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RESEARCH ARTICLE

PATHOPHYSIOLOGICAL MECHANISM BEHIND DIABETIC CARDIOVASCULAR DISORDERS

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ABSTRACT

Fatal and non-fatal Coronary Artery Diseases (CAD) are increased 2-4 fold in patients with diabetes and autopsy as compared to non-diabetic patients with Coronary Heart Disease (CHD). Immediate and long-term post- Myocardial Infarction (MI) mortality is increased 1.5-2 fold among diabetic patients. Despite a comparably small infarct size, diabetic patients have a far greater risk of developing highly fatal post-MI complications when compared to non diabetic patients. Following MI, the surviving myocardium of non-diabetic patients becomes hyperkinetic to compensate for non-viable infarcted myocardium in an attempt to maintain cardiac output. However, in diabetic patients, these areas of myocardium cannot achieve this compensatory enhancement in function due to a complex set of intra- and extra-myocardial factors superimposed on an already reduced coronary artery flow reserve. Endomyocardial samples from diabetic patients show enhanced thickening of capillary basement membrane, myocellular atrophy and hypertrophy with myocardial and, interstitial fibrosis, which further reduces the function of the myocardium. In this review the author have looked into various cardiovascular complications in diabetic condition and the pathophysiological mechanisms lying behind each.

INTRODUCTION

Diabetes mellitus is a metabolic disorder of multiple etiologies characterized by chronic hyperglycemia with disturbances in carbohydrate, fat and protein metabolism resulting from defects of insulin secretion, insulin action, or a combination of both and is associated with the development of specific long term organ damage due to microvascular diseases (Williamson *et al.,* 1993). Type 1diabetes is due to virtually complete lack of endogenous pancreatic insulin production, whereas in type 2 diabetes, the rising blood glucose results from a combination of genetic predisposition, unhealthy diet, physical inactivity and increasing weight with a central disturbance resulting in complex pathophysiological processes (Nishikawa *et al.,* 2000). Patients with diabetes are at higher risk of cardiovascular, cerebrovascular and peripheral artery disease. Among the several risk factors associated with CVD such as hypertension, cigarette smoking and dyslipidemia, diabetes is an important contributor to CVD risk and mortality. The reverse association is equally strong (Thomas *et al.,* 1994). Today atherosclerosis accounts for about 70-80% deaths in diabetic individuals as compared to 30% in general populations. The increased risk of CVD in diabetic individuals can be explained in part by the clustering of traditional risk factors such as dyslipidemia, hypertension, hyperglycemia, and an increased tendency to thrombosis. Recent evidences show that increased oxidative stress and excess production of advanced glycation end products contribute to the development of diabetic complications, which are mediated at least by endothelial dysfunction (Graier *et al.,* 1995). Since the worldwide prevalence of diabetes is increasing in ever-alarming proportions, CVD is becoming the most frequent cause of death. The various types of CVD associated with diabetes are acute myocardial infarction, diabetic cardiomyopathy, Cardiac Autonomic Nephropathy (CAN) and Cardiac Allograft Vasculopathy (CAV). The complexity and pandemic proportions of heart diseases and diabetes call for a comprehensive understanding of the pathophysiological mechanisms involved and their integration into a broader picture.

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Hyperglycemia and Coronary Heart Diseases

Hyperglycemia may accelerate atherogenesis through various mechanisms, such as glycation of collagen and other vessel wall proteins, excess production of atherogenic lipoproteins and, reactive oxygen species, increased oxidative stress, glycation of several lipids and lipoproteins and also through endothelial damage, and hemorrheological abnormalities. In hyperglycemic conditions, glucose is reduced by Aldolase reductase to sorbitol which in some tissues is further oxidized to fructose upon sorbitol-dehydrogenase-catalyzed oxidation. The conversion of glucose to fructose (the polyol pathway) results not only in the utilization of NADPH but also in the accumulation of reduced NAD. This shift in the redox state of pyridine coenzymes induces a state of pseudohypoxia resulting into hypoxia like responses (Williamson *et al.,* 1993). Polyol

pathway mediated alterations in pyridine nucleotides have been linked to diverse metabolic changes such as block of Nitric Oxide (NO) and activation of protein kinases (Nishikawa *et al.,* 2000). The increase in NADH due to elevated polyol pathway activity could increase the synthesis of diacylglycerol (DAG) from dihydroxy acetone phosphate (Thomas *et al.,* 1994). DAG level activates phospholipase C and members of protein kinase C family that plays a key role in mesangial expansion and smooth muscle cells proliferation induced by high glucose (Graier *et al.,* 1995). In the presence of normal glucose (5.5mM) Aldolase Reductase (AR) catalysed reduction of glucose represents less than 3% of total glucose utilization, whereas in presence of high glucose (20mM), more than 30% of glucose is used by AR (Srivastava *et al.,* 2005). This reduction pathway imposes a significant strain on NADPH supply. Because NADPH is used for several critical reductive metabolic steps, such as detoxification of reactive oxygen species and hydroperoxides by the glutathione reductase/ glutathione peroxidase system, a large drain on the NADPH pool could compromise the ability of the cell to protect itself from oxidative stress (Dvornik *et al.,* 1992). Hyperglycemia leads to the formation of advanced glycation end products (AGES), which are proteins or lipids that become glycated after exposure to sugars (Goldin et al. 2006). The presence and accumulation of AGES in many different cell types affects extracellular and intracellular structure and function. AGES cause cross-linkage of vessel wall proteins, leading to thickening and leakage of the vasculature and the formation of irreversible and abnormal deposits of plasma-derived proteins in the sub intimal layers of arteries (Goldin *et al.,* 2006). In addition they engage the receptors of nuclear factor kappa B (NF-kB), a transcription factor that coordinates the inflammatory response. Furthermore soluble AGES activate monocytes and block Nitric Oxide (NO) activity in the endothelium (Yan *et al.,* 2006), (Wautier and Schmidt, 2004). Higher cellular glucose causes increased production of ROS by several mechanisms (Fig 1). ROS mediates direct endothelial cell damage, oxidizes AGES and low density lipo-proteins (LDLs) thereby increasing the chances of atherogenesis.

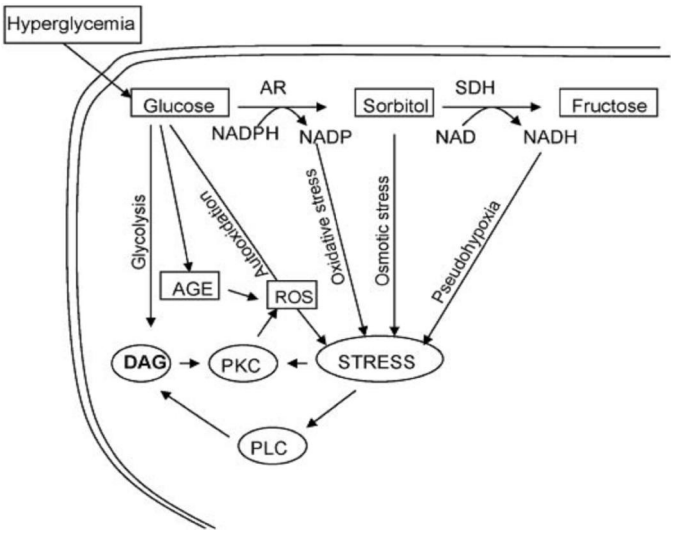

Fig. 1. Involvement of polyol pathway in diabetic complications (Source: Srivastava *et al.*, 2005)

During hyperglycemia, reduction of glucose to sorbitol by AR constitutes the first and the rate-limiting step of the polyol pathway that converts glucose to fructose via sorbitol dehydrogenase (SDH). In this pathway both NADPH and NAD^+ are consumed as cofactors for the enzymes AR and SDH. Osmotic stress due to accumulation of sorbitol and oxidative stress due to changes in the ratio of NADPH/$NADP^+$ and reduced NAD (NADH)/NAD^+ are the major cause of various complications of secondary diabetes (Srivastava *et al.,* 2005).

Insulin resistance and CVD

Insulin resistance is associated with both T1 and T2 diabetes mellitus (Daneman, 2006). In addition it may cluster with several classical CVD risk factors, such as visceral obesity, lipid abnormalities, hypertension and impaired glucose tolerance to form a condition known as metabolic syndrome (Eckel *et al.,* 2005). Controversy remains regarding involvement of insulin resistance in the pathogenesis of atherosclerosis (Ferrannini and Iozzo, 2006). At the cellular level, there are two major insulin-regulated pathways, known as the metabolic and mitogenic pathways (Van Gaal *et al.,* 2006). Normally, insulin binds to Its Receptor (IR), and activates Insulin Receptor Substrate (IRS-1) by phosphorylation of tyrosine residues. This, in turn activates phosphotidylinositol 3-kinase (PI-3K). In people with obesity, impaired glucose tolerance (IGT), type 2 diabetes mellitus (T2DM) and other insulin resistant states, there is a severe defect in the activation of IRS-1 which results into impaired glucose transport into the cell. This leads to a rise in blood glucose level and the resultant hyperglycemia, stimulates insulin release and development of hyperinsulinemia (Van Gaal *et al.,* 2006). Although the metabolic pathway (IRS-1/PI-3K pathway) is severely impaired in any condition of insulin resistance, the mitogenic pathway (proceeding through mitogen-activated protein; MAP-kinase) (Fig.2) seems to retain its sensitivity to insulin, and any prevailing hyperinsulinemia would therefore, lead to an excessive stimulation of this pathway (Cersosimo and DeFronzo, 2006). This may result in the release of a number of growth and inflammatory factors and, promote proliferation and migration of vascular smooth muscle cells (Eckel *et al.,* 2005).

Oxidative stress plays a casual role in insulin resistance and might be linked with visceral adiposity (Houstis *et al.,* 2006). Mature adipocytes functions as an endocrine/paracrine organ that secretes numerous adipokines, cytokines and growth factors, in insulin resistance. A significant number of these proanthrogenic factors can be released from components of visceral fat, such as infiltrating macrophages that are not adipocytes (Weisberg *et al.,* 2003). Several mechanisms link obesity to CAD such as the increased levels of Nonesterified Fatty Acids (NEFA) that results from increased lipolysis, and disturbances in adipokine and cytokine secretions. These processes in turn are linked with insulin resistance (Van Gaal *et al.,* 2006). Several adipokines and cytokines, such as adiponectin, interleukin-6 (IL-6), retinol binding protein-4 (RBP-4), reisistin, and tomor-necrosis factor-α are associated with insulin resistance. RBP-4 is an adipocyte derived molecule that is elevated prior to the onset of diabetes (Graham *et al.* 2006), and it appears to impair insulin signaling in muscle

and promote insulin resistance (Yang *et al.,* 2005). Visceral fat releases IL-6, which can contribute to local and systemic imflammation, and elevation of C-reactive protein levels (Van Gaal *et al.,* 2006). Thus, insulin resistance is intricately linked with visceral adipocity, and oxidative stress, and it may promote endothelial dysfunction and CAD.

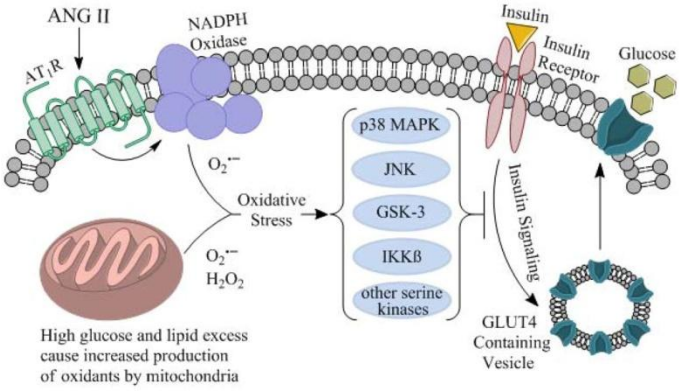

Fig.2. Schematic representation of the overproduction of oxidants from NADPH oxidase and, mitochondrial sources in mammalian skeletal muscle, with subsequent enhanced engagement of p38 MAPK and other stress-activated kinases, including JNK, GSK-3, IKKβ, and others, associated with diminished insulin-stimulated insulin signaling and reduced glucose transport activity. (Source: Van Gaal *et al.*, 2006).

Abnormalities in fatty acid metabolism and CVD

Lipid abnormalities are often found in diabetic patients (Chahil and Ginsberg, 2006). In T1 Diabetes Mellitus (T1DM), sustained hyperglycemia is associated with increased concentrations of total cholesterol, LDL and triglycerides and low concentration of HDL. In T2DM, dyslipidemia is associated with insulin resistance and is characterized by raised triglyceride, and low HDL concentration. LDL cholesterol is present in the form of highly atherogenic small, dense LDL particles (Chahil and Ginsberg, 2006). These LDL particles bind to the receptors on monocytes or macrophages and lead to the formation of foam cells. They can undergo oxidation through several mechanisms thereby contributing to atherogenesis at an early age (Mehta *et al.,* 2006). Small dense LDL particles oxidize more readily than their counterparts and due to their small size they are likely to penetrate the arterial wall more easily. These particles possess high affinity for arterial wall proteoglycans thus prolonging their residence time in the subendothelial space (Packard, 2006). Elevated triglyceride promotes the increase in triglyceride-rich lipoprotein that is found to be involved in the development of atherosclerosis. Chylomicrons and large VLDLs are not capable of entering the arterial wall whereas small VLDLs and intermediate density lipoproteins (LDLs) can easily enter the arterial intima (Steiner, 1998). As a result certain triglyceride rich lipoproteins are atherogenic while others are not (Steiner, 1998). α, β unsaturated aldehydes which are produced during β-oxidation of alkoxy radicals derived from ω-6 polyunsaturated fatty acids are highly reactive (Esterbauer *et al.,* 1991). They are generated in high concentrations by peroxidative reactions of lipids and lipoproteins and have been found to mediate and amplify the cellular effects of the free radical precursors (Esterbauer *et al.,* 1991). HDL particles have a role in reverse cholesterol transport (from non-hepatic cells to the liver), have direct effects on the endothelial cells and possess antioxidant properties like inhibition of LDL oxidation by transition metal ions, prevention of lipid hydroperoxide formation, reduction of apoptosis by inhibiting caspases and activating protein kinase Akt, activating eNOS to produce NO. In addition to lipid peroxidation, high concentrations of α, β unsaturated aldehydes are also generated by other biochemical processes, like myeloperoxidase catalysed oxidation of amino acids and oxidative modification of nucleosides (Assmann and Gotto, 2004). Accumulation of these unsaturated aldehydes and their products are found to be associated with increased formation of ROS leading to atherosclerosis, ischemia-reperfusion etc.

Hypertension and Diabetic CVD

Hypertension is at least twice as common in people with diabetes as in general population and is also more frequent in people with impaired glucose tolerance. It affects upto 70% of patients with diabetes mellitus and has some unique characteristics such as increased salt sensitivity, volume expansion, loss of nocturnal dipping of pulse, and isolated systolic hypertension (Yudkin, 2002). Sustained hypertension is associated with structural and functional alterations of both large arteries and arterioles. Hypertensive arteries experience remodeling of arterial walls due to increased vascular stiffness probably caused by accumulation of collagen and smooth muscle cell proliferation (Lehoux, 2006). The co-existence of hypertension and, diabetes increases the risk of developing macrovascular complications (myocardial infarction, stroke) and also microvascular complications (nephropathy, retinopathy etc) (Wahren *et al.,* 2000). The vigorous treatment of hypertension may reduce the progression of these complications. In T1D, hypertension develops years after diagnosis usually already reflecting the development of diabetic nephropathy (Piero *et al.,* 2008). Blood pressure tends to increase three years after the onset of micro albuminuria (Wahren, 2004). In patients with T2D, hypertension may be present at diagnosis and even before the elevation of blood glucose levels as reported by Kannel and collegues (Kannel *et al.,* 1974). The association between hypertension and, obesity is well established leading to a higher rate of cardiovascular morbidity and mortality in patients with these two conditions (Kannel *et al.,* 1974). The treatment of hypertension in diabetic patients aim at the prevention of CVD, minimizing the progression of renal disease and diabetic retinopathy. T2D patients may benefit more from tight control of blood pressure than with strict control of blood glucose levels. Initial treatments should include non-pharmacological measures such as weight reduction (in overweight and obesity), regular excercising, reducing salt intake (<1500mg/day), avoiding excessive alcohol consumption and smoking cessation. Pharmacological therapy should be initiated in all diabetics who persist with BP>130/80mmHg, when a change in lifestyle has already been implemented for 3 months or when the maximum BP levels are already higher than 140/90mmHg at diagnosis.

Endothelial dysfunction and CVD

Endothelial dysfunction is a precursor of atherosclerosis. Endothelial plays a vital role in regulation of leukocyte

adhesion and trafficking, prevention of platelet adhesion and regulation of blood flow via modulation of vessel patency (Feletou and Vanhoutte, 2006). These functions of the endothelium are mediated by various molecules such as nitric oxide, prostacyclin, C-type natriuretic peptide, Angiotensin II, plasminogen activator and so on (Feletou and Vanhoutte, 2006). In diabetics, hyperglycemia promotes the formation of ROS/AGEs, which stimulates the endothelial expression of pro-inflammatory cytokines such as interleukin-1 and monocyte chemoattractant protein-1, as well as leucocyte adhesion molecules (Lum and Rockbock, 2001). Oxidative stress due to excess production of ROS leads to reduction in the level of NO, and degradation of eNOS cofactor tetrahydrobiopterin (BH4) (Quagliaro *et al.,* 2007). Insulin resistance also, causes alterations of PI-3K/Akt pathway which in turn lead to a marked decrease in eNOS activation. All these alterations confer a strong proatherogenic profile, which plays a major role in the development of CAD (Joshua *et al.,* 2005). Endothelial dysfunction in T1D is an important determinant of inflammatory activity regardless of the presence or absence of complications, and hence can be considered as early marker of CVD (Schram *et al.,* 2003). The disturbances in vascular responses can be seen by impaired flow mediated dilation responses associated with increased carotid artery intima-media thickness. Several markers of endothelial function in T1D such as, von Willebrand factor, thrombomodulin, selectin, plasminogen activator inhibitor-1(PAI-1), Type-IV collagen and tissue plasminogen activator (tPA) are increased. It has been shown that the cellular adhesion molecule E-selectin may enhance CAD prediction beyond traditional risk factors in T1D (Khan *et al.,* 2000). Other markers of low grade inflammation levels such as oxidized LDL, monocyte IL-6, superoxide anion, plasma C-Reactive Proteins (CRP), Scd40L and nitrityrosine levels are found to be elevated in T1D patients (Hadi and AlSuwaidi, 2007). Thus endothelial dysfunction in T1D represents a high risk for micro and, macro angiopathy and hyperglycemia, appears to be one of the main causes along with other factors like environment, and genes (Hadi and AlSuwaidi, 2007). T2D is independently associated with impaired flow mediated dilatation. Endothelial dysfunction is considered to be the determinant factor for the vascular complications that is aggravated, rather than caused by hyperglycemia, because of the presence of many other risk factors such as obesity, hypertension, dislipidemia and ageing (Kolluru *et al.,* 2012). This may be due to increased calpain dependent decrease in the association with eNOS. Inhibition of calpain activity decreases endothelial cell surface expression of the pro-inflammatory adhesion molecules ICAM-1 and, VCAM-1 during hyperglycemia (Stalker *et al.,* 2003). T2D is associated with insulin resistance that causes eNOS inhibition by alterations in PI-3K/Akt pathway. Abnormalities in vasculature along with insulin resistance are also found in first degree relative to T2D patients even without presence of classic cardiovascular risk factors (Basha *et al.,* 2012).

Oxidative stress and diabetic vascular complications

Increased intracellular glucose concentration results in the activation of alternative pathways of metabolism such as hexosamine and aldolase reductase pathways, both involved in the pathophysiology of chronic complications of diabetes. These pathways trigger an increased production of ROS, leads to the formation of advanced AGEs and the activation of protein kinase C (PKC) resulting into increased oxidative stress. NADPH oxidase, nitric oxide synthase (NOS), xanthine oxidase, mitochondrial chain electron transport, lipooxygenase, cycloxygenase and cytochrome P450 are the main sources of ROS in the body. The ROS produced by these enzymes act as second messengers regulating the expression of redox signal sensitive gene (NF-kB) and also play vital role in production of inflammatory mediators (Griedling, 2004). ROS produced in the vascular wall are involved in various cellular events such as mitosis, apoptosis, hypertrophy, gene transcription and protein synthesis (Heerebeek *et al.,* 2002). In diabetics, mitochondrial O_2^- anion act as a factor initiating a cascade of events that results in increased production of ROS and RNS through activation of NF-kB. In addition, NOS can divert the production of nitric oxide (NO) to generate O_2^- in deficiency of L-arginine or tetrahydrobiopterin (BH4) in the endothelium of diabetic patients. When both L-arginine and BH4 are produced and, antioxidant enzymes are absent, the formation of peroxynitrite (NOO^-) occurs, causing damage to cellular structures such as DNA, lipids, proteins etc. (Ballinger, 2000).

Under normal conditions the presence of ROS induces the expression of antioxidant enzymes as a defense mechanism. But even a short duration of diabetes without any chronic complications, less plasma antioxidants and uric acid levels suggests oxidative stress early in the disease (Marra *et al.,* 2002). Non-enzymic extracellular antioxidants like α-tocopherol, vit. A, β-carotene, ascorbic acid, albumin and uric acid are particularly important to protect against lipid, protein and DNA damage. Another important component of antioxidant defense in diabetes is hepatoglobin that binds free hemoglobin resulting in the inhibition of iron-induced oxidative damage, since hemoglobin released in the blood after hemolysis of senescent erythrocytes is a potent oxidant (Levy *et al.,* 2002). The failure in the removal of ROS in the absence of the various enzymatic and non-enzymatic antioxidants results to atherosclerosis which is a state of heightened oxidative stress characterized by lipid and, protein oxidation in the vascular wall. The uncontrolled production of ROS and failure of body's defense system to handle this condition contributes to coronary artery disease such as endothelial dysfunction and plaque growth/disruption (Berry *et al.,* 2001). Of the established cardiovascular risk factors, diabetes is highly predictive of increased oxidative stress, being associated with enhanced levels of circulating markers of free radical-induced damage, and reduced oxidant defense. The drivers of oxidative stress include hyperglycemia, hyper-insulinemia, elevated free fatty acids, lipids and, leptin. Hyperglycemia-induced ROS production is a key event in the activation of all pathways involved in the pathogenesis of diabetic vascular complications and as a key biological event leading to inflammation and endothelial dysfunction in human diabetes. Insulin resistance, impaired glucose tolerance, and overt diabetes are associated with an increased risk of CVD. The presence of oxidative stress represents a pathogenic mechanism linking insulin resistance with dysfunction of both endothelial cells and β-cells leading to overt diabetes and CVD. This could explain why therapeutic strategies, having only ability to reduce oxidative stress appears to simultaneously reduce cardiovascular mortality and lower incidence of diabetes.

Inflammation Cascade, Diabetes and Atherosclerosis

Diabetes, obesity and insulin resistance are associated with subclinical inflammation characterized by over expression of cytokines produced by adipose tissue, activated macrophages and other cells. Inflammatory mediators, such as TNF-α, interleukin-1 (IL-1), IL-6, leptin, resistin, monocyte chemoattractant protein-1(MCP-1), plasminogen activator inhibitor-1 (PAI-1), C-reactive protein (CRP), fibrinogen, angiotensin, visfatin, retinol binding protein-4 and adiponectin are involved in signaling pathways, in insulin action and perpetuation of inflammatory response (Shoelson *et al.,* 2006). These cytokines are involved in the chronic inflammatory process of the vessel wall, promoting lipid accumulation with consequent development of atherosclerosis and CVD (Vicenova *et al.,* 2009) (Fig. 3) Atherosclerosis is a complex multifactorial disease, and its acceleration in diabetes may be explained by several conditions including hyperglycemia, increased oxidative stress, advanced glycation end products (AGE), dyslipidemia, autonomic imbalance, hyperinsulenemia, excess inflammatory markers and genetic variables (Ait Oufella *et al.,* 2011). It is assumed that the adipose tissue initiates obesity-induced inflammation and leads to the recruitment of immune cells which contributes to the maintenance of inflammatory response, besides leading to endothelial dysfunction with increased expression of adhesion molecules (ICAM-1, V-CAM-1, P-selectin and E-selectin), migration of monocytes, neutrophiles and T-lymphocytes (Wellen and Hotamisligil, 2005). Insulin resistance induces chronic elevation in free fatty acids (FFA) plasma concentration leading to increased storage of triglycerides in muscle, promoting reduction of muscle glucose uptake and increased hepatic glucose production that have been shown to impair insulin action and promote hyperinsulenemia (De Fronzo, 2004).

Hyperinsulenemia can induce cardiomyocyte hypertrophy through myocyte growth induced by the activation of P13K/Akt-1 pathway and also by enhancing FFA levels. FFA are also implicated in the development of myocardial contractile dysfunction (Poornima, 2006). Several cytokines described to be related with insulin resistance are also involved with the development of atherosclerosis and CVD. TNF-α and other cytokines, FFA and ROS, activate inflammatory pathways and promote the expression of numerous genes involved in insulin resistance (Wellen and Hotamisligil, 2005). IL-1is another cytokine produced as a consequence of stress and cell injury mainly by macrophages that modulate key events in the process of atherosclerosis such as vessel wall inflammation, leukocyte chemotaxis and adhesion by increasing expression of VCAM-1 and MCP-1, angiogenesis through vascular endothelial growth factor (VEFG) induction, upregulation of matrix metalloproteinases (MMP), and destabilization of atheromatous plaques, that can lead to plaque rupture and thrombosis (Vicenova *et al.,* 2009). CRP is an acute phase protein and is primarily derived from IL-6 hepatic biosynthesis. Atherogenic mechanisms of CRP include impaired production of endothelial NO and prostacyclin; increased production of endothelin-1 and other cell adhesion molecules, MCP-1, IL-8 and PAI-1; ROS and proinflammatory macrophage production; monocyte adhesion and chemotaxis; uptake of oxidized LDL; CRP also stimulates the expression of metalloproteinases, activates NF-kB and promotes cell proliferation in vascular smooth muscle cells due to upregulation of the angiotensin type 1-receptor (Chait, 2005). Adiponectin has many protective actions in the atherosclerosis process due to the inhibition of LDL oxidation, activation of macrophages, reduction of adhesion molecule (VCAM and ICAM), inhibition of proliferation, and migration of smooth cells, and an increased production of NO in endothelial cells (Ferrarezi, 2007). Adiponectin is markedly reduced with increased obesity, and in diabetes and, hypoadiponectinemia is associated with an increase in CVD rates (Yamauchi, 2002). Leptin is a hormone secreted by adipose tissue and primarily involved in the regulation of energy expenditure and, food intake. Plasma leptin concentrations are increased in obese and diabetic patients (Yang and Barouch, 2007). Leptin has been shown to participate in the development of atherosclerosis in several ways: inducing oxidative stress; increasing the production of MCP-1, endothelin-1 (ET-1) which leads to cardiomyocyte hypertrophy; promoting migration, proliferation, hypertrophy of vascular smooth muscle cells (VSMC) and vascular cell wall calcification; stimulating platelet aggregation, attenuating cardiomyocyte contractility through increased nitric oxide production, reduction of intracellular calcium and decreased β-adrenergic response (Yang and Barouch, 2007).

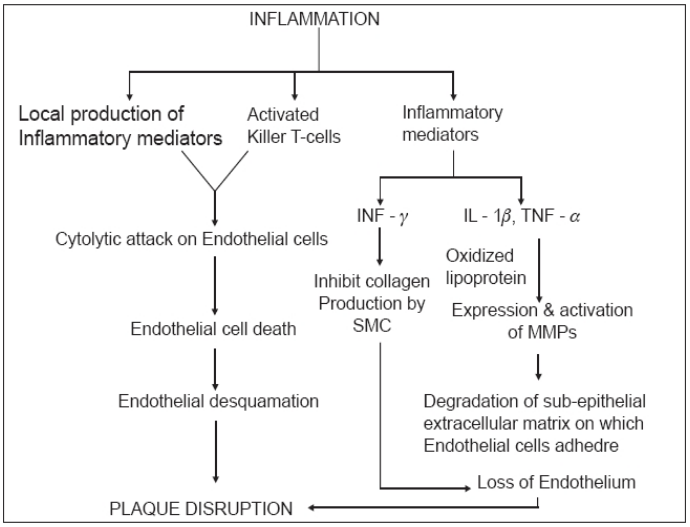

Fig.3. Role of inflammation in plaque disruption leading to Atherosclerosis. (Source: Vicenova *et al.*, 2009).

Diabetic Cardiomyopathy

Diabetic cardiomyopathy refers to a disease process which affects the myocardium in diabetic patients causing a wide range of structural abnormalities eventually leading to left ventricular hypertrophy (LVH) and diastolic, and systolic dysfunction or a combination of these. The concept of diabetic cardiomyopathy is based upon the idea that diabetes is the factor which leads to changes at the cellular level, resulting into various structural abnormalities as outlined above. Diabetic cardiomyopathy (DCM) leads to cardiac dysfunction and coronary artery disease and is the most common form of cardiac manifestation in diabetes mellitus (Fonarow and Srikanthan, 2006). However, non-ischemic heart failure is also an important cause of morbidity and mortality in diabetic

patients. Early pathological features of DCM include non-specific interstitial changes within preserved monocytes which progress to more marked interstitial and perivascular fibrosis, with deposition of periodic acid Sciff-positive material, myocyte hypertrophy, microvascular alterations (thickening of basement membrane and micro-aneurysms), ventricular dilatation and dystolic dysfunction with either decreased or maintained systolic function (Fonarow and Srikanthan, 2006), (Marwick, 2006). Metabolic and hormonal factors, autonomic neuropathy and, microangiopathic alterations are the main ethiopathologic factors. The most important mechanisms of diabetic cardiomyopathy are metabolic disturbances (depletion of glucose transporter 4, increased free fatty acids, carnitine deficiency, changes in calcium homeostasis), myocardial fibrosis (association with increases in angiotensin II, IGF-I, and inflammatory cytokines), small vessel disease (microangiopathy, impaired coronary flow reserve, and endothelial dysfunction), cardiac autonomic neuropathy (denervation and alterations in myocardial catecholamine levels), and insulin resistance (hyperinsulinemia and reduced insulin sensitivity) (Fang *et al.,* 2004). It is shown that diabetes is associated with a cardiomyopathy, independent of comorbid conditions, and that metabolic disturbances, myocardial fibrosis, small vessel disease, cardiac autonomic neuropathy, and insulin resistance may all contribute to the development of diabetic heart disease. In summary, various pathogenic factors of diabetes most likely induce ROS that in turn causes the endoplasmic reticulum stress and associated cell death. Cardiac cell death will initiate the cardiac inflammation and remodeling and eventually cardiac dysfunction, that is, diabetic cardiomyopathy. The pathogenic factors of diabetes include hyperglycemia, hyperlipidemia, and Angiotensin II and so on.

Molecular basis for diabetic cardiomyopathy

Hyperglycemia, hyperlipidemia and increased ROS induce alterations in downstream transcription factors which result in changes in gene expression, myocardial substrate utilization, myocyte growth, endothelial function, and myocardial compliance. Hyperglycemia may mediate its damaging effects through a series of secondary transducers. One of the principle abnormalities is the excess generation of AGEs, which deactivate NO and impair coronary vasodilation. Sustained hyperglycaemia causes excess formation of mitochondrial ROS, which affects transcription, leading to contractile dysfunction (Rosen *et al.,* 1998). An increase in ROS decreases NO levels, which leads to myocardial inflammation and endothelial dysfunction via poly ADP-ribose polymerase (PARP), inhibition of which has been shown to reverse diabetic endothelial dysfunction (Soriano *et al.,* 2001). The severity of diastolic dysfunction correlates with HbA1c (glycated haemoglobin) levels and the likely cause is AGE induced formation of ROS, resulting in myocardial collagen deposition and fibrosis. Enhanced expression of metallothionein, a potent antioxidant, limits the development of diabetic cardiomyopathy and, by breaking collagen cross-links improves diastolic function (Candido *et al.,* 2003). Recently, the process of advanced glycation has been related directly to alterations in myocardial calcium handling and hence contractility (Lee and East, 2001). Sarcoplasmic/ endoplasmic-reticulum Ca^{2+}-ATPase 2a (SERCA2a) is responsible for replenishing intracellular calcium stores following release; this results in the termination of contraction thus playing an integral part in cardiac relaxation. SERCA2a is a P-type ATPase that utilizes energy from the hydrolysis of the terminal phosphate bond of ATP to pump calcium against its electrochemical gradient (Lee and East, 2001). The turnover rate of SERC2a is low, which makes it susceptible to post-translational modification, especially in a chronic condition like diabetes. Thus advanced glycation of SERCA2a has been shown to lead to a decrease in its activity and a prolongation of cardiac relaxation (Bidasee *et al.,* 2004). Independent of the effects of hyperlipidaemia on coronary artery endothelial function, the increased dependence of diabetic myocardium on fatty acid supply results in several major cellular metabolic perturbations. Thus there is increased *β*-oxidation and mitochondrial accumulation of long-chain acyl carnitines, leading to uncoupling of oxidative phosphorylation (Stanley *et al.,* 1997). Enhanced fatty acid oxidation decreases glucose and pyruvate utilization by inhibiting pyruvate dehydrogenase. The net result is an excess of glycolytic intermediates and increased synthesis of ceramide (a toxic lipid compound) leading to apoptosis, which can be prevented by the peroxisome-proliferator-activated receptor (PPAR- *α* and *γ)* agonist, troglitazone (Zhou *et al.,* 2000). Thus impaired glycolysis, pyruvate oxidation, lactate uptake and a greater dependence on fatty acids as a source of acetyl CoA, leads to a perturbation of myocardial bioenergetics and contraction/relaxation coupling (Rodrigues *et al.,* 1998). Classic pharmacotherapy is aimed at restoring the balance between ATP synthesis and breakdown by increasing oxygen delivery (i.e. long-acting nitrates or Ca^{2+} channel antagonist) or by decreasing cardiac power by reducing blood pressure and heart rate (Ca^{2+} channel antagonist or *β*-blocker). An alternative agent which may readdress the altered bioenergetics of diabetic cardiomyopathy is trimetazidine [1-(2,3,4-trimethoxibenzyl)-piperazine], as it partially inhibits myocardial fatty acid oxidation, increases carbohydrate oxidation and reduces lactate production (Stanley and Marzilli, 2003). It has been found that in Type II diabetic patients with ischaemic cardiomyopathy randomized to receive either trimetazidine or placebo for 6 months, a beneficial effect was observed on LV volumes and LV ejection fraction (Rosano *et al.,* 2003).

Role of Metabolic and Hormonal factors

The overall myocardial response to the diabetic milieu is a reduction in glucose uptake and oxidation as well as, an increase in fatty acid uptake and oxidation (Giles and Sander, 2004). It has been proposed that in people with DM, myocytes cannot metabolize pyruvate in the normal manner and in case of energy deficit, they sustain reperfusion injuries (Giles and Sander, 2004). Accumulation of pyruvate inhibits glycolysis and hence excess glucose is converted to glycogen. Since, ATP derived from glycolysis is used by the myocyte for calcium reuptake in sarcoplasmic reticulum, reduced glycolysis results in impaired myocyte relaxation. In earlier stages of DM, glucose metabolism is regulated by compensatory hyperglycemia. At the same time, the myocyte responds to the increased fatty acid levels resulting from insulin resistance and, increased systemic lipolysis by upregulating mitochondrial β-oxidation. Exacerbation of chronic hyperglycemia induces lipid esterification and intracellular triglyceride accumulation which leads to ceramide production, oxidative stress, apoptosis and

decreased myocardial function (Cai and Kang, 2003). In addition, hyperglycemia increases the oxidative stress and glycosylation processes. Glycosylation of p53 protein leads to activation of angiotensin II synthesis and, necrosis (Farhangkhoee *et al.,* 2006). Hyperglycemia also activates the protein kinase Cβ11 pathway again promoting myocardial necrosis and fibrosis (Farhangkhoee *et al.,* 2006).

Cardiac autonomic neuropathy (CAN)

Cardiac autonomic neuropathy (CAN) have been associated with myocardial dysfunction and the development of CAN reduces the survival rate in DM patients by 44% to 85% (Vinik *et al.,* 2003). Other studies found that in coronary resistance vessels, CAN was associated with an impaired vasodilator response to increased sympathetic stimulation so that 20% of DM patients with no ischemic heart disease suffers from abnormal diastolic filling related to severity of CAN (Vinik *et al.,* 2003). Ventricular filling abnormalities are also prominent in patients with CAN. Catecholamines regulate the contractility of cardiac myocytes by acting on sarcoplasmic reticulum calcium uptake and, under conditions of β- adrenergic receptor stimulation cardiac performance is enhanced (Kogler and Ruegg, 1997). These effects are mediated by cAMP-dependent phosphorylation of proteins located in the sarcolemma, the membrane of the sarcoplasmic reticulum, and in the myofibrils of the cardiomyocytes. In DM, the cardiac-β adrenergic system may be enhanced, which can induce myocyte hypertrophy, interstitial fibrosis and reduced contractile function, accompanied by myocyte apoptosis (Marwick, 2006). α- adrenergic stimulation, which has anti-apoptotic effects, seems to be decreased in DM (Lee and East, 2001). CAN may contribute to impaired diastolic function and is associated with an increased cardiovascular risk in diabetic patients. Diabetic autonomic neuropathy is associated with an impaired vasodilator response of coronary resistance vessels to increased sympathetic stimulation (DiCarli *et al.,* 1999).

Twenty one percent of patients with Type I diabetes without ischemic heart disease have abnormal diastolic filling which is associated with the severity of CAN (Kahn *et al.,*. 1986). Similarly ventricular filling abnormalities are most prominent in patients with autonomic neuropathy (Airaksinen *et al.,* 1989). Studies have shown a correlation between myocardial sympathetic innervation derived from scintigraphy and the *E*/*A* ratio (ratio of early to late peak mitral filling wave velocities) in Doppler echocardiography, providing evidence that an abnormal sympathetic innervation of the heart may contribute to a disturbance in LV filling. Sympathetic dysfunction has been related to both systolic and diastolic dysfunction in Type II diabetes (Annonu *et al.,* 2001). An abnormal systolic blood pressure response to standing was correlated significantly with a reduced mitral *E*/*A* ratio (Fig. 4). Studies also reflect an association between parasympathetic and cardiac dysfunction as evidenced by the association between significantly lower mean heart rate variation during deep breathing, and abnormal diastolic peak filling rate in diabetic patients (Uusitupa *et al.,* 1988). The mitral *E*/*A* ratio have been shown to be significantly reduced in patients with autonomic neuropathy and a significant correlation was observed between the *E*/*A* ratio and autonomic neuropathy (Monteagudo et al. 2000).

Cardiac Allograft Vasculopathy (CAV)

CAV is a CVD that occurs in heart transplant recipients (Valantine, 2004). It is a rapidly progressive form of atherosclerosis characterized by intimal proliferation, and luminal stenosis of epicardial branches, occlusion of small arteries, and MI with the progression of the disease. Both immunologic and non-immunologic mechanisms are involved in the pathogenesis of CAV. The initiating event is subclinical endothelial cell injury in the coronary graft, caused by

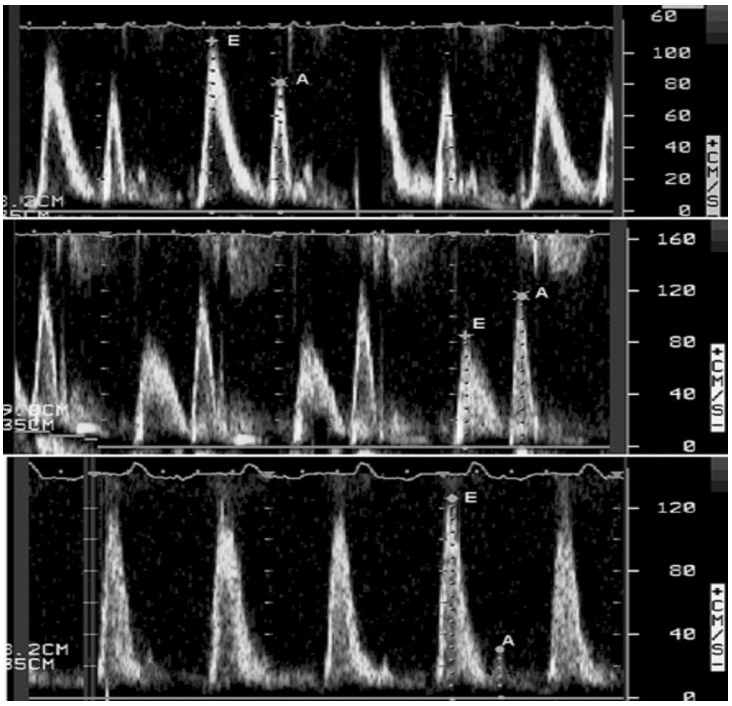

Fig.4. Trans-mitral valve spectral Doppler flow pattern in a normal subject (upper panel), in a patient with mild diastolic dysfunction (abnormal relaxation; middle panel), and in a patient with severe (restrictive) diastolic dysfunction (lower panel) In the upper panel, the E/A wave ratio is approx. 1.5 to 1.0, and in the middle panel the E/A wave ratio is <1.0. In the lower panel, the E/A wave ratio is abnormally high and A wave velocity is very low. (Source: Uusitupa *et al.*, 1988).

ischemia-reperfusion damage or host versus graft immune response. This leads to a cascade of destructive events involving cytokines, inflammatory mediators, complement activation and leukocyte adhesion molecules (Ramzy *et al.,* 2005). These changes produce inflammation, thrombosis, SMC proliferation and vasoconstriction. The non-immunologic factors leading to CAV are DM, both pre existing and new onset after transplantation (caused by immunosuppression), and metabolic abnormalities associated with insulin resistance. These factors play a vital role in accelerating vascular damage through various mechanisms as involved in CAD in non-transplant cases (Valantine, 2004). The histological changes that characterize CAV are not uniform. Pathological examination of coronary arteries from human cardiac allografts has shown a broad spectrum of abnormalities, ranging from concentric fibrous intimal thickening to complicated atherosclerotic plaques that bear a close resemblance to spontaneous atherosclerosis (Pucci *et al.,* 1990). It has been demonstrated that early intimal proliferation progresses with time and with subsequent increases in lipid deposits and, calcification of the coronary vessel (Billingham, 1992). Atheromas formation and diffusion of intracellular and, extracellular, accumulation of lipids in both intimal and medial walls are frequent occurrences (McManus *et al.,* 1995).

The internal elastic lamina remains almost intact except for small breaks (Billingham, 1995). Early after transplantation, diffused fibrous intimal thickening or a vasculitis predominates. Late after transplantation, focal atherosclerotic plaques, intimal thickening, or a mixture of both is found. The smaller branches are often occluded before the larger epicardial arteries, resulting in small, stellate infarcts (Neish *et al.,* 1992). Despite exuberant intimal proliferation, the media of the vessel is rarely thickened and sometimes becomes narrower than in normal conditions (Billingham, 1995). The cellular infiltrate of intimal proliferative lesions consists of modified smooth muscle cells, macrophages/monocytes, and T lymphocytes (Billingham, 1995). Although the exact pathogenesis of CAV remains to be established, several lines of data suggest that it is primarily an immune-mediated disease (Treasure and Alexander, 1995). Limitation of the proliferative vascular disease to the allograft arterial and venous tree, the often diffuse nature of allograft vascular involvement, the development of CAV in cardiac allografts of animal models with some histocompatibility mismatch, and the lack of development in isografts support the immunologic hypothesis of CAV development. Studies suggest that immunologic mechanisms operating in a milieu of nonimmunologic risk factors constitute the principal stimuli that result in progressive myointimal hyperplasia (Treasure and Alexander, 1995). The initial event of CAV is probably a subclinical graft coronary endothelial injury. The endothelial cell is the major determinant of vessel wall function. It normally inhibits thrombus formation and leukocyte adhesion, regulates vasomotor function, and inhibits vascular smooth muscle cell proliferation. Damage to the endothelium could alter any or all of these functions, predisposing the artery to inflammation, thrombosis, vasoconstriction, and vascular smooth muscle cell growth (Treasure and Alexander, 1995). After human cardiac transplantation, humoral or more important cellular responses to HLA antigens and vascular endothelial cell antigens are potential sources of endothelial damage. CD4 lymphocyte–induced upregulation of MHC class II antigens on endothelial cells (subsequent to MHC-I antigen detection by CD8 lymphocytes) elicits a cellular immune response (Libby *et al.,* 1992).

The role of MHC donor-recipient differences in the pathogenesis of CAV has not yet been completely elucidated. The ability to produce CAV in animals transplanted with an MHC-identical graft and, more recently, to document the occurrence of allograft rejection in genetically engineered animals lacking MHC genes should spur further investigations of other allograft-specific antigens, distinct from those of the MHC, which may play an important role in the development of CAV. Irrespective of the initial specific immune-mediated injury, the cascade of events that follows appears to be a physiologically nonspecific inflammatory response (Duquesnoy and Demetris, 1995). It is important to note that activated lymphocytes secrete interferon-γ, which stimulates production of ICAM-1 (Hayry *et al.,* 1989). The involvement of adhesion molecules plays a crucial role in regulating the interaction of inflammatory cells with cells in the vascular wall because the adherence of leukocytes to vascular endothelium is a prerequisite for transmigration. Expression of vascular adhesion molecules (VCAM-1, ICAM-1, and ELAM-1) on endothelial cells and medial smooth muscle cells in cardiac transplant patients has been observed and, early ICAM-1 expression could be correlated to early development of angiographically visible CAV (Labarrere *et al.,* 1995). The intercellular network, via macrophages, T lymphocytes, endothelial cells, and smooth muscle cells, generates a variety of stimulatory cytokines (IL-1, IL-2, IL-6, and tumor necrosis factor-α) and growth factors (PDGF, FGF, EGF, TGF-β etc) that promote the development of the chronic allograft lesion (Duquesnoy and Demetris, 1995).

Thus, at the end of the "endothelial injury process," chronic inflammation elicits a repair response that causes the production of a connective tissue matrix and the migration and proliferation of vascular wall smooth muscle cells that compromise the vascular lumen (Rabinoviteh *et al.,* 1995). Recently apoptosis, a genetically encoded cell-death program, has been proposed to be involved in human coronary atherosclerosis, especially during restenosis (Isner *et al.,* 1995). Pathological evidence has been demonstrated for Fas-mediated apoptotic cytotoxicity in CAV (Dong *et al.,* 1996). Nitric oxide has the capacity to influence apoptosis and is induced during cardiac allograft rejection. Moreover, induction of inducible nitric oxide synthase (iNOS) was associated with CAV in a rat cardiac allograft transplant model (Russell *et al.,* 1995). Conceivably, there is a possible link between nitric oxide–mediated apoptosis in smooth muscle cells and transplant intimal thickening. However, the development of clinically evident CAV depends on the interplay between the lesion-formation responses of the allograft to injury versus the adaptive process of vascular remodeling (Gibbons, 1995). The expansion of the intimal lesion eventually overcomes the capacity of the vessel to undergo compensatory enlargement remodeling such that the plaque creates a vessel stenosis. Indeed, the pathogenesis of clinically relevant CAV may be due in part to the possible lack of compensatory dilation (enlargement) of the vessel wall over time.

Conclusion

Diabetic heart disease is caused by complex interactions that result from various mechanisms; associated with hyperglycemia, dyslipidemia, hypertension and possibly insulin resistance. All these lead to increased oxidative stress and enhanced glycosylation of several humoral and vessel wall proteins, which cause endothelial damage, and structural changes in coronary arteries. The damaged endothelial cells become a source of ROS and RNS which along with several other factors leads to proatherosclerotic processes. Some of these mechanisms progresses into the development of diabetic cardiomyopathy, in which myocyte substrate utilization and neural influences play a major role. Further investigations are needed to elucidate the beneficial role of oral anti-diabetic agents in case of diabetic heart disease. Also, early initiation of therapies aimed at reducing inflammation and oxidative stress may be beneficial in reducing CVD in diabetes. Casual anti-oxidant therapies with compounds that acts as intracellular scavengers or as anti-oxidant enzyme can modulate ROS-sensitive signaling pathways may represent a potential avenue of therapy in diabetics to prevent the onset and progression of cardiovascular complications.

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