Diabetic heart disease: risk factors and pathogenesis

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Introduction
Diabetes mellitus is a chronic metabolic disease affecting about 200 million people globally. Its incidence and prevalence has significantly increased in recent decades, driven largely by increases in type 2 diabetes and obesity. It has been estimated that about 380 million people will have the disease by 2025. Cardiovascular disease (CVD) is responsible for most diabetes-associated morbidity and mortality. The Framingham study showed that diabetes increased the relative risk of coronary artery disease (CAD) by 66% in men and 23% in women, without the effects of age, smoking, blood pressure, and cholesterol. The Whitehall study reinforced these observations by demonstrating that subclinical glucose intolerance also increased coronary risk. The Multiple Risk Factor Intervention Trial (MRFIT), with its very large population of middle-aged men, was able to provide more detailed information about the interaction between diabetes and other co-morbid factors in determining coronary risk. Young individuals are at particular risk of future CVD and, by the age of 50 years, 33% of those requiring insulin have died from CAD. Indeed, 75% of all deaths in patients with diabetes are from this cause. The cause of CVD in diabetes is multifactorial; and several interwoven risk factors, co-morbidities, and pathogenic mechanisms will be discussed in this review.

Risk factors and pathogenic mechanisms

Hyperglycaemia
Hyperglycaemia can cause generalised endothelial dysfunction, which also involves the coronary arteries. This may lead to a reduction in the generation of nitric oxide which is a crucial endothelium-derived vasodilator. In addition, locally produced endothelial nitric oxide may be inactivated by interactions with advanced glycosylated end-products formed via non-enzymatic interactions between glucose and amino groups of proteins, lipids, and nucleic acids. The nitric oxide metabolism may be further impaired by angiotensin II, which increases vascular production of free radicals and consequently worsens the oxidative stress. The free radicals destroy nitric oxide and enhance leucocyte adhesion to the endothelium. They also promote platelet aggregation and cytokine expression leading to macrophage infiltration at the atherosclerotic site and increased risk of plaque instability and acute coronary syndrome.

Coronary atherosclerosis
CAD is the leading cause of death among patients with diabetes, and women have a higher risk. Angina may occur in up to 40% of diabetic adults and the risk of acute myocardial infarction is 50% and 150% greater in diabetic men and women respectively, than in the non-diabetic population. Diabetes independently predisposes to a higher mortality rate, re-infarction, and heart failure rates during and after acute myocardial infarction. Ischaemic syndromes are often ‘silent’ or present asymmetrically. This is largely due to impaired perception caused by autonomic neuropathy.

Systemic hypertension
Hypertension and type 2 diabetes are commonly associated conditions, each of which is an independent risk factor for CVD. The prevalence of hypertension is higher than in the general population and, by the age of 45 years, about 40% of patients with type 2 diabetes would have hypertension, with the proportion increasing to 60% by 75 years. Several studies have demonstrated the benefit of blood pressure reduction.

Diabetic cardiomyopathy
In diabetes, there is an excess of heart failure independent of CAD, raising the possibility of the existence of a specific diabetic cardiomyopathy. This has been an area of intense research and controversy since the 1970s. Some pathologic findings, such as myocyte atrophy, interstitial fibrosis, increased periodic acid Schuff-positive materials, and capillary microaneurysms have been described, although these findings are not diabetes-specific. Despite the controversial status of a specific diabetic cardiomyopathy, some specific mechanisms have been implicated in association with contractile dysfunction. Relative or absolute insulin deficiency results in abnormal substrate metabolism with reduced glucose and increased fatty acid utilisation, respectively in the diabetic heart. This may lead to dysfunction of sarcoplasmic reticulum, and subsequent contractile failure. There is also an up-regulation of...
the systemic and local rennin-angiotensin-aldosterone system (RAAS) and resultant increase in production of angiotension II, which augments the realise of inflamatory cytokines, particularly Interleukin (IL)-1β and IL-6, within the myocardium.21,22

Obesity
Obesity is commonly associated with type 2 diabetes. It is an independent risk factor for CVD, and CVD risk has been documented in obese children.23,24 Obesity increases total blood volume and cardiac output, partly due to the increased metabolic demand induced by excess body weight. The increased cardiac output is attributable mostly to increased stroke volume. Thus, at any given level of activity, the cardiac workload is greater in obesity. Also, the Frank-Starling curve is shifted to the left because of incremental increases in left ventricular filling pressure and volume that over time may produce chamber dilation. This may then lead to increased wall stress, which predisposes to an increase in myocardial mass and ultimately to left ventricular hypertrophy.25,26 That is an independent risk factor for cardiovascular morbidity and mortality. Also, obesity-related cardiomyopathy has been described as being characterised by infiltrative and/or metaplastic fatty deposition in the myocardium with resultant lesions ranging from cardiac conduction defects to restrictive ventricular diastolic dysfunction.27 Thus, obesity predisposes to CVD through different but interwoven mechanisms.

Dyslipidaemia
Dyslipidaemia is common in diabetic patients and further increases the risk of CAD. The typical lipid abnormalities are hypertriglyceridaemia and reduced high-density lipoprotein (HDL) cholesterol. Usually, there is no real increase in total or low-density lipoprotein (LDL) cholesterol.

Autonomic neuropathy
Autonomic neuropathy brings about autonomic dysfunction with resultant increased risk of cardiovascular morbidity and mortality.28 There is increased sympathetic activity which results in higher resting heart rate and an imbalance between the myocardial oxygen demand and supply. There may also be prolongation of QT intervals with increased potential for arrhythmogenesis. It may also cause impaired perception of ischaemic cardiac pain leading to atypical CAD presentations.29 This may delay access to emergency treatment or result in inappropriate triage decisions in the emergency room.

Diabetic nephropathy
The risk of CVD is increased with diabetic nephropathy. There is a direct relationship between cardiovascular risk and renal dysfunction. Renal dysfunction confers a 9-fold increase in relative cardiovascular mortality, which worsens to 20-fold in patients on maintenance haemodialysis.30 Microalbuminuria, which is the earliest and most sensitive predictor of diabetic nephropathy, is an independent marker of increased cardiovascular morbidity and mortality.31 The RAAS, which plays a critical role in the development of diabetic nephropathy, also has a mediation effect for most of the other pathogenic mechanisms and risk factors for diabetic heart disease.32

Conclusion
There is no doubt that the global diabetes prevalence has reached epidemic proportions and that the disease threatens to overwhelm health systems and undermine economies. A practical knowledge of risk factors, co-morbidities, and pathogenic mechanisms for CVD would not only improve the overall management of diabetes, but may also reduce associated morbidity and mortality.

References
17. Heart Outcome Prevention Evaluation (HOPE) Study Investigators. Effect of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: result of the HOPE

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