Review

Cardiovascular disease in diabetes: An enigma of dyslipidemia, thrombosis and inflammation

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The purpose of this review is to explain cardiovascular problems and different risk factors that lead to cardiovascular disease (CVD). Moreover, the possible mechanisms that lead to accelerated atherogenesis in DM are also discussed. According to ATP III guidelines Diabetes Mellitus is considered to be a coronary heart disease (CHD) equivalent. From cardiovascular medicine aspect, it may be appropriate to say that "diabetes is a cardiovascular disease." Diabetics have a very high prevalence of cardiovascular disease morbidity and mortality. The conditions of insulin resistance, impaired glucose tolerance (IGT) and overt diabetes, appear to be associated with an increased risk of CVD to a variable degree. One question which still remains unresolved is whether hyperglycemia or insulin resistance leads to CVD in DM. It seems that both DM and CVD originate from a common soil. Still the pathophysiology of CVD is poorly understood and many new concepts have emerged the new enigma of dyslipidemia, thrombosis and inflammation has emerged. Since this concept has emerged, many new markers of cardiovascular risk prediction have come up and prove to be important clinically because infarction often occurs among diabetics without traditional risk factors. This has lead to intense research in novel cardiovascular risk markers which will help in assessment and identification of persons who are prone to premature atherothrombosis. Still the relative contribution of each of these markers to CVD risk is beyond understanding. In coming future we may have excellent risk markers in our routine clinical practice which would allow a better prediction of patients at high risk for designing more effective strategies for primary and secondary prevention. The research areas that need to be focused on are metabolic stress, oxidative stress, endothelial dysfunction, inflammation and thrombosis/fibrinolysis. Studies are needed in each of these areas relevant to basic and clinical sciences to elucidate the complex interaction of hyperglycemia, dyslipidemia and inflammation at all stages of CVD.

Keywords: Diabetes Mellitus, Cardiovascular disease, Risk Factors, Dyslipidemia, Thrombosis, Inflammation

INTRODUCTION

Thus, diabetes must take its place along with the other major risk factors as important causes of cardiovascular disease (CVD) (National Cholesterol Education Program (NCEP) 2002). The pathophysiologic pathways of CHD in DM are a complex interplay of dyslipidemia, inflammation and a prothrombotic state (Rana et al., 2007; Roos et al., 2012). In this review, we are explaining cardiovascular problems and different risk factors that lead to cardiovascular disease (CVD) in DM. Moreover, the possible mechanisms that lead to accelerated atherogenesis in DM are also discussed.

Burden of disease

World Health Organization reported in 1998 that between 1995 and 2025 the number of the adult population affected by diabetes mellitus in the developing countries is expected to increase by 170% from 84 to 228 million (Global burden of diabetes 2005). In a recent report, the total number of people with diabetes is projected to rise from 171 million in 2000 to 366 million in 2030 (Wild et al., 2004).

In Saudi Arabia prevalence of DM is 23.7% with males
having higher prevalence than females. Diabetes mellitus is more prevalent among Saudis living in urban areas as compared to rural areas (Al-Nozha et al., 2004). The prevalence of diabetes and glucose intolerance is also extremely high among adult Arab Americans (32.2 %) in Michigan and represents a major clinical and public health problem (Jaber et al., 2003). Both excess body fat and physical inactivity predispose to type 2 diabetes. Several ethnic groups are particularly susceptible to type 2 diabetes for example, Hispanics, Native Americans, and Asians (especially South Asians) (Lindeman et al., 1998).

**Cardiovascular diseases in diabetes mellitus**

The conditions, i.e., impaired fasting glucose (IFG), impaired glucose tolerance (IGT), and overt diabetes, appear to be associated with an increased risk of CVD to a variable degree. Recently, IFG and IGT have been officially termed “pre-diabetes.” Both categories, IFG and IGT, are risk factors for future diabetes and CVD (American Diabetes Association 2006; Stern 1995). One of the question which still remains unresolved is whether hyperglycemia or insulin resistance lead to CVD in DM. It seems that both DM and CVD originate from a common soil as discussed below. Diabetic patients may have the following cardiovascular problems.

Diabetic patients have both microvascular and macrovascular complications. Microvascular complications start with the onset of DM while macrovascular complications are present long before overt symptoms of DM start. Intervention at this stage would be really useful. Earlier development of large vessel atherosclerosis suggests that rather than atherosclerosis being a complication of diabetes, both conditions have common genetic and environmental antecedents, i.e., they spring from a “common soil” (Stern 1995). Patients with type 2 diabetes mellitus have a two to threefold increased incidence of diseases related to atherosclerosis (Garcia et al., 1974) and those who present in their 40s and 50s have a twofold increased total mortality (PanzramG 1987).

In United Kingdom the incidence of macrovascular complications in patients with type 2 diabetes mellitus is twice that of microvascular problems (United Kingdom Prospective Diabetes Study Group 1996).

The greater mortality in patients with type 2 diabetes mellitus than in the general population cannot be explained only by the presence of the three classic risk factors for coronary artery disease which are smoking, hypertension, and elevated plasma cholesterol levels (Stamler et al., 1993).

Both type 1 diabetes and type 2 diabetes are independent risk factors for CVD (Wilson et al., 1998; Wilson 1998; McGill HC and McMahan 1998). Moreover, myocardial ischemia due to coronary atherosclerosis is commonly asymptomatic in patients with diabetes (Wingard et al., 1993). As a result, multivessel atherosclerosis often is present before ischemic symptoms occur and before treatment is instituted. A delayed recognition of various forms of CVD undoubtedly worsens the prognosis for survival for many diabetic patients.

**Diabetic cardiomyopathy**

The poor prognosis in patients with both, diabetes and ischemic heart disease seems to be due to diabetic cardiomyopathy, which is an enhanced myocardial dysfunction leading to accelerated heart failure (Mahgoub and Abd-Elfattah 1998). Several factors probably underlie diabetic cardiomyopathy for example severe coronary atherosclerosis, prolonged hypertension, chronic hyperglycemia, microvascular disease, glycosylation of myocardial proteins, and autonomic neuropathy. Improved glycemic control, better control of hypertension, and prevention of atherosclerosis with cholesterol-lowering therapy may prevent or mitigate diabetic cardiomyopathy.

**Cardiovascular risk factors in diabetes mellitus**

Identification of risk factors is the first major step for developing a plan for risk reduction in persons with diabetes. Following are different risk factors which are involved in the development of CVD.

**Major risk factors**

The major risk factors which are related to CVD are elevated blood pressure, abnormal serum lipids & lipoproteins, hyperglycemia and cigarette smoking.

**Hypertension**

Hypertension is a well-established major risk factor for CVD (Wilson 1998). It increases risk for both CHD and stroke and contributes to diabetic nephropathy (Nelson et al., 1993). (Edelson and Sowers 1993; Sowers 1990; Reaven et al., 1996). When hypertension coexists with overt diabetes, which it commonly does, the risk for CVD, including nephropathy, is raised two fold. Improved control of blood pressure in diabetic patients has been shown to be effective in reducing the risk of cardiovascular complications (Hansson et al., 1998),
(Hansson et al., 1998; Tuomilehto et al., 1999).

**Dyslipidemia**

**Diabetic Dyslipidemia**

Atherogenic dyslipidemia is characterized by lipoprotein abnormalities: elevated very-low-density lipoproteins (VLDL), small dense LDL particles, and low high-density-lipoprotein cholesterol. The lipid triad occurs frequently in patients with premature CHD and appears to be an atherogenic lipoprotein phenotype independent of elevated LDL cholesterol (LDL-C) (Austin et al., 1990; Grundy 1997). Most patients with atherogenic dyslipidemia are insulin resistant (Grundy 1998; Mostaza et al., 1998). Atherogenic dyslipidemia in diabetic patients often is called diabetic dyslipidemia. Many patients with atherogenic dyslipidemia also have an elevated serum total apolipoprotein B (Lamarche et al., 1997). Although there is evidence that each component of the lipid triad low HDL, LDL, and some other remnant lipoproteins is individually atherogenic, yet it is not possible to determine the relative quantitative contribution of each component. For this reason, the lipid triad is viewed as a whole a “risk factor.”

**LDL Cholesterol in Diabetic Patients**

An elevated concentration of serum LDL cholesterol is a major risk factor for CHD (Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults 1994). In fact, some elevation of LDL cholesterol appears to be necessary for the initiation and progression of atherosclerosis. In populations having very low LDL cholesterol levels, clinical CHD is relatively rare, even when other risk factors hypertension, cigarette smoking, and diabetes are common (Grundy et al., 1990). In contrast, severe elevations in LDL cholesterol can produce full-blown atherosclerosis and premature CHD in the complete absence of other risk factors (Goldstein et al., 1985).

Most patients with diabetes do not have marked elevations of LDL cholesterol, but these patients do carry high enough levels to that may lead to atherosclerosis (National Center for Health Statistics 1981). The Scandinavian Simvastatin Survival Study (Pyorala et al., 1997) the Cholesterol and Recurrent Events (CARE) trial, (Goldberg et al., 1998) and the Long-Term Intervention with Pravastatin in Ischemic Disease (The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group 1998.

Syndrome X, the association of raised concentrations of glucose, insulin, and triglyceride, decreased concentrations of high density lipoprotein cholesterol, and increased blood pressure, describes a combination of previously reported risk factors for coronary artery disease (Reaven 1988). Increased concentrations of low density lipoprotein cholesterol may be more pathogenic in patients with type 2 diabetes mellitus than in non-diabetic patients because of the presence of small dense low density lipoprotein cholesterol particles (Austin et al., 1988) and oxidation of glycated low density lipoprotein cholesterol (Kawamura et al., 1994).

The 1.57 increased risk for an increment of 1 mmol/l in low density lipoprotein cholesterol concentration equates to a 36% risk reduction for a decrement of 1 mmol/l, similar to the 31% risk reduction achieved with a 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor in men with hypercholesterolaemia (Shepherd et al., 1995).

**Metabolic Syndrome**

Most patients with type 2 diabetes have insulin resistance. Indeed, insulin resistance seems to predispose to both CVD and diabetes (Reaven 1996). Research suggests that insulin resistance is a multisystem disorder that induces multiple metabolic alterations. Factors that contribute to insulin resistance are genetic tendency (Warram et al., 1990), obesity (Bogardus et al., 1984) physical inactivity (Perseghin et al., 1996) and advancing age (Rowe et al., 1983). Patients with insulin resistance often have abdominal obesity (Abate et al., 1995). Metabolic risk factors that occur commonly in patients with insulin resistance are atherogenic dyslipidemia, hypertension, glucose intolerance, and a prothrombotic state.

**Hyperglycemia**

The relative risk for myocardial infarction seems to increase with any increase in glucose levels above the normal range (Balkau et al., 1998; Fuller et al., 1983). Fasting and postprandial glucose levels typically are normal for several years after onset of insulin resistance. During this period, pancreatic β-cells are able to increase insulin secretion in response to insulin resistance and thereby maintain normal plasma glucose levels. In some people, however, insulin secretion declines with aging, and elevated glucose concentrations appear. The first abnormality in plasma glucose in patients with insulin resistance is IFG (or impaired glucose tolerance) (The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus 1997). The presence of IFG usually accompanies long-standing insulin resistance. It is currently estimated that 13.4 million adults, 7.0% of the US population, have IFG (Diabetes Statistics. National Diabetes Information Clearinghouse 1999). Many prospective studies (Haffner 1997; Laakso and Lehto 1998) show that IFG (or impaired glucose tolerance) is a risk factor for CVD: the degree of independence as a risk factor, however, is uncertain, because IFG commonly
Predisposing Risk Factors

Several predisposing factors simultaneously affect the development of CVD and DM. These factors are obesity, physical inactivity, heredity, sex and advancing age. The mechanisms by which they predispose to chronic diseases are complex and often overlapping. Predisposing risk factors exacerbate the major risk factors (dyslipidemia, hypertension and hyperglycemia) and they may cause other pathways as well. To a large extent, both CVD and diabetes must be prevented through control of the predisposing risk factors but some factors can be controlled while others could not be controlled. Life style modification is the key component of the public health programs for prevention of CVD and diabetes mellitus. Prevention of obesity and promotion of physical activity remain on the top of list. Drug therapy may be required to control the metabolic risk factors. Effective drugs are currently available for treatment of hypertension and dyslipidemia (Grundy et al., 1999).

Emerging novel risk factors

According to National Cholesterol Education Program (NCEP) guidelines explain that although the major risk factors including LDL-C, are powerfully associated with the development of CHD, still their power to predict CHD is still limited. When major risk factors are present, they account for only about half of the variability in CHD risk. There are other risk factors which may add to the predictive power of the major risk factors or can be independent predictors by themselves (National Cholesterol Education Program (NCEP) 2002). The association between LDL-C levels and CVD is well accepted but yet a relatively high proportion of cases with CVD have LDL in the normal range (Lamarche et al., 1997). Myocardial infarction often occurs among diabetics without traditional risk factors. This has lead to intense research in "novel" cardiovascular risk markers which will help in assessment and identification of persons who are prone to premature atherothrombosis. In this regard, five promising markers of cardiovascular risk have been identified which include: lipoprotein(a), total plasma homocysteine, fibrinolytic capacity, fibrinogen, and high-sensitivity C-reactive protein (Acevedo et al., 2001). There is an independent association (Azzaruso et al., 2002).

Novel risk factors also include oxidative stress or endothelial dysfunction; psychosocial factors, such as environmental stress and responsiveness to stress; plasma insulin levels and markers of insulin resistance; and activation of the renin-angiotensin system, which is in part a function of polymorphisms in genes for components of the system, such as angiotensinogen and the angiotensin II type 1 receptor (Oparil and Oberman 1999). The association between microalbuminuria and peripheral markers of endothelial damage or dysfunction, such as von Willebrand factor, suggests that microalbuminuria may be a simple, cheap and easy index of endothelial abnormalities in cardiovascular disease (Lydakis and Lip 1998). To improve the accuracy of risk stratification non traditional risk factors should be easily measurable in the population and potentially modifiable. These risk factors are associated with subclinical or clinical cardiovascular events in large populations, included markers of lipoprotein and lipid metabolism, vitamin B12 metabolism, fibrinolysis, coagulation, inflammation, infection, endothelial dysfunction, rennin angiotensin system, and oxidative stress as risk factors. Atherosclerosis is a multifactorial condition and possibly
only a subset of factors are the main determinants of disease in a given patient. A better understanding of cardiovascular risk profile will help to target at primary and secondary levels of prevention. (Pahor et al., 1999). According to Frishman and colleagues risk markers of CVD are; (I) altered glucose metabolism, particularly insulin resistance (II) hyperlipidemia (III) elevated levels of lipoprotein(a) and homocysteine (IV) increased levels of molecules reflecting decreased fibrinolysis and increased activation of the coagulation cascade (V) elevations in cell adhesion molecules and other markers of endothelial function; and (VII) elevations in molecules associated with infection, inflammation, and vascular remodeling (Frischman 1998).

Evidence also links haemostatic variables to the future risk of myocardial infarction and stroke. So far, a variety of markers of a procoagulatory tendency e.g. elevated fibrinogen, coagulation factor VII, factor VIII and von Willebrand factor, platelet hyperaggregation, increased plasma levels of D-dimer, and decreased fibrinolytic capacity characterized by increased levels of t-PA concentrations have been identified (Schmidt et al., 1999). Changes in molecules associated with increased risk usually occur in clusters. This clustering suggests that effective treatment of one marker may have positive effects on multiple markers (Frischman 1998). Increased and decreased tissue plasminogen activator (tPA) activity could be considered a true component of the metabolic syndrome (MetS) associated with an increased risk of developing and fibrinolytic abnormalities (Al-Hamodi et al., 2011). Targeting the factors that led to the down regulation of PAI-1 in older patients with type 2 DM might offer an attractive strategy for reducing cardiovascular risk (McBane et al., 2010). Still the independent predictive power of these markers is not known and their assays are not standardized. This limits their use in routine clinical up till now.

Therefore, diabetes must take its place along with the other major risk factors as important cause of CVD. Hyperglycemia by itself does not raise risk to the level of a CHD risk equivalent. Instead, type 2 diabetes generally is accompanied by a constellation of metabolic risk factors that combine with hyperglycemia to impart a high risk. There are three reasons for CHD equivalency of diabetics. Firstly the absolute risk for first major coronary events for persons with type 2 diabetes in high-risk populations approximates that for recurrent events in non-diabetic persons with clinical CHD. Secondly type 2 diabetics have an increased case fatality rate with a myocardial infarction. Thirdly the overall prognosis for survival is much worse once diabetics develop CHD than it is for CHD patients without diabetes. Although persons with type 1 diabetes are clearly at increased risk for CHD, it is still not elucidated that type 1 diabetic subjects have a risk of CHD as high as age- and sex-matched non-diabetic subjects with pre-existing CHD (National Cholesterol Education Program (NCEP) 2002).

The concept of CHD risk equivalency is also debatable. Most diabetic individuals in Strong Heart Study had CHD risk equivalency according to ATP III guidelines, but only those with multiple risk factors had rates of CHD events equivalent to patients with established CHD. Therefore, it may be prudent to consider therapeutic goals for risk factors based on the entire risk factor profile, rather than just the presence of diabetes (Al-Hamodi et al., 2011) (Howard et al., 2006). The different categories of risk factors are summarized (National Cholesterol Education Program (NCEP) 2002); Smith et al., 2000).

**The changing concepts**

Atherosclerosis, which was formerly considered a disease of lipid storage only, involves an ongoing inflammatory response. Recent advances in basic science have established a fundamental role of inflammation in mediating all stages of this disease from initiation to progression and, ultimately leading to thrombosis also. Clinical studies have shown that this emerging biology of inflammation in atherosclerosis applies directly to human patients. Elevation in markers of inflammation predicts outcomes of patients with acute coronary syndromes, independently of myocardial damage. In addition, low-grade chronic inflammation, as indicated by levels of the inflammatory marker C-reactive protein, prospectively defines risk of atherosclerotic complications, thus adding to prognostic information provided by traditional risk factors. It is well known that dyslipidemia, prothrombosis and inflammation are ongoing processes in DM. However, their relationship is complex and it seems that through many unraveled mechanisms they cause CVD in DM. Figure 1.

**Pathogenesis of cardiovascular disease in diabetes**

The pathogenesis of CVD in diabetes is multifactorial and can be affected by metabolic and other factors. Under physiological conditions, the endothelial cells (ECs) layer acts as a barrier to separate circulating factors and cells from the arterial intima and media. It also serves as an anticoagulant and fibrinolytic surface producing tissue plasminogen activator, which counters the effects of procoagulant factors. Circulating factors (hyperglycemia, increased free fatty acids, altered lipoproteins, and derivatives of glycation and oxidation) and hypertension, all of which are common in diabetes, can damage ECs and cause their dysfunction. Lipoproteins, cross the endothelial barrier, where they can be retained by subendothelial matrix molecules such as collagen and proteoglycans (Vlassara et al., 1994) which are produced by ECs and smooth muscle cell (SMCs). Endothelial cells produce nitric oxide (NO), which is a vasodilator and restricts SMCs migration and proliferation. Both type 1...
Table 1. Categories of risk factors that lead to cardiovascular disease in diabetes mellitus.

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<thead>
<tr>
<th>Predisposing Risk Factors</th>
<th>Major risk factors</th>
<th>Novel risk factors</th>
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<tbody>
<tr>
<td>Obesity</td>
<td>Cigarette smoking, Hypertension</td>
<td>Hs-C-reactive protein</td>
</tr>
<tr>
<td>Physical inactivity</td>
<td>Abnormal serum lipids &amp; lipoproteins (LDL is the major cause of CHD)</td>
<td>Lipoprotein(a)</td>
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<tr>
<td>Sex</td>
<td>Hyperglycemia</td>
<td>Small LDL particles</td>
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<td>Advancing age</td>
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<td>HDL subspecies</td>
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<tr>
<td>Family history of premature CHD</td>
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<td>Apolipoproteins B &amp; A-I</td>
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<td>Psychosocial factors, such as</td>
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<td>Homocysteine,</td>
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<td>environmental stress and</td>
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<td>Microalbuminuria</td>
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<td>responsiveness to stress</td>
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<td>Thrombogenic/Hemostatic Factors</td>
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<td>Insulin resistance</td>
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<td>(Plasminogen activating inhibitor-1 and</td>
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<td>Oxidative stress or</td>
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<td>endothelial dysfunction</td>
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<td>Renin-angiotensin system</td>
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Figure 1. The complex relationship of dyslipidemia, inflammation and prothrombotic state in DM leading to CVD. All these processes occur under the umbrella of major and predisposing factors. The factors related with prothrombosis, inflammation and dyslipidemia have additive effects in pathogenesis of CVD as well as they affect each other. AGEs (Advanced Glycation End Products), IL-6 (Interleukin 6), CRP (C Reactive Protein), PAI-1 (Plasminogen Activator Inhibitor -1 and TFPI (Tissue factor pathway inhibitor).

and type 2 DM are associated with a reduced endothelium-dependent relaxation, although the response to exogenous NO-donors is often normal, suggesting a reduced bioavailability of NO. Insulin has been shown to activate endothelial NO and induce NO-dependent relaxation of blood vessels. Interestingly, diabetic subjects have reduced anti-oxidant capacity which favors oxidative stress leading to enhanced destruction of NO by O$_2^-$ in diabetes-induced vascular dysfunction (Naseem 2005). A dominant mechanism reducing the bioavailability of vascular NO relates to its rapid oxidative inactivation. In addition, there is evidence that persisting oxidative stress renders eNOS dysfunctional such that it does not produce NO any longer, but O$_2^-$ instead (Capellini et al., 2010; Pitocco et al., 2010). Blood components can be modified by oxidation and glycation (Bucala et al., 1994). Modified proteins and
Dysglycemia can alter EC and SMC gene expression, leading to increased production of procoagulants, adhesion molecules, chemotactic factors, and cytokines. This results in adhesion and penetration of circulating monocytes into the arterial intima, where they undergo differentiation and activation to macrophages. Lipids can accumulate intracellularly after uptake of modified lipoproteins (glycation, oxidation, and glycoxidation) by different scavenger receptors on macrophages and SMCs, as well as extracellularly by attaching to matrix molecules (Mazzone 2000). The resulting lesion is termed the fatty streak. Both ECs and macrophages produce cytokines and growth factors that permit SMCs to migrate from the media to the intima. In the intima, SMCs proliferate in response to several growth factors. These SMCs and the matrix molecules that they secrete form the fibrous cap, a hallmark of the advanced atherosclerotic plaque. Cell death occurs after exposure of cells to glucose, free fatty acids (FFAs), glycoxidation products, and modified lipoproteins in the milieu of the arterial intima. The presence of a large lipid core, necrotic tissue, macrophages and a thin fibrous cap predisposes to plaque rupture (Falk et al., 1995). Conversely, a relative absence of lipid and macrophages and the presence of a thick fibrous cap renders a plaque stable. Thrombosis results from an imbalance between coagulation and fibrinolysis. Plaque rupture and hemorrhage can occur as a result of proteases secreted by vascular cells and from hemodynamic stress, leading to disruption of the fibrous cap (Galil et al., 1994). Plaque rupture and thrombosis often underlie clinical events such as acute coronary syndromes, including myocardial infarction. Ruptures also can heal, resulting in complex and sometimes stable plaques.

All of these processes can be potentiated by diabetes. Diabetes can also affect cardiac function independently of coronary artery atherosclerosis. The processes by which cardiac dysfunction might occur include endothelial dysfunction in the microcirculation, reduced cardiac compliance, microangiopathy, disturbed sympathetic function, impaired calcium cycling, limited myocardial glycolytic oxidative metabolism, and diastolic dysfunction (Mahgoub et al., 1998). The pathophysiology underlying diabetic cardiomyopathy needs further investigations.

The hyperglycemia associated with diabetes can lead to modification of macromolecules, for example, by forming advanced glycation end products (AGEs). By binding surface receptors such as RAGE (receptor for AGE), these AGE-modified proteins can augment the production of proinflammatory cytokines and other inflammatory pathways in vascular endothelial cells. Beyond hyperglycemia, the diabetic state itself promotes oxidative stress mediated by reactive oxygen species and carbonyl groups (Baynes and Thorpe 1999). Endothelial dysfunction, associated with oxidative stress in DM, predicts future cardiovascular disease (Ceriello and Motz 2004). In DM, protein kinase B (PKB/Akt) and atypical protein kinase C (aPKC) activation are diminished in muscle, and hepatic Akt activation is diminished, hepatic aPKC activation is conserved. Imbalance between muscle and hepatic aPKC activation by insulin results from differential downregulation of insulin receptor substrates that control phosphatidylinositol-3-kinase. Conserved activation of hepatic aPKC in hyperinsulinemia states of T2DM, obesity and MetSyn is problematic, as excessive activation of aPKC-dependent lipogenic, gluconeogenic and proinflammatory pathways may increase cardiovascular risk markers (Farese and Sajan 2012; Farese et al., 2005).

The three conditions of dyslipidemia, inflammatory state and prothrombotic tendency all occur in DM. Still the exact mechanisms of metabolic stress in atherosclerosis are not known. Inflammatory processes are important contributors in the pathogenesis of CVD, but the importance of inflammatory processes specifically in diabetes is unclear. The relative contribution of all these processes to CVD is uncertain at present. The mechanisms leading to all these changes are not well understood. It is not clear, however, whether these effects were due to the increase in plasma glucose or the accompanying hyperinsulinemia (Eckel et al., 2002). This complex interaction has been explained in figure 1. It has been reported that an increased release of adipocytes block insulin signal transduction pathway, release inflammatorycytokines, induce endothelial dysfunction. Thus, dyslipidemia, associated with high levels of LDL specially oxidized forms, triglycerides and low concentrations contribute to a proinflammatory state. Inflammation, which is the key pathogenic component of atherosclerosis, promotes thrombosis, a process that underlies acute coronary events and strokes. Tissue factor, a potent trigger of the coagulation cascade, is increased in diabetes with poor glycemic control (Meerarani et al., 2006; Holvoet 2008). Therefore, although many studies report that using statins can diminish atherosclerosis in diabetic patients and lower high sensitivity c reactive protein levels. However, anti-inflammatory drugs could not provide a perfect prevention because of the complex interactions of other pathophysiological links (Pyorala et al., 1997; Goldberg et al., 1998; The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group 1998).

**Future prospects and suggestions**

Type 2 diabetes is the end product of years of metabolic stress accompanying a state of insulin resistance. It seems that in patients with insulin resistance, the "clock starts ticking" for acceleration of atherogenesis long before the onset of hyperglycemia. Thus, early detection of the risk factors associated with the metabolic syndrome is needed for institution of appropriate primary prevention.
measures in patients at risk for diabetes (Stern 1995). The predominant risk factor for CVD in diabetics is duration of disease. Nonetheless, smoking, hypertension, renal disease and dyslipidemia remain important. Effective treatment of hyperglycemia reduces microvascular complications. It also may reduce risk for macrovascular disease. Modification of other CVD risk factors almost certainly will reduce risk. In primary prevention goals for smoking cessation, blood pressure control, physical activity and weight management are the same as for nondiabetic patients. However, more aggressive management of cholesterol and other lipids is indicated for diabetic patients.

For a better understanding of risk assessment and the pathophysiological mechanism that lead to CVD in diabetes the areas that need to be focused are metabolic/oxidative stress (hyperglycemia, AGEs and dyslipidemias, endothelial dysfunction, inflammation and thrombosis/fibrinolysis). Studies are needed to elucidate the exact mechanisms and potential benefits of correcting hyperglycemia, glycoxidation, AGEs and lipoprotein abnormalities. Moreover, signaling pathways for endothelial dysfunction due to hyperglycemia, free fatty acids and AGEs are needed to be explored. The specific role of inflammation in DM needs further clarification. Studies are needed in each of these areas relevant to basic science and clinical science to elucidate the complex interaction of hyperglycemia, dyslipidemia and inflammation (Eckel et al., 2002).

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