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Review Article

RISK DETERMINANTS THAT ESCALATE CARDIO VASCULAR DISORDERS

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ABSTRACT: Notwithstanding credible advances in cardiovascular health progress contributed by scientific studies during the preceding few decades, cardiovascular disease (CVD) relics a large number of deaths in developing as well as developed countries. Out of total of 161 articles screened. 87 articles were excluded based on the preliminary scrutiny of abstract and titles and the study was restricted to remaining 74 articles to capture the most relevant literature. **T**he risk factors of cardio vascular diseases have been recognized as modifiable and non-modifiable risk factors. Modifiable cardio- vascular risk factors involve tobacco usage, hypertension, elevated blood glucose, dyslipidemia, overweight, environmental tobacco smoke (ETS), unhealthy diet, alcohol intake, lack of physical activity. The non modifiable cardio vascular risks are age, sex, family history and racial locale. A public awareness of risk factors contributing cardio vascular disorders is imperative for health of individuals and suggested to investigate time and again during life. Risk factors identified in this research are sufficient markers of changes in heart health during aging process. In future, risk factors of cardio vascular diseases should be included in secondary classes' syllabi for the early awareness and prevention of cardiovascular diseases in new generation. Public awareness should be enhanced through print and electronic media. Annual, work place surveys are required to be conducted for early identification of cardio vascular disorders in workers of government and private institutions/sectors, an effort that should be done on the part of employers to retain healthy and high quality employees.

Key words: Cardio vascular disorders, modifiable risk factors, Non-modifiable risk factors, Heart diseases

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INTRODUCTION

Cardio vascular diseases are in fact a set of diseases distressing the cardiovascular system. These take account of: angina; myocardial infarction, congenital heart failure; coronary heart disease; arterial disease; rheumatic heart disease, peripheral aortic aneurysm and deep vein thrombosis as well as rare cardiovascular diseases (WHO, 2021)..

The term angina derived from the Latin word "pain/infection in the throat" even as pectoris derived from the Latin term "pectus" meaning chest, though Osler in 1897 described, "true angina is a rare disease" (Jay, 2000). It's an established fact for the past many centuries that angina pectoris is an extensive state of degenerative health with significant mortality and morbidity.

Myocardial infarction (MI) generally known as heart attack, is the necrosis of cardiac muscles secondary to protracted deprivation of oxygen delivery (ischemia). The early diagnosis of acute myocardial infarction (AMI) is extremely imperative in the emergency departments or set ups (Milosevic *et al.,* 2016). Poor management of cardio vascular diseases may drive to long lasting disability due to complicated states of heart failure, heart attacks, brain strokes, and terminal-stage renal disorder (Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, 1997).

Congenital heart disease (CHD) can be depicted in terms of a variety of abnormalities in heart structure and function associated with anomalous or chaotic heart development before the delivery of fetus. A number of congenital heart diseases may be managed with medicine only, although others involve surgeries. Progress in Congenital heart surgery and adoption of other interventional strategies has helped substantially in reducing the mortality rate (Su *et al.,* 2022).

Coronary artery disease (CAD) is the state of building atheromatous plaques (Chronic inflammatory accumulations of macrophages,smooth muscle cells and lymphocytes) in the interior of arterial walls that provide oxygen and blood to myocardium (heart muscles). In spite of the fact that signs and symptoms of coronary heart disease are identified at advanced disease state, the majority of persons suffering coronary heart disease presented no sign of illness for years and years since illness progresses ahead of the first appearance of symptoms, a "sudden" heart attack, arise. Long after the disease development, number of formed atheromatous plaques may possibly split and (associated with beginning of the system of blood clotting) and induce

restrictive flow of blood to heart muscles. The Coronary heart disease is considered to be a major factor of sudden death.

In peripheral arterial disease, vessels of blood (arteries) which provide blood to lower extremities may get reduced in diameter interiorly or entirely get blocked by deposition of some sorts of substances. The peripheral arterial disease is due to deposition of fatty substances inside arterial walls (atherosclerosis). The reduction of blood vessels lumen generally happens in higher parts of legs. The presence of atheroma may be responsible for thrombus formation that blocks arteries completely. The Individuals suffering from peripheral arterial disease may experience narrowing of blood vessels in other areas of body also. The narrowed blood vessels which provide less amount of blood to muscles of heart may induce angina pectoris and myocardial infarction as blood supply disturbed in blood vessels which supply blood to neck region causing restricted or no supply to the brain area result brain stroke (Thom *et al*., 2006).

Rheumatic heart disease is a state in which streptococcal bacterial infection damage the valves of heart while rheumatic fever causes the inflammation of connective tissues particularly skin, brain joints and heart regions. Rheumatic fever can affect individuals of any age but children of 5 to 15 years old are more vulnerable to this disease. Rheumatic fever is an inflammatory disease that can affect many of the body's connective tissues especially those of the heart, joints, brain or skin. The rheumatic heart disease can affect patients for entire life. An aortic aneurysm is characterized by balloon shaped swelling in aorta (blood vessel), when it breaks result in large amount of internal bleeding (Cleveland clinic, 2022).

A deep vein thrombosis (DVT) is a blood clot (thrombus) which develops in deep veins, typically in lower legs. Deep vein thrombosis causes pain in the lower extremities leading to other complications. A deep vein thrombosis is though typically formed in deep veins of the legs, however it may arise in other parts of body as well i.e. the upper entireties. The deep vein thrombosis is unlike blood clots which formed in superficial veins underneath the skin. This type clots are known as superficial thrombophlebiti that are not much severe. This is rare for deep vein thrombosis to cause any additional complications but possible disorders include post-thrombotic syndrome and Pulmonary Embolism. Pulmonary Embolism occurs when a clot of the blood splits,enters the blood stream and get stuck in lungs resulting in discontinuation of blood flow. It may last from hours to days after clot development in calf vein; this may result in chest pain along with dyspnea. The Post thrombotic syndrome happens when deep vein thrombosis damages valve in veins, consequently the blood pools in lower legs instead of flowing upward. Pain, swelling and ulcers on lower extremities are among the reported consequences.

Additionally cardiovascular diseases may comprise of tumors of heart, disease of heart valves, heart muscle disorders (cardiomyopathy), disorders of the heart lining, and vascular tumors of brain.

RISK FACTORS OF CARDIO VASCULAR DISEASES: The under developed and developing countries major death toll occurs because of cardio vascular diseases, as individuals of these countries are more prone to cardio vascular disease risk factors such as lack of awareness, tobacco usage, obesity and less access to quality health care facilities. At the advent of last decade of 20th century, experts became attentive to the cardio vascular disease risks factors, as sedentary life style, tobacco usage, dyslipidemia, hypertension, diabetes, and factors regarding diet, resulted in premature deaths, the cardio vascular diseases being the major underlying cause (Capewell *et al*., 2010).

CLASSIFICATION OF RISK FACTORS: Precisely, the risk factors of cardio vascular diseases are categorized as modifiable risk factors and non modifiable risk factors. Tobacco usage, hypertension, obesity, elevated blood glucose, dyslipidemia, overweight, environmental tobacco smokes (ETS), unhealthy diet, alcohol intake, lack of physical activity are among the modifiable risk factors. The non modifiable risks encompass age, sex, familial history and racial background.

A) *MODIFIABLE CARDIO VASCULAR DISEASES RISK FACTORS*:

Tobacco usage: Tobacco usage elevates the risk of development of cardio vascular diseases about 2 to 4 times more. Smoking is among potent risk factors which causes sudden cardiac arrest in peoples with coronary heart disorder because smokers are two times more vulnerable than non smokers for cardio vascular diseases (Banks *et al.,* 2019). Passive smoking augnments the danger of heart disease among non smokers. The British Heart Foundation alarmed that passive smoking can raise chance of coronary heart diseases and stroke (BHF, 2021). Cigarette smoke interacting with other risk factors significantly enhances coronary heart disease possibility. The major risk is an increased affinity for thrombosis observed in population associated with smoking, that may lead to myocardial infarction (Smith *et al.,*2000). Moreover smoking increase heart rate, blood pressure, atherosclerosis and coronary blood flow. The smoking produces and elevates level of carbon monoxide in body The binding affinity of carbon monoxide with hemoglobin is more than oxygen, Carbaminohemoglobin generated suppresses the affinity for oxygen (Patel *et al.*, 2022). The number of cigarettes smokers in year 2000 has been estimated to be about 5,500 billion individuals. According to one of the reports published, approximately

one billion males and two fifty million females are daily tobacco users (WHO, 2002).

High blood pressure: High blood pressure is inextricably linked to cardiac disorders. Hypertension makes heart to work harder as it stiffens and thickens and finds substantial difficulty to force blood which induces heart attacks. The consequence of high blood pressure on cardio vascular system actually is designated to stress created on vasculature walls, causing aneurisms and brain stroke. Diabetes mellitus and hypertension are considered additive risk escalating factors for CVD (Martín-Timón *et al.*, 2014).

Obesity: The obesity is the deposition of surplus fat in the region of waist, which enhances the probability of developing coronary heart disease. Over weight worsens various risk factors, thus aggravating their effects like tension on heart, elevated blood pressure, blood cholesterol levels, triglyceride and lower level of HDL cholesterol. These factors may enhance the atherosclerosis risk and thrombolytic embolism. Additionally the rising overweight tendency enhances the chances of suffering from type II diabetes that is the cause of silent heart attack (myocardial infarction)

Elevated blood glucose: Diabetes is a metabolic disorder that influences a person's capacity to maintain blood glucose level at normal range. The diabetes associated disorders are divided as diabetes Type I and II, where Type I is close to total reliance on exogenous insulin as body is incapable of producing any insulin. Coronary cardiac illness, cardio-pathy, peripheral artery disease as well as cerebro-vascular disorders, nephropathy, neuropathy and retinopathy are reported to be the consequences of chronic metabolic disorders (Ansari *et al.*, 2021). Susceptibility to micro vascular complications, mainly nephropathy, retinopathy and neuropathy, specific to diabetes and to nonspecific macro vascular disease (coronary artery disease (CAD) and peripheral vascular disease, increases in Type I diabetes. The Type II diabetes characterized by the insulin resistance or insulin deficiency, is widespread diabetic disease; it is mainly attributed to the obesity or sedentary life style and common among middle age persons. The Type I and Type II diabetes cause risk of cardio vascular diseases through elevated levels of cholesterol; high blood pressure and atherosclerosis (Leon and Maddox, 2015). A combined constellation of metabolic risk factors with hyperglycemia impart a high risk of CVD in diabetic patients.

Dyslipidemia: Dyslipidemia is characterized by abnormal level of triglycerides, cholesterol and fat phospholipids in cardio vascular system. In developing and developed countries, dyslipidemias is hyperlipidemias which are characterized by the elevated level of lipids in blood. Dyslipidemia is known to endorse atherosclerosis, which is a complex disease and is a main hazard for undesirable cardiovascular events like myocardial infarction as well as peripheral artery disease (Farooqui, 2021). Elevated levels of LDL and HDL are linked with myocardial infarction (MI) and stroke. The LDL cholesterol increases the chances of cardio vascular diseases by formation of fat deposits in blood vascular system, developing atherosclerosis (Ference *et al.*, 2017). Studies have recommended that low density lipo-protein cholesterol (LDL-C) impart the pathogenic role in atherosclerosis (Jin *et al.*, 2022). It is also proven that even if the modifiable risk factors are taken care of, the non-modifiable risk factors like genetics, age can still lead to the development of atherosclerosis because of dyslipidemia.

Socio-economic risks: Cardio vascular diseases are linked with low socio-economic status. Various risk variables involving behavioral, biologic and psycho-social factors are considered as determinants of link between SES and CVD (Schulz *et al.*, 2018). Non-fatal myocardial infarction risk and sudden cardiac deaths are related to smoking and alcohol consumption (Mähönen *et al.*, 2004; Mostfsky *et al.*, 2015). The Low-income underprivileged individuals that lack access to healthy, inexpensive foods are called food deserts. The low socioeconomic status (SES) is found to be linked to diet-related chronic disorders and obesity. Educational attainment may have an effect on health in numerous ways. Less education may confer high cardiovascular disease risk. Probable predictor of cardio vascular disease risk is the substantial association among literacy and health education. (Cajita *et al.*,2016).Population with low health literacy are further found to be less adherent with the regular use of medications (Saqlain *et al.*, 2019) and less knowledge amplify all mortality causes (Bostock and Steptoe, 2012). Neighborhood individuality may change with time and endow with additional insight into the association between environmental factors and cardiovascular health. Increasing the density of neighborhood healthy food resources was reported to be associated with lower coronary artery calcium over the time (Wing *et al.*, 2016). Moderate increase in Cardiovascular disease (CVD) or stroke risk is found to be associated with stress due to work (Kivimäki and Kawachi, 2015); many people spend their 1/3 of life time on work place and work stress accumulated throughout life distressing cardiac as well as mental health lead to increasing mortality rate. Two case-control studies conducted on multiple developing countries clearly reported that besides the most commonly described the CVD risk factors, psychosocial stress, involving work stress, was significantly attributed to myocardial infarction and stroke across all genders age groups (Li *et al.*, 2016).

Environmental tobacco smoke (ETS): Environmental tobacco smoke left from burning end of cigarette in between puffs is denoted as side stream smoke (SS) whereas mainstream smoke (MS) is the term used for the smoke inhaled by the smoker. Environmental tobacco smoke is composed of 85% SS and 15% MS. Toxic substance for example volatile ammonia, amines, nicotine, nitrosamines, substances, and cyclic amines are present in high proportion in concentrated side stream smoke when compared to concentrated mainstream smoke. Environmental tobacco smoke comprised of aerosol chemical substances are found in the form of hydrophobic or hydrophilic vapors (DiGiacomo *et al*., 2019). The hydrophilic vapors contain environmental tobacco smoke, which gets effortlessly engrossed in upper portion of respiratory tract; however hydrophobic components are easy to enter into the lung. The particles with the size slighter than 2.5 µm are called respirable suspended particles (RSPs) as defined by US National Research Council Committee on passive smoking, may be inhaled in parenchyma of lungs. The concentration of environmental tobacco smoke particles range depends on degree of air dilution of side stream smoke particles and may range from 300 to 500 mg/m^3. The biological markers for the purpose of assessing the exposure of environmental tobacco smoke are identified as nicotine and cotinine (Benowitz,1999). Environmental tobacco smoke exposure develops athero-thrombosis by means of platelet adhesion inflammation, endothelial dysfunction and plaque instability (Srikanth *et al.,* 2016). The toxic primary components of environmental tobacco smoke (side stream smoke) are conscientious for major morbidity and mortality due cardiovascular diseases generation to generation causing pro atherogenic milieu. The endothelium, various molecules and blood cells play significant role in coagulation occurring comparative hypercoagulable condition (Di- Giacomo *et al*., 2019).

Quality of Food: Most essential risk factors frequently reported is diet, with poor nutrition effecting directly and rising concentration of lipids in body (risk of obesity and elevated level of cholesterol), raising risk of suffering type II diabetes and raising level of minerals in blood may lead to hypertension and risk of stroke (Anand *et al*., 2015).

Alcohol intake: Alcohol consumption is also an established risk factor. Less alcohol intake may reduce risk of cardio vascular diseases as antioxidant polyphenols inhibit the oxidation of LDL on the other hand high intake of alcohol induces chances of coronary heart disease and brain stroke due to elevation of blood pressure (GBD, 2018).

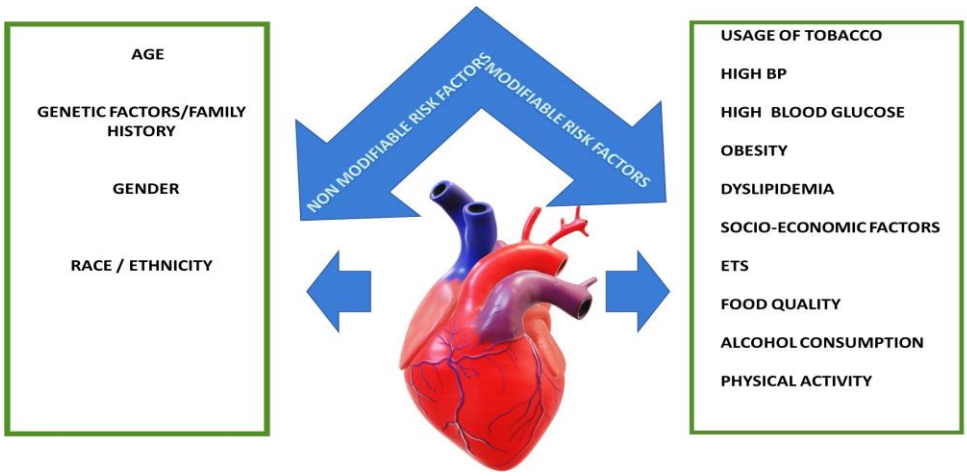
Physical activity: Physical activity is consistently associated with the reduction of cardio vascular disorders as it lower the level of cholesterol, obesity and may strengthen heart muscles to pump blood throughout the body efficiently (Gerovasili *et al.,* 2015).

B) *NON-MODIFIABLE CARDIO VASCULAR DISEASE RISK FACTORS:*

Gender and Age: Sexual categorization in transcriptome may occur due to the Y-encoded genes expression and responsible for male specific cardiovascular phenotypes. It is observed that gene variants for hypertension are present on Y chromosome which accentuates risk of cardiovascular disorder in males in comparison to females. Additionally, it is reported that a genes on Y chromosome may possibly affect LDL level, without involving testosterone level (Charchar *et al.,* 2004). Particularly, it was concluded that coronary artery disease in males was associated with genes on Y chromosomes (Charchar *et al.,* 2012). In this way genes on Y chromosomes participate in the development of cardiovascular phenotypes in males (Bloomer *et al.,* 2014). Proteomic analysis has led to the exploration of sex differences regarding cardiovascular diseases. Using this approach, investigation has been carried out on extracellular matrix proteins'(ECM) samples of left ventricle of people with no cardiovascular disease, to determine sex-specific and age-dependent risk components. Findings showed that therapeutic strategies targeting ECM hemostasis could be a feasible preventive option for age mediated heart problem (Dworatzek *et al.,* 2016). In general, levels of specific proteins in young people were fewer in females than males, while in aged peoples these proteins were high in females than males.

An understanding of such processes in intracellular signaling, gene transcription, function of organelles and integrated cross talk is making known novel targets for inhibition or activation of specific aspects of cardiovascular system which are associated to differences among men and women as well as sex hormones (Regitz-Zagrosek and Kararigas, 2017). The functional alterations occurring in aging adult's hearts have been identified, that comprise systolic and diastolic dysfunction including electrical dysfunction, together with development of arrhythmias (Steenman and Lande, 2017). Metalloproteinase (MMP) and tissue inhibitor of metalloproteinase (TIMP) expression levels dysregulation in matrix are commonly attributed to high collagen deposition and the cardiac hypertrophy and fibrosis development in old age hearts (Meschiari *et al.*, 2017). Hypertrophy and Fibrosis are together noteworthy structural changes which lead to final cardiac dysfunction in old age patients(Martos *et al*., 2007). Oxidative stress, including the production of surplus ROS (reactive oxygen species) that occurs with cardiac aging, may lead to mitochondrial dysfunction. Cardiac aerobic metabolism is significantly dependent on ATP production by mitochondria; therefore, the retardation of mitochondrial function plays a key role in the development of cardiac

dysfunction among old adults (Martin-Fernandez and Gredilla, 2016). Age is linked to amplified oxidative stress that may leads to an increased vulnerability for functional aberrations that lead to cardio vascular diseases. These disorders comprise heart failure (HF), and atrial fibrillation (AF) that are a consequence of increased reactive oxygen species (ROS) because of oxidative stress and amplify production of inflammatory signal molecules (Nakou *et al.*, 2016). Age is also linked with an increased vulnerability for diabetes, obesity and frailty. These factors are also considered as independent risk factors for cardio vascular diseases. Numerous risk factors result in a high incidence of cardio vascular diseases in old people (Xie, *et al.*, 2015). Estrogen is frequently documented for its cardio protective role and is observed to be directly linked with on the whole lower incidence of cardio vascular diseases in premenopausal females, as compared with same aged males (Villa *et al.*, 2015; Iorga *et al.*, 2017). Estrogen was reported to impart a cardio protective effect in males as well (Cooke *et al.*, 2017). Men have probability to develop cardio vascular diseases 10-15 years earlier than women due to the gradual decrease in estrogen values after puberty. Conversely, males with 70 years old have lesser cardiovascular risk as compared to women of 50 years old, that is an average age of menopause in women (Lloyd-Jones *et al.*, 2006). This is indicative and a powerful sign that less production of estrogen has a greater impact on cardio vascular diseases risks in female than in males. Overall there is an amplified risk for cardio vascular diseases in females at menopausal stage due to elevated LDL hypertension, cholesterol level, diabetes, and obesity, that additionally increase cardiovascular risk factors in both peri-menopausal and post-menopausal females (Costello *et al.*, 2017).Testosterone, the sex hormone in males, has also been demonstrated to exert cardio protective function (Ruige *et al.*, 2011). In males, low level of testosterone because of hypogonadism is linked with aging and other factors, as obesity. High risk for cardiovascular diseases in old age males has been described to be associated with hypogonadism, including declined level of testosterone (Kloner *et al.*, 2016; Liao e*t al.*, 2016). Low level of testosterone was also autonomously associated with a high risk for acute Myocardial infarction in type II diabetic men (Daka *et al.*, 2015) and a higher incidence of coronary artery disease in men (Nettleship *et al.*, 2009). In advanced age men, low level of testosterone has been associated to a higher risk for brain stroke (Yeap and Wu, 2019). A study reported that males, at 40 years of age, having serum testosterone levels below the suggested threshold level, had a higher mortality risk due to obesity that is the induced effect of hypogonadism due to low levels of testosterone (Lin *et al.*, 2011).



RISK FACTORS OF CARDIO-VASCULAR DISORDERS.

Family History: The family history studies of the 1st (full sibling) and 2nd degree (half sibling) relatives indicates that they share 50% and 25%, genes respectively. Genetic relatedness measures how many genes a person shares. Medical and health information serve as connection between genetics and genomics in medical practices for the reason that they may present a sign for not solely disorder of single gene but also share genes which can be accountable for polygenic disorders and gene environment interactions which may induce risk (Khoury, 2003). As family history is self-regulating cardio vascular diseases risk factor, it can serve as a screening tool to recognize individuals, particularly asymptomatic young individuals who are at high risk for cardio vascular diseases (Valdez *et al.*, 2007).

Ethnic background: Genetic and biological determinants and demography take part in indubitable role posing cardio vascular diseases in particular minority populations. The social circumstances have causal function in cardio vascular diseases progression (Kuzawa and Sweet, 2009). The burden of cardio vascular diseases in disadvantaged populations is due to low income status.

Low economic social status and social agony are being the root causes of mortality and morbidity (Chang and Lauderdale, 2003). The structural barriers to health of peoples and psychosocial pressure have played significant role in enhancing uneven cardiovascular diseases, particularly in ethnic minorities the prevalence and incidence of CVD has been reported absolutely (Betancourt *et al.,* 2003).

Low socioeconomic status has been linked with low income, deprived living status and low educational achievement, inaccessibility to primary or special health care due to insurance or other cost issues. Individuals in such minority neighborhood may travel beyond residence in purview of primary and secondary health care. The populations approach to emergency department for acute and chronic disease management that poses both economic burden and require significant patient care (Fei *et al.,* 2017). Scientists have also reported a high coronary heart disease incidence association with high exposure to individual level chronic stressors (Kershaw *et al.,* 2015). Cultural disparity in cardiovascular health status has been described and reported in literature. Structural, psychological and social obstacles as well as burden of insurance, health illiteracy, lack of provider cultural competency and limited access to care contribute to the complications regarding the prevention, proper diagnosis and timely management of cardio vascular disorders in ethnic minority populations (Muncan, 2018). Moreover, recognition as ethnic minority reflects distinctive complexity in suitable treatment of diagnosed cardio vascular diseases (Havranek *et al.,* 2015).

Additional markers and risks of cardio vascular diseases risk factors: The increased amounts of investigative parameters such as Ischemia modified albumin, Lipoprotein, hsCRP, glycated hemoglobin, caeruloplasmin, decreased HDL-C and fibrinogens, linked coronary artery calcium scores (Pfeiffer *et al*., 2008), arylesterase activity, homocysteine levels, , ankle brachial index, periodontal disease, B type natri-uretic peptide (BNP), N-terminal pro BNP (NT-pro BNP) carotid intima-media thickness are cardio vascular diseases markers that can be used to identify cardio vascular diseases. Additionally, inflammatory markers such as (IL-6), (IL-18), albuminuria, endothelial dysfunction markers (PTX3), (VCAM) are analytical markers of cardio vascular diseases that are linked to chronic kidney disease (CKD) (Stenvinkel *et al.,* 2008) Adiponectin level along with insulin resistance, abdominal obesity, dyslipidemia, contributes to cardio vascular diseases. It has been observed that adiponectin also regulates energy metabolism of the body through stimulation of fatty acid oxidation, lower triglyceride level, and modified metabolism of glucose *via* elevation of insulin sensitivity (Barrios *et al.,* 2008).

Conclusions: The review suggests the importance of public enlightenment and biomedical understanding of the cardio vascular diseases risk factors including identification of contributing factors of CVD development. Awareness among masses will help mitigate risk factors leading to CVDs. Risk factors discussed in this study are adequate predictors of changes in vulnerable individual's heart health. Public awareness should be taken into account through both print and electronic media. Annual surveys, cost effective and disease specific screening strategies should be conducted for early identification of CVD in workers of government and private institutions by employers, as well as among general population. Furthermore because of the disease inequality and burden, major population based interventions are required that may reduce the high clustering of risk factors in deprived parts of the society/community.

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