brothers and sisters, parents, aunts and uncles, nieces and nephews, grandparents, and

cousins[44]. In CVD risk assessment, family history plays an important role. There are multiple evidences that positive family history is closely linked to CVD risk.

In a Framingham offspring study with 2302 participants from both sexes having positive parental history of premature CVD were analyzed for CVD risk. After 8 years of follow up, CVD risk increased 75% with paternal and about 60% with maternal positive history of premature CVD [45].

In the same cohort, Murabito JM et al proved that CVD increased about 40% in those whose siblings had CVD [46].

The Cooper Centre Longitudinal Study, which included 49, 255 primarily white men from United States, with a follow up period of 16 years, proved that there is a 44% increased risk of CVD mortality if there is a positive family history of premature CAD [47].

EMERGING RISK FACTORS

These are relatively newer risk factors which have been identified in connection with CVD. In the last few years, more than 100 emerging risk factors have been discovered which can improve cardiovascular risk assessment[48]. However, it is beyond the scope of this paper to discuss each of them. Few most important emerging risk factors will be reviewed here.

Vitamin D

Vitamin D is a fat soluble vitamin. It is naturally present in very few food items. Most people partially fulfil their Vitamin D requirement from Sun exposure. People with limited and inadequate sun exposure can be deficient in Vitamin D.

A study published in the Journal of the American College of Cardiology in 2008 proved that deficiency of Vitamin D increases CVD risk [49]. In the Framingham Heart Study, the link of Vitamin D deficiency and CVD risk was further confirmed. Participants with low vitamin D levels (< 15 ng/mL) at the time of enrolment had twice higher risk of cardiovascular events than participants with higher levels of vitamin D [50].

Lipoprotein (a)

Lipoprotein (a) [Lp(a)] is a "low density lipoprotein variant" discovered around more than 50 years ago. It is similar to low-density lipoprotein (LDL), but contains an additional protein, apo(a). It has a high affinity for the arterial wall. It has atherogenic and thrombogenic properties. Its cut off plasma concentration limit is 30 mg/dl, above which it can put an individual on higher CVD risk. Multiple large clinical trials have proved that elevated levels of Lp(a) is an independent risk factor for developing CVD [51, 52, 53].

Carotid Intima-Media Thickness (CIMT)

The carotid intima-media thickness (CIMT) is an imaging modality used to diagnose the extent of carotid atherosclerotic vascular disease. This measures the thickness of the two inner layers of the carotid artery i.e the tunica intima and the tunica media. CIMT can be measured by ultrasound. Thickening of any arterial wall is a hallmark sign of atherosclerosis. In the past few years it has been found that there is strong association between CIMT and CVD risk. The Kuopio Ischemic Heart Disease Risk Factor Study (KIHD) done in eastern Finland showed 11% increased risk of myocardial infarction with each 0.1 mm incremental increase of CIMT[54]. A meta-analysis published in 2007 reported that there is strong association between CIMT and prediction of future cardiovascular events[55]. However, few other researchers are of opinion that there is no added advantage of CIMT over conventional risk factors. Hence a clear guideline is yet to be finalized.

Coronary Artery Calcium (CAC) Scoring

Coronary artery calcium (CAC) scoring is an imaging test, done through CT scan that measures the amount of calcium in the coronary arterial walls. It is also called coronary calcium scan. The results are expressed in terms of a score ranging from 0 to over 400. The presence of calcium in the walls of the coronary artery is an early sign of atherosclerosis. Thus CAC score can be a predictor of CVD risk and future cardiac events. In a cohort study it was found that there is a strong and graded association between CAC score and cardiac events like MI [56]. A meta-analysis in low risk women published during 2016 found that CAC score>0 was associated with an increased risk for atherosclerotic cardiovascular disease [57].

Homocysteine

Homocysteine is a common amino acid in the blood. It is a non-proteinogenic α-amino acid. An elevated level of serum homocysteine is called hyper-homocysteinemia which has been claimed to be a significant modifiable risk factor for the development of CVDs. Moderately elevated levels of plasma homocysteine are associated with subsequent risk of MI independent of other cardiovascular risk factors. Every 5 μmol/L rise in serum homocysteine levels conferred approximately 9% increase in the risk of cardiac events[58]. An Indian study involving 250 subjects from rural areas of Maharashtra also found a positive correlation between serum homocysteine levels and cardiovascular risk[59]. Another Indian study conducted at JNMCH, AMU, Aligarh, U.P found that elevated serum homocysteine is an independent risk factor for young MI patients [60].

C - Reactive Protein (CRP)

C-Reactive Protein (CRP) is an annular, pentameric protein produced by liver and found in blood plasma. It is classified as an acute phase reactant which means that its level rises in response to inflammation. Patho-physiologically, atherosclerotic plaque formation, plaque rupture and subsequent thrombosis involve inflammatory response. Hence an elevation in CRP is quite obvious. Research findings are suggestive of the fact that chronic elevations in CRP levels have biological effects on endothelial function, coagulation, fibrinolysis, oxidation of LDL, and atherosclerotic plaque stability [61]. High sensitive CRP (hs - CRP) is a new and emerging predictor of CVD risk. Evidence suggest that there is a strong and independent association between elevated hs-CRP and incidental cardiac events. According to the CDC and AHA guidelines, low risk for cardiovascular disease is defined as hs-CRP <1 mg/L, average risk as 1 to 3 mg/L, and high risk as >3 mg/L [62]. An hs-CRP level >10 mg/L has been found in acute plaque rupture, which may lead to thrombosis [63]. Moreover, an elevated hs-CRP is not only predictive of cardiac events but also have some prognostic importance as well.

Ankle Brachial Index (ABI)

The Ankle Brachial Index (ABI) is a ratio of systolic blood pressure at the ankle to that of the systolic blood pressure at the arm. A low ankle-brachial index number can indicate narrowing or blockage of the arteries in the legs. ABI is an easy, non-invasive and sensitive method to diagnose peripheral Arterial Disease (PAD) and generalized atherosclerosis. Apart from these, ABI has also been found to be useful in improved CVD risk prediction independent of traditional risk factors [64]. A study published in 1995 by L. H. Kuller et al found an association between ABI and subclinical atherosclerosis. The authors reported that an ABI score≤0.90 was an indicator of subclinical atherosclerosis and led to an increased incidence of MI, stroke and cardiovascular mortality [65]. In another study published in 2008, it was found that sensitivity of low ABI in screening for CAD was 82.61%, while the specificity was 77.27% [66].

Myeloperoxidase (MPO)

Myeloperoxidase (MPO) is a heme-containing peroxidise enzyme, mainly released by activated neutrophils. MPO is having potent pro-oxidative and pro-inflammatory properties. In the last two decades MPO has emerged as a new biomarker of inflammation in ischemic Heart Disease and acute coronary syndrome (ACS). MPO plays an important role in initiation, propagation, and acute complication phases of the atherosclerotic process [67]. Elevated level of MPO is strongly associated with presence and severity of coronary artery disease (CAD) [68]. Measurement of plasma MPO can independently predict the early risk of myocardial infarction, as well as the risk of major adverse cardiac events in patients presenting with chest pain [69].

CONCLUSION

It is a fact that CVDs are the leading cause of morbidity and mortality worldwide. Proper identification of various risk factors plays a key role in planning treatment and preventive protocols. Most of the presently available CVD risk assessment tools are based on traditional risk factors. The emerging risk factors find a few places in these tools. The future need is to develop comprehensive CVD risk assessment tools which include both traditional and emerging risk factors with appropriate weightage.

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