Cardiovascular Disease in Type 2 Diabetics: Epidemiology, Risk Factors and Therapeutic Modalities

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Abstract

Macrovascular complications associated with chronic hyperglycemia in type 2 diabetes mellitus is a major global health problem that is currently on the rise. Accelerated cardiovascular and cerebrovascular atherosclerosis is the major cause of mortality in patients with type 2 diabetes. Many of the risk factors for cardiovascular disease are operative or even exacerbated in diabetic patients, including hypercholesterolemia, hypertriglyceridemia, hypertension, central obesity, and smoking. Other diabetes-specific factors, such as increased levels of plasminogen activator 1 and fibrinogen, chronic inflammation, genetic susceptibility, and accelerated glycosylation end-products-mediated vascular damage, are thought to play a role in the development of CVD among patients with type 2 diabetes. Further studies will hopefully elucidate the clinical relevance of such factors. In addition, recent studies indicate that hyperglycemia is an important and independent risk factor for CVD. Increased risk of CVD is directly related to elevated 1 and 2 hour post-prandial blood glucose averages, as well as to fasting hyperglycemia. Thus, specific treatment regimens designed to reduce the development rate of cardiovascular complications in patients with type 2 diabetes must consider the impact of risk factors and their control, as well as the need for optimal metabolic and glycemic control.

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Type 2 (non-insulin-dependent) diabetes mellitus is one of the most serious public health problems facing both developed and developing countries. The incidence of type 2 diabetes is reaching near-epidemic proportions as a result of changing socioeconomic conditions that contribute to increased nutritional intake and a sedentary lifestyle [1]. The severe long-term complications associated with chronic hyperglycemia complicate the course of type 2 diabetes and impact heavily on the diabetic patient's quality of life. Of all the long-term complications of type 2 diabetes, cardiovascular disease is related to the most serious outcomes in terms of morbidity and mortality [2].

Diabetes mellitus and CVD share several important characteristics. The incidence of both conditions increases with age; both are associated with an adverse lipid profile, obesity and a sedentary lifestyle; and the risk of both can be reduced by lifestyle modifications of common risk factors. Diabetes is also a potent independent risk factor for CVD. Cross-section epidemiologic studies have consistently shown an association between diabetes and the prevalence of CVD [3].

This paper provides an up-to-date review of the literature on diabetes and its relationship to cardiovascular complications, with an emphasis on findings from epidemiologic, pathophysiologic, and treatment-based studies. Special attention will be given to risk factors associated with diabetic cardiovascular disease and the contribution of an altered metabolic environment to the severity of diabetic cardiovascular disease.

Epidemiology of cardiovascular complications in type 2 diabetes

Patients with type 2 diabetes have a manifold increase in the risk for developing CVD as compared to non-diabetics, and this risk increases with age. The higher risk is believed to be due to the greater prevalence of cardiovascular risk factors among diabetics, including an abnormal lipoprotein profile, prothrombotic tendency, hypertension and obesity. Additionally, the altered metabolic environment (i.e., hyperglycemia, hyperinsulinism, and insulin resistance) and endothelial dysfunction resulting from the diabetic state directly impact on cardiovascular status [4].

Accelerated cardiovascular and cerebrovascular atherosclerosis is the major cause of mortality in patients with diabetes. This was well documented in the Wisconsin Epidemiology Study of Diabetic Retinopathy. The median follow-up in this study was 10 years in the younger-onset group and 8.3 years in the older-onset group [5]. There were 122 (12.9%) and 655 (51.8%) deaths in each group respectively. In the older-onset group, 47.2% patients died from heart disease and an additional 9% from cerebrovascular events.

Increased incidence of cardiovascular complications in diabetic patients of similar or even higher magnitude has been reported in a number of other reports [6]. In the presence of diabetes, the death rate attributable to cardiovascular disease is increased by 1.5 to 4.5-fold, and all-cause mortality is increased by 1.5 to 2.7-fold [7]. In addition to its very high prevalence, diabetes-associated macrovascular disease develops earlier than microvascular disease at a stage when there is only impaired glucose tolerance and plasma glucose levels are in the prediabetic range [8]. The Fungata Diabetes Study, which focused on the initial stages of abnormal glucose metabolism, revealed a relatively early dissociation of the

CVD = cardiovascular disease

survival curves for individuals with IGT as compared to matched controls with normal glucose tolerance [9]. After 6 years of follow-up the study showed that cardiovascular mortality was higher in individuals with IGT as compared to those with normal glucose tolerance, and that these differences were evident as early as 4 years after the detection of IGT. This observation suggests that even a very mild derangement of glucose homeostasis associated with the pre- or early diabetic state can adversely impact on the severity of the process leading to cardiovascular complications.

Several epidemiologic findings regarding CVD in type 2 diabetes are of clinical significance. The prevalence of cardiovascular disease varies according to ethnicity [1]. For instance, Pima Indians have a high incidence of type 2 diabetes but a relatively low rate of CVD, in contrast to Asian Indians who migrated to western countries and have a high incidence of CVD due to factors associated with type 2 diabetes including hyperinsulinemia and abdominal obesity [10]. The prevalence of CVD is increased even in newly diagnosed type 2 diabetics as compared to matched non-diabetic controls. This is especially true for females with type 2 diabetes [11]. The increased rate may be due to a delay in the diagnosis of overt type 2 diabetes, the long-term presence of impaired glucose tolerance that precedes overt type 2 diabetes, or a combination of both. As pointed out by Zimmet and Alberti [1], many of the risk factors associated with the development of CVD are operative prior to the development of overt diabetes. Factors such as glucose intolerance, an abnormal body mass index, increased waist/hip ratio, hypertension, hyperuricemia, hypertriglyceridemia, insulin resistance and hyperinsulinemia are found in a higher proportion of subjects destined to develop type 2 diabetes than in the background population. The pathophysiologic processes responsible for CVD in these patients include factors associated with the diabetic state, e.g., hyperglycemia, dyslipidemia, and advanced glycosylation end-products, as well as obesity and hypertension that precede the diabetic state [3].

A key issue in many of the epidemiologic studies pertaining to heart disease and diabetes is the identification of specific factors that are unique to diabetes. One of the early reports on the outcome of acute myocardial infarction in diabetic patients originated from Sweden in 1985 [12]. In this study, mortality and re-infarction rates were evaluated in a group of 73 diabetic and non-diabetic patients with AMI who were followed for 5 years. The only clinical differences between the diabetics and the non-diabetics were a lower serum cholesterol level and higher blood pressure among the diabetic patients. During the course of follow-up, the cumulative death rate was 52% in diabetics and 25% in non-diabetics, indicating that the higher prevalence of hypertension among diabetics may be a contributing factor. In a recently published study by the UKPDS (United Kingdom Prospective Diabetes Study), 3,055 white patients with a relatively new onset of type 2 diabetes without evidence of coronary artery disease were followed for a median duration of 7.9 years. Of this group, 335 individuals developed CAD. The study investigators identified five modifiable risk factors associated with the development of coronary artery disease in type 2 diabetic subjects: high low density lipoprotein, low high density lipoprotein, hypertension, hyperglycemia, and smoking [13].

Severity of cardiovascular disease in diabetics

A review of the available reports on diabetic patients with AMI reveals an early and late mortality that is extremely high when compared to non-diabetics [4]. The impact of CVD on diabetics is reflected by the high rate of mortality in diabetics who experience AMI. As shown in several studies, case-fatality is increased by 25–100% in diabetic patients as compared to non-diabetics admitted with AMI [4]. Mortality remains high even after correction for other prognostic factors related to cardiovascular disease outcome.

The increased case-fatality rate of type 2 diabetic patients with AMI has been partially attributed to altered myocardial energy metabolism, impaired cardiac remodelling after infarction, and a higher incidence of congestive heart failure in the first year after the infarction [14]. Glucose intolerance in the prediabetic state prior to the development of overt type 2 diabetes may also contribute to the later increase in cardiovascular mortality [Table 1].

Diabetics who develop coronary artery disease are more likely to suffer from cardiovascular complications including re-infarction and conduction abnormalities. In the Swedish study previously cited, Ulvenstam et al. [12] found that significantly higher numbers of diabetic patients (31 cases, 42%) suffered from re-infarction as compared to non-diabetic subjects (371 cases, 30%). In another study of 341 patients with AMI, the in-hospital mortality was higher in the diabetic group (25% vs. 16%). Those with diabetes also had an increased cumulative 1 year mortality rate (53 vs. 28%). While there were no significant differences between groups with regard to re-infarction rates (41 vs. 33%), the prevalence rate of fatal re-infarction was higher in the diabetic group (30 vs. 14%). This contributed to the overall increased mortality rate among diabetics in the re-infarction group (72 vs. 44%) [15]. In a more recent study, the 5 year rate for re-infarction was 55% vs. 22% for diabetics as compared to non-diabetics, with the 5 year mortality rate being 72% in diabetics as compared to 50% in non-diabetics [16].

Analysis of various independent prognostic variables indicated that diabetes itself doubles the risk for cardiovascular mortality when adjustment is made for age, type of treatment, and left ventricular functional status. The poor prognosis for diabetics with

Table 1. Causes of increased case-fatality rate in type II diabetics with acute myocardial infarction

Increased prevalence of cardiac risk factors among diabetics
Abnormal lipoprotein profile
Prothrombotic tendency
Hypertension
Central obesity
Myocardial parameters
Altered myocardial energy metabolism
Impaired cardiac remodeling after infarction
Higher incidence of congestive heart failure after myocardial infarction

IGT = impaired glucose tolerance
AMI = acute myocardial infarction

existing coronary heart disease was also observed in a study by Yudkin and Oswald [17] that followed 83 diabetic patients with AMI. In this study, pump failure occurred more frequents in diabetic patients than in non-diabetic individuals. The presence of microvascular complications also exacerbates the clinical course of patients with diabetic cardiovascular disease. The outcome of patients with CVD is much worse in the presence of diabetic nephropathy. Studies at the Steno Diabetes Center documented an increase in both the incidence of first myocardial infarction and other atherosclerotic complications in patients with type 2 diabetes and microalbuminuria [18].

The presence of diabetes also impacts on the prognosis of those undergoing specific therapeutic interventions for ischemic heart disease. Diabetic patients with coronary heart disease who undergo a coronary artery bypass graft procedure have a worse prognosis as compared to non-diabetics undergoing the same procedure [19]. A significant risk factor for poor outcome related to the diabetic state is the presence of proteinuria. A recent study among diabetics undergoing isolated CABG found that the 5 year mortality rate for non-proteinuric and proteinuric groups was 20.2% and 29.1%, respectively [20].

What is more worrisome about CVD and diabetes is the fact that although there has been a decline in the mortality associated with coronary artery disease in the general population during the past four decades, the same trend has not been observed in diabetics. This fact is even more alarming given that the number of individuals with type 2 diabetes has been increasing dramatically [1]. As a result of the discrepancy between cardiovascular outcomes in diabetics and non-diabetics, much emphasis has been placed on finding the unique factors associated with diabetes – related either to the metabolic state or to treatment modalities – which contribute to the severity of CVD in diabetic patients.

Traditional cardiovascular risk factors in diabetics

Among the traditional risk factors for CVD, smoking, hypercholesterolemia, hypertriglyceridemia, fasting plasma glucose concentration and hypertension are probably the most important in diabetic patients [Table 2]. However, several factors, unique to diabetes, may confound the impact of these traditional factors and independently influence the atherosclerotic process, thereby increasing the morbidity and mortality in this group. These additional risk factors include chronic inflammation (C-reactive protein and interlukin-6), endothelial dysfunction, AGEs, plasminogen activator I, fibrinogen, and genetic susceptibility.

Serum total cholesterol is a powerful predictor of ischemic heart disease morbidity and mortality in both diabetics and non-diabetics [21]. However, the impact of hypercholesterolemia in diabetics is much greater and as a result they have a two to three times higher risk for ischemic heart disease than their non-diabetic counterparts for the same level of total serum cholesterol [22]. Besides total cholesterol, elevated triglycerides, high LDL cholesterol, and low HDL cholesterol have also been shown to independently increase cardiovascular mortality in diabetic patients [3]. In addition, LDL particles from diabetic patients are smaller and denser and may be more easily oxidized, a modification likely to enhance atherosclerotic progression. Furthermore, a reduction in serum lipids, especially cholesterol, improves outcome for diabetics as a group. In the Scandinavian Simvastatin Survival Study, 202 diabetic patients with evidence of ischemic heart disease were treated with a variety of modalities [21]. The investigators found that lowering cholesterol with HMG-CoA reductase inhibitors reduced the risk of a major macrovascular event in patients with diabetes. Similarly, subgroup analysis of the Helsinki Heart Study, a 5 year ischemic heart disease primary prevention trial using gemfibrozil, provided additional evidence for the potential benefit of lipid-lowering agents for both non-diabetics and diabetics [23]. In another study of non-diabetic and diabetic patients who underwent CABG, mortality risk, incidence of AMI, and subsequent need for CABG or percutaneous transluminal coronary angioplasty were assessed [24]. Patients were randomized to more aggressive and less aggressive lipid-lowering treatment arms, with or without anticoagulants. Composite endpoint analysis indicated that diabetic patients who were not aggressively treated had a significantly higher cardiovascular risk as compared to either non-diabetics with similar non-aggressive treatment regimens or diabetics who were aggressively treated.

Table 2. Reducing risk factors for cardiovascular disease in diabetics

Primary prevention
Lifestyle changes
Smoking
Weight reduction
Exercise
Low fat diet
Therapeutic agents to normalize
Dyslipidemia
Hypertension
Hyperglycemia
Aspirin
Secondary prevention
Platelet aggregation inhibition (aspirin, clopidogrel, ticlopidine, IIbIIIa receptor inhibitors)
Beta-blockers
Sulfonyureas (controversial)
Angiotensin-converting enzyme inhibitors
Calcium channel blockers (controversial)
Selective angiotensin-II receptor antagonist (losartan)

CABG = coronary artery bypass graft
AGE = accelerated glycosylation end-product
LDL = low density lipoprotein
HDL = high density lipoprotein

There is considerable debate concerning appropriate target levels for LDL lowering among diabetics (as well as non-diabetics). Most of the intervention studies show consistent risk reduction across the range of LDL levels; i.e., there is little evidence for a threshold below which LDL reduction does not mitigate CVD risk. Currently, the National Cholesterol Education Program ATP III guidelines indicate a goal of 100 mg/dl for individuals with diabetes [25].

The American Diabetes Association recommends a target LDL of 100 mg/dl for all such individuals because of their known high risk for CVD and tendency to have multiple risk factors. High LDL levels in diabetic patients are thought to be particularly atherogenic because of altered composition, glycation, and susceptibility to oxidation.

Obesity and central obesity are important contributors to the insulin resistance syndrome and predictors of coronary heart disease in non-diabetic individuals. However, according to several studies, they are not independently associated with coronary heart disease or other cardiovascular complications in patients with type 2 diabetes [13].

The role of hypertension as a factor in the increased mortality among type 2 diabetics has been extensively investigated. Not only is the prevalence of hypertension in type 2 diabetes high, but hypertension develops early in the course of the disease. The prevalence of hypertension is already twice as high in patients with impaired glucose tolerance as compared to normal controls. The association of hypertension with type 2 diabetes is ominous; mortality is increased by a factor of 4 to 7 in patients with type 2 diabetes and hypertension when compared to normotensive non-diabetic matched controls [26]. The UKPDS clearly demonstrated the link between hypertension and the high risk for cardiovascular complications in type 2 diabetic patients [27]. In this study more than 1,000 hypertensive diabetic subjects were randomized to either tight (144/82 mmHg) or less tight (154/87 mmHg) control blood pressure. The 10/5 mmHg difference in blood pressure was associated with a 15% decrease in CVD, a 32% decrease in death due to diabetes, and a 44% reduction in the incidence of cerebrovascular attack.

Although the optimum target blood pressure for hypertensives with diabetes has not yet been determined with certainty, completed trials indicate that reducing systolic blood pressure to at least 130 mmHg provides substantial reduction in both macro- and microvascular disease progression. Clinical trials have also demonstrated that treatment of blood pressure even in the so-called normotensive range of type 2 diabetes is associated with prevention of blood pressure elevation and increased urinary protein excretion, and would likely reduce the risk of CVD and the progression of renal disease [28]. A recent pooled analysis of 11 large randomized controlled trials demonstrated that the optimal systolic blood pressure for preventing progression of non-diabetic renal disease is approximately 110 mmHg [29]. Thus, these data show that earlier and more rigorous blood pressure control, particularly with angiotensin-converting enzyme inhibitors, prevents progression of renal disease, and strongly suggest that the risk of CVD also will be reduced.

Non-traditional cardiovascular risk factors in diabetics

Researchers are already beginning to focus on the involvement of other non-traditional, or diabetic-specific, risk factors in the development of CVD in diabetic patients. It has been proposed that markers of inflammation – such as interleukin-6, C-reactive protein – are part of a complex of pro-CVD risk factors characterizing the insulin resistance syndrome, and that these markers contribute to CVD risk independently of established metabolic abnormalities commonly observed in insulin resistance. C-reactive protein is an acute-phase protein produced mainly in the liver. *In vivo* studies have shown that adipose tissue secretes IL-6, which regulates CRP production and could, potentially, induce chronic systemic inflammation in subjects with excess body fat. Therefore, patients with type 2 diabetes who are usually obese could potentially have high IL-6 and CRP. Studies have shown that type 2 diabetic patients with an elevated CRP have a high risk for coronary heart disease and an up to 8.5-fold increase in morbidity and mortality [30].

Recently, there has been an accumulation of data linking AGEs and diabetes-associated vascular damage. Through several mechanisms, the accumulation of AGEs in tissue is thought to result in increased vascular permeability and thickened, inelastic vessel walls [3]. *In vitro* study has demonstrated that AGEs accelerate linking of plasma lipoproteins with matrix proteins, a process that slows the efflux of lipoproteins from the tissues. Another mechanism potentially linking diabetes with CVD via AGEs is the induction of endothelial cell surface adhesion molecules resulting from the interaction of AGEs with their receptors (RAGE) [3]. Prothrombotic and fibrinolytic factors act in concert to maintain hemostasis. Plasminogen activator inhibitor 1 is an enzyme needed to lyse a thrombus once formed. The shift toward the prothrombotic state is highly correlated with an increased risk of myocardial infarction. In an analysis of the Framingham population, levels of PAI-1 were measured in men and women with normal glucose tolerance, or those with impaired glucose tolerance or previously undiagnosed diabetes. In the latter two groups, levels of PAI-1 were consistently twofold higher than in the group with normal glucose tolerance. This finding suggests that these individuals have a reduced ability to eliminate clots once they have formed [31].

Genetic susceptibility may play a key role in determining the severity of vascular complications in diabetic individuals. Intriguing new data suggest the existence of genes that confer differential susceptibility to complications. One such gene encodes haptoglobin, a hemoglobin-binding protein that protects against oxidative stress. Oxidative stress has been implicated as an important mediator of numerous pathophysiologic processes, including diabetic vascular complications. Three recent studies examining the haptoglobin gene in relation to diabetic retinopathy, diabetic nephropathy and coronary restenosis showed that individuals who are homozygous for the haptoglobin 1 allele appear to be protected against the development of these diabetic complications [32]. As

IL-6 = interleukin-6
CRP = C-reactive protein
PAI-1 = plasminogen activator inhibitor 1

the field of genetics continues to develop, new strategies for risk stratification of diabetic patients may be tailored to fit their genetic profile.

Impact of therapeutic interventions for diabetic cardiovascular disease

Different interventions have been attempted to reduce cardiovascular mortality in type 2 diabetic patients [Table 2]. Lifestyle changes such as cessation of smoking, weight reduction, a low saturated fat diet and exercise are beneficial. Exercise is particularly valuable both as a primary prevention for type 2 diabetes and because of its positive effects on dyslipidemia and glycemic control. The recently completed UKPDS study provides an indication that improved glycemic control in type 2 diabetes may improve cardiovascular outcome. In this study, a reduction of 1% in HbA1c was associated with a 14% and 37% reduction in the risk for myocardial infarction and microvascular complications, respectively [33].

The ETDRS research group (Early Treatment Diabetic Retinopathy Study), which included diabetics with or without cardiovascular disease, demonstrated a reduction in myocardial infarction. Bleeding complications were not significant even in the presence of proliferative diabetic retinopathy [34]. The use of aspirin to reduce the risk of cardiovascular disease was also confirmed by the Israeli Bezafibrate Infarction Prevention Study Group, which showed aspirin to be more effective in reducing both cardiac and total mortality in diabetics compared with non-diabetics [35]. Clopidogrel, a thienopyridine, ADP-mediated platelet inhibitor, was studied in the CAPRIE trial (Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events) and compared with aspirin. A small advantage was shown for clopidogrel. The development of inhibitors of fibrinogen, which binds to the platelet glycoprotein IIb/IIIa receptor, has expanded the therapeutic spectrum for the treatment of thrombotic disorders. In diabetic patients a significant benefit of these new drugs was demonstrated in various clinical indications [36].

The use of beta-blockers for prevention of a second myocardial infarction in patients with diabetes is well documented. Retrospective analysis of the Bezafibrate Infarction Prevention Study demonstrated a 44% reduction in the 3 year mortality rate in patients receiving beta-blockers as compared to those who were not [37]. Several studies indicate that treatment with calcium channel blockers has a beneficial effect in preventing stroke and AMI.

The HOPE study (Heart Outcome Prevention Evaluation) found that ramipril has a beneficial effect in diabetic patients in terms of both the incidence of myocardial infarction and the cardiovascular mortality rate [38]. Recently, this observation was strengthened by the LIFE study (Losartan Intervention For Endpoint reduction) in 1,195 diabetic patients. This study showed that losartan was more effective than atenolol in reducing cardiovascular morbidity and mortality in the diabetic patients [39].

The UKPDS study [40] was designed to investigate whether intensive blood glucose control could reduce the risk of macrovascular or microvascular complications in newly diagnosed patients with type 2 diabetes, and whether any particular therapy was advantageous. Patients were randomly assigned to an intensive treatment arm with sulfonylurea or insulin, or to a conventional non-treatment arm with diet restrictions. The treated group had a 12% reduction in microvascular and macrovascular complications ($P = 0.029$), a 10% reduction in any diabetes-related death ($P = 0.34$), a 6% reduction in all-cause mortality ($P = 0.44$), a 16% reduction in myocardial infarction ($P = 0.052$), and a 25% reduction in microvascular complications (retinopathy, nephropathy) ($P = 0.009$) [Table 3]. The results confirm that the lowering of blood glucose is beneficial in preventing diabetic complications, but that the treatment effect on cardiovascular disease was limited.

Table 3. Risk reduction of different endpoints with glucose treatment in the UKPDS

Endpoint	Risk reduction (%)	*P* value	RR for intensive policy
Any diabetes-related endpoint	12	0.029	0.88 (0.79-0.99)
Deaths related to diabetes	10	0.34	0.90 (0.73-1.11)
All-cause mortality	6	0.44	0.94 (0.08-1.10)
Myocardial infarction	16	0.052	0.84 (0.71-1.00)
Fatal	6	0.63	0.94 (0.68-1.30)
Non-fatal	21	0.57	0.79 (0.58-1.09)
Stroke	11	0.52	1.11 (0.81-1.51)
Amputation or death from peripheral vascular disease	35	0.15	0.65 (0.36-1.18)
Microvascular disease	25	0.099	0.75 (0.60-0.93)

RR = relative risk
(Modified from Laakso Markku, *Diabetes* 1999;48:937–41)

Summary

Diabetes remains a growing public health problem. The aging of the population, along with increasing obesity and decreasing physical activity, will ensure that the number of diabetic individuals will continue to grow. Among diabetic patients, aggressive modification of traditional cardiovascular disease risk factors remains a cornerstone of risk reduction. As clinical applications of modern genetics and molecular biology continue to develop, new therapies will likely focus on novel targets in the multiple pathways between hyperglycemia and CVD.

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