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Cardiovascular Disease Continuum- An Update

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Abstract
The objective of this study is to determine the various risk factors responsible for causing the cardiovascular disease like diabetes mellitus, dyslipidemia, hypertension, smoking and visceral adiposity. High cholesterol levels have long been considered an independent risk factor for cardiovascular disease. Diabetes mellitus, especially type 2 accounts for over 97% of the adult diabetic population. Lack of exercise and increased consumption of sweets, soft drinks and decreased consumption of fruits and vegetables has contributed increasingly to overweight and obesity in young persons and adults. Cigarette smoking and hypertension is a well established risk factor for cardiovascular disease continuum. There are hardly any studies assessing about the risk factors responsible for causing cardiovascular disease. Hence, this review will help in determining those factors responsible for cardiovascular disease continuum.
Key Words: *cardiovascular, hypertension, diabetes mellitus, smoking*

INTRODUCTION

The cardiovascular disease continuum (CVDC) is a chain of events chiefly precipitated by several cardiovascular risk factors, which if left untreated will, inexorably, culminate in end stage heart failure and mortality. The basic concept of cardiovascular risk continuum was first proposed by Dzau and Braunwald as a new paradigm for cardiovascular disease pathogenesis.[1]

Atherosclerotic cardiovascular disease particularly coronary artery disease develops over decades and ill-effects of cardiovascular risk-factors such as hypertension, dyslipidemia, obesity and insulin resistance accrues over a period of time leading to endothelial dysfunction, culminating in acute myocardial infarction or chronic coronary artery disease, left ventricular remodeling and ultimately to heart failure. Interruption of this chain of events with appropriate interventions at multiple sites along this continuum can substantially decrease the morbidity and mortality associated with cardiovascular disease. The development of HMG-CoA reductase inhibitors, or statins, that lower cholesterol effectively has transformed the management of lipid disorders. Large-outcome trials have conclusively proved that statins prevent myocardial infarction and mortality not only in patients who have already developed

cardiovascular complications but also in individuals who have not had any cardiovascular events and who do not even have elevated cholesterol levels.[2] Antihypertensive drugs and statins demonstrate the clinical utility of the cardiovascular continuum concept, namely, that the correction of cardiovascular risk factors prevents the escalation of cardiovascular disease and the downstream complications, including the ultimate event, death. Angiotensin-converting enzyme inhibitors, in particular, address different parts of the continuum, including hypertension, diabetes, left ventricular hypertrophy, remodeling, and heart failure

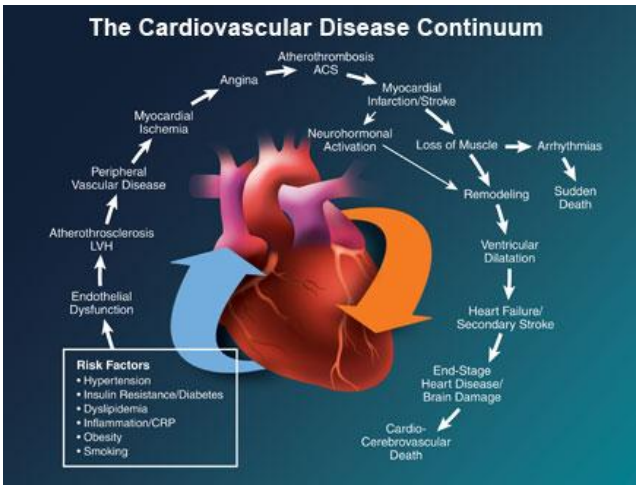

Figure :1

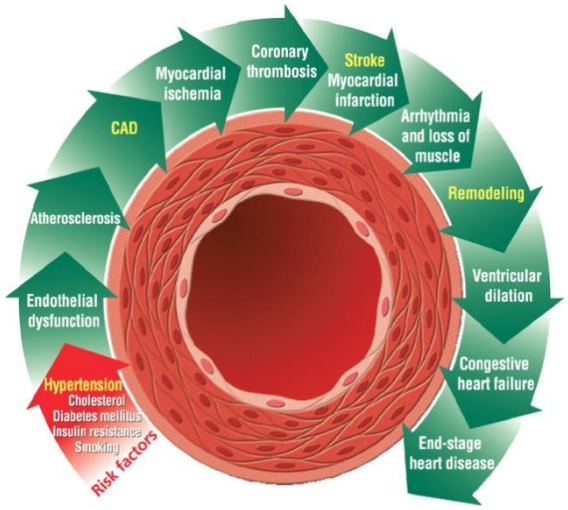

Figure :2

PATHOPHYSIOLOGY OF THE CONTINUUM

Oxidative Stress and Endothelial Dysfunction

Normal endothelial function appears to depend greatly on the homeostatic balance between nitric oxide (NO) and reactive oxygen species, such as superoxide anion and hydrogen peroxide. [3] Oxidative stress results when an increase in reactive oxygen species generation leads to a reduction in NO activity and subsequent endothelial dysfunction. This imbalance is a known effect of established CVD risk factors such as cigarette smoking, diabetes mellitus, and obesity. In addition, oxidative stress induces the expression of proinflammatory mediators such as vascular cell adhesion molecule, intracellular adhesion molecule, and chemoattractant proteins that play a role in early atherogenesis.

Through receptor-mediated and non–receptor-mediated mechanisms, endothelial cells regulate vascular tone, inflammation, lipid metabolism, cell growth and migration, and interactions with the extracellular matrix.[4] Any disruption of normal endothelial function can induce pathological vascular responses, such as smooth muscle cell proliferation, vasoconstriction, inflammation, and thrombosis. For example, endothelial dysfunction may shift relative concentrations of tissue-type plasminogen activator and plasminogen activator inhibitor type 1 toward thrombosis. Plasminogen activator inhibitor-1 is the primary inhibitor of tissue-type plasminogen activator, and elevated levels of plasminogen activator inhibitor-1 relative to tissue-type plasminogen activator lead to inhibition of the fibrinolytic system.[5] Endothelial dysfunction is also associated with changes in concentrations of important local inflammatory mediators, such as chemokines, adhesion molecules, and cytokines.

Role of Risk Factors in Oxidative Stress and Endothelial Dysfunction

Oxidized low-density lipoprotein (LDL) inactivates NO, which results in increased

oxidative stress and enhanced expression of cellular adhesion molecules.[6] Higher oxidized LDL content in the lipid core of atherosclerotic plaques may also promote plaque instability.[7] Small, dense LDL particles are highly atherogenic and are associated with increased triglyceride levels. The structure of small, dense LDL particles contributes to their atherogenicity, with increased susceptibility to oxidation, easier penetration into the arterial wall, and altered interactions with the LDL receptor.

Elevated blood pressure promotes the development of atherosclerotic plaques and increases the risk of CVD complications. [8] Endothelial dysfunction in chronic hypertension is associated with decreased endothelium-dependent relaxation. In hypertensive vessels, increased expression of matrix proteins, matrix proteinases, and growth factors leads to structural changes, such as decreased lumen diameter, increased extracellular matrix, and thickened media. In addition, hypertension is associated with increased production of free radicals and oxidative stress that may promote an inflammatory state and enhance the atherosclerotic process. Indeed, results from the Women's Health Study[9] and other epidemiological studies demonstrate that levels of C-reactive protein, a marker of systemic inflammation, correlate significantly with future risk of developing hypertension.

The metabolic syndrome comprises a group of lipid and nonlipid risk factors, such as insulin resistance and its associated hyperinsulinemia, atherogenic dyslipidemia, central obesity, and hypertension. [10] Insulin resistance and hyperinsulinemia appear to contribute to endothelial dysfunction and impaired NO responses. [11, 12] Furthermore, the chronic exposure of vascular smooth muscle to hyperinsulinemia may promote intimal hyperplasia. In addition, the excess adipose tissue characteristic of the metabolic syndrome secretes prothrombotic factors and proinflammatory cytokines, which may contribute to vascular disease.[13] Changes in the distribution of adipose tissue, namely, a shift from subcutaneous to visceral locations, may also be associated with a loss of antiinflammatory mediators such as adiponectin.[14,15]

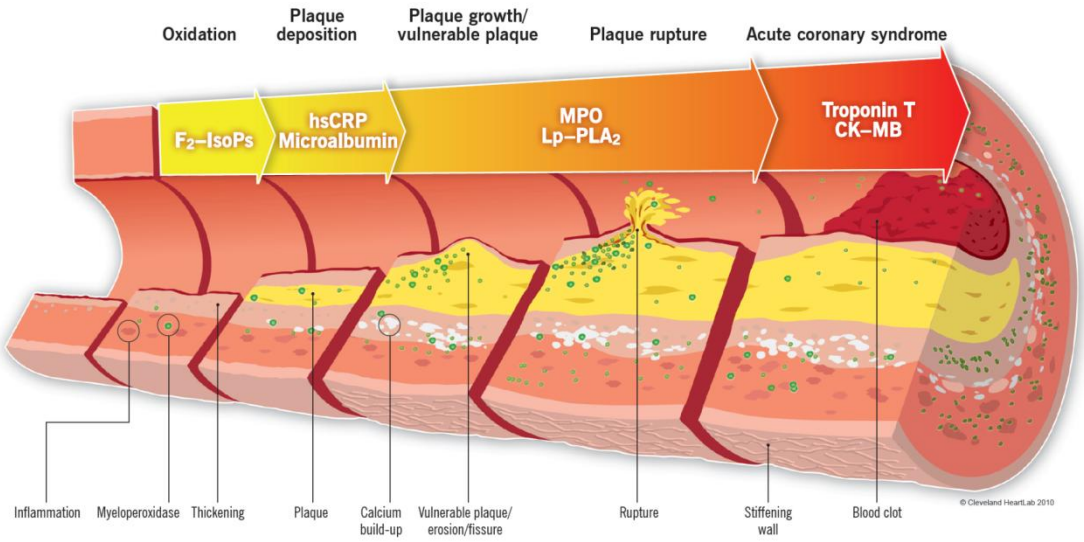

Figure :3

Role of Renin- Angiotensin system blockade

Angiotensin II acts via specific receptors, of which 4 subtypes (AT1-4) have been identified. Pathologic effects are mediated by AT1 receptors, activation of which results in vasoconstriction, sodium retention, aldosterone secretion, fibrosis, cellular proliferation, superoxide formation, inflammation and

thrombosis. By contrast AT2 receptors results in potentially beneficial vasodilatory and antiproliferative effects but promotes apoptosis. The function of AT3 receptor is not known and the AT4 receptor primarily mediates release of plasminogen activator inhibitor 1 (PAI-1) and thus may be prothrombotic. The angiotensin II can also be generated by a number of non-ACE pathways, through action of enzymes, such as the chymostatin-sensitive angiotensin II-generating enzyme and cathepsin G, which convert angiotensinogen directly to angiotensin II, and chymase, which cleaves angiotensin I to form angiotensin II. Chymase is responsible for generation of > 80% of tissue angiotensin II formation in human heart, and >60% in arteries. ACE 2, a homologue of ACE that has been found in heart, kidney, testis and gastrointestinal tract has been found to convert Angiotensin I to angiotensin (1-9) and it also converts Angiotensin II to angiotensin (1- 7). Angiotensin (1-7) has been shown to have vasodilatory properties as it stimulates nitric oxide synthesis. Angiotensin (1-7) may also be generated through action of neutral endopeptidases. These pathways are potential therapeutic targets of RAS blockade in the future. ACE also catalyzes the breakdown of bradykinin which is a vasodilator and is thought to promote tissue plasminogen activator production. Another important physiologic correlate is inhibition of aldosterone by agents like spironolactone and eplerenone which is directly stimulated by angiotensin II. ACE inhibitors has been shown to have beneficial effects on endothelial function, cardiovascular remodeling, the progression of atherosclerosis, and protection against clinical events such as myocardial infarction and heart failure. [16, 17]

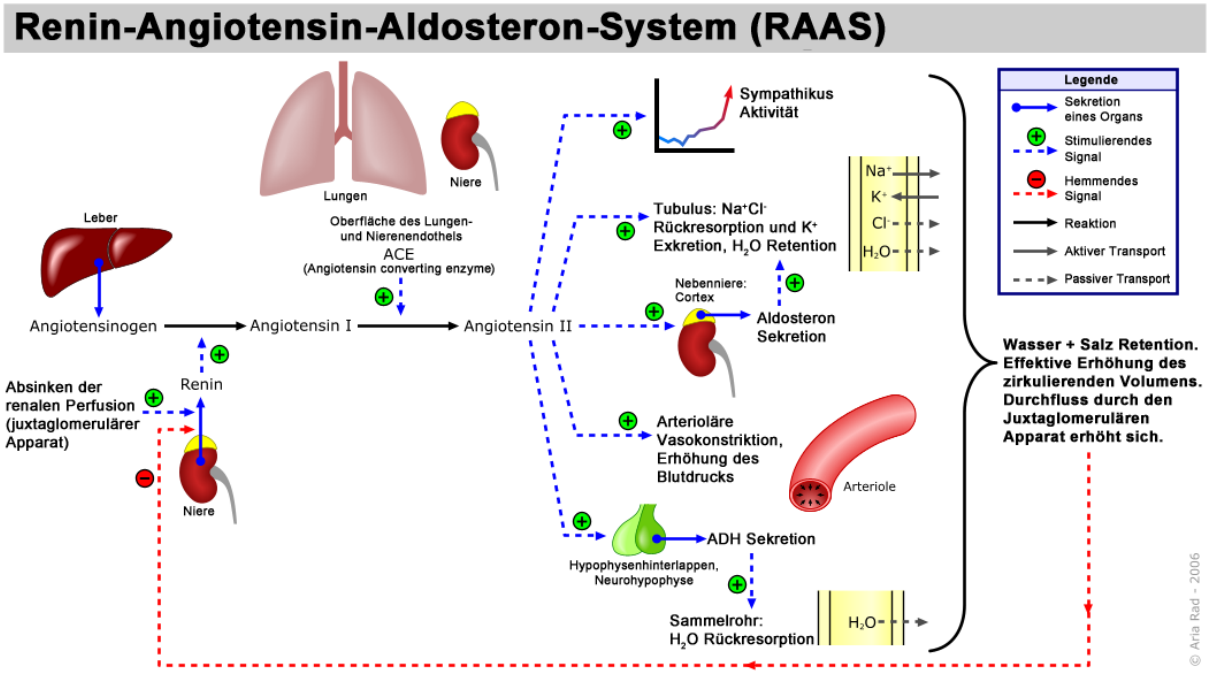

Figure :4

Inflammatory Processes

An inflammatory state has been associated with atherosclerosis. In the inflammatory response to endothelial injury, release of chemokines promotes entry of monocytes into the vessel wall, where they can transform into macrophages. Macrophages then take up modified and oxidized LDL, becoming foam cells. Foam cells contribute to formation of fatty streaks, an early stage of atherosclerotic plaque.[18] Repetitive cycles involving ongoing arterial injury, lipid uptake, and vascular remodeling can result in complicated plaques with large necrotic cores, thin fibrous caps, and accumulation of macrophages in the

shoulder regions, where plaque rupture tends to occur. When activated by T cells, macrophages release proteolytic matrix metalloproteinases that degrade the fibrous cap and interstitial collagen, which promotes rupture. [19] One important signaling pathway between T lymphocytes and macrophages is the CD40:CD402 system. Macrophage accumulation appears to be associated with increased levels of inflammatory markers, such as fibrinogen and C-reactive protein.[20] Thrombosis that results in a clinical event may also be caused by a superficial erosion, rather than intimal rupture, of the atherosclerotic plaque; in either case, the immediate site of plaque rupture or erosion is always marked by an inflammatory process.[21]

C-reactive protein has emerged as a useful predictor of atherosclerotic cardiovascular disease risk. [22] C-reactive protein may also be a mediator and not just a marker of inflammation. C-reactive protein induces the expression of tissue factor and cell adhesion molecules, binds and activates complement, stimulates monocytes to enter the vessel wall, promotes the production of monocyte chemotactic protein-1, and mediates macrophage uptake of LDL.

Coagulation Cascade

When a plaque ruptures, the thrombogenic lipid core is exposed to circulating blood, which activates the coagulation cascade that initiates and sustains thrombus formation. During this process, platelets adhere to the site of trauma and contribute to the formation of thrombin, which converts fibrinogen into strands of fibrin. Fibrin strands trap additional platelets, blood cells, and plasma to form a clot that can partly or completely block an artery.

Vascular Remodeling

Vascular remodeling occurs in response to chronic alterations in hemodynamic conditions that precipitate structural changes in the vessel wall, such as increased ratio of wall to lumen width, changes in luminal dimensions with minimal changes in wall thickness, neointima formation in response to injury, and rarefaction of the microcirculation. Inward remodeling typically occurs in response to reduced blood flow and results in decreased vessel size; conversely, outward remodeling usually is a reaction to increased flow and results in increased vessel size.[23] Locally produced biologically active mediators, such as NO and matrix metalloproteinases, and growth factors, such as platelet-derived growth factor and transforming growth factor-β, in addition to hemodynamic stimuli, such as shear stress, interact to promote cell migration, cell growth, cell death, and the production and degradation of extracellular matrix, which results in these structural alterations. The pathophysiological changes in vascular structure that result from alterations in endothelial function have clinical implications. Vascular remodeling in small resistance arteries may be the initial step in the progression from hypertension to target-organ damage.[24] Small resistance arteries that have undergone hyperplastic/hypertrophic remodeling have an enhanced response to vasoconstrictor substances, further reducing vascular reserve. This reduction may contribute to tissue ischemia if surrounding arteries are stenotic. Small-artery remodeling is more common among persons with hypertension than those without, and patients with the highest blood pressures are also the most likely to develop left ventricular hypertrophy (LVH) and have the greatest incidence of small-artery changes. [25]

Cardiac Remodeling and Target-Organ Damage

Cardiac remodeling is mediated by diverse endocrine, paracrine, and autocrine effects of a number of different hormones that result in hypertrophy. The hormones involved in changing the structure, function, and phenotype of the myocardium include angiotensin II, vasopressin, peptide growth factors, endothelin, natriuretic peptides, cytokines, and NO. Evidence indicates that insulin and insulin-like growth factor may be

myocardial growth factors, which suggests that altered glucose and insulin metabolism, such as occurs in diabetes and the metabolic syndrome, further contributes to LVH and accelerated heart failure. [26] Oxidative stress also plays an important role in the cardiac remodeling process; in animal studies, inhibition of antioxidant systems disrupts normal cell growth and apoptosis in cardiac myocytes. If uninterrupted, cardiac remodeling results in impaired systolic and diastolic functioning and progresses to heart failure. [27]

Basic science investigations have rendered obsolete the concept that each disease event on the CVD continuum is mediated by a specific and single pathophysiological pathway; rather, common pathophysiological processes participate in multiple steps across the continuum. It is now apparent that common and overlapping mechanisms are involved in disease development across the entire spectrum of CVD. This understanding has therapeutic implications in that many interventions and drugs are effective in treating multiple disease events across the CVD continuum.

Effects on glucose metabolism and obesity

Obesity and hypertension are both closely related cardiovascular risk-factors and both conditions are associated with RAS activation. Higher levels of angiotensin II, renin, aldosterone and ACE have been found in obese women. Such activation in obese persons is thought to increase insulin resistance in skeletal muscle, resulting in induction of metabolic syndrome along with beta cell impairment leading to type 2 diabetes. ACE inhibitors have been shown to increase glucose uptake first by vasodilation and improved skeletal muscle perfusion and secondly by stimulating GLUT-4 mediated glucose uptake in skeletal muscle.[28] The DREAM trial showed that ramipril reduced to hypertensive patients taking atenolol in Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) trial. Various studies have shown that RAS blockade also leads to reduced progression of atherosclerotic plaque and comparable results have been obtained in various major clinical trials.[29] The SECURE trial has shown that treatment with 10 mg of ramipril compared to placebo over 4.5 years resulted in mean 37% reduction in carotid intima-media thickness in high-risk participants with vascular disease or diabetes, and ≥1 other cardiovascular risk factor.[30] RAS activation also causes an increase in PAI-1 levels in vascular smooth muscles and endothelial cells resulting in a prothrombotic state. RAS blockade has been shown to reverse this effect.

CONCLUSION

The cardiovascular risk continuum remains as relevant today as it was when the perspective was first launched in 1991. It is based on the fact that cardiovascular risk factors need to be treated as a composite whole and not each risk factor in isolation. Creating awareness about the risk factors involved in cardiovascular disease continuum is the major punch-line in this context.

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