Pathogenesis of Cardiovascular Disease in Diabetes

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KEYWORDS

• Cardiac autonomic neuropathy • Diabetic cardiomyopathy • Coronary flow reserve
• Microangiopathy • Diabetic heart disease

KEY POINTS

- Cardiovascular disease is the most common cause of morbidity and mortality in both type 1 and 2 diabetes.
- The "glucose hypothesis" states that hyperglycemia directly contributes to development of cardiovascular disease.
- Insulin resistance and metabolic changes present in diabetes accelerate atherosclerosis development.
- Diabetic cardiomyopathy results in diastolic dysfunction, ventricular hypertrophy, and cardiac remodeling in the absence of coronary artery disease.
- Pathogenesis of cardiac autonomic neuropathy is multifactorial, including metabolic changes, inflammatory cytokines, and autoimmune destruction.

INTRODUCTION

The role of diabetes in the pathogenesis of cardiovascular disease (CVD) was uncovered in the late 1970s when data from the Framingham Heart Study demonstrated a clear link between the 2 conditions. A far greater percentage of patients with diabetes compared with those without the disease have cardiovascular comorbidities (eg, hypertension, dyslipidemia) and complications (eg, heart and vascular disease).[1] The prevalence of CVD among individuals with diabetes overall increased over the last 5 decades but recently appears to be improving presumably because of better adherence to risk factor modification (by both clinicians and patients) in the course of clinical

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care.[2] However, CVD remains the most common cause of death and complications in both type 1 (T1D) and type 2 diabetes (T2D).[2,3] Although it is also known that lifestyle changes, control of blood pressure and lipids, and antiplatelet therapy can reduce the development, progression, and complications associated with diabetes, the timing of these interventions is likely critical to reduce cardiovascular morbidity over a lifetime.[4]

Since these early associations, scientific knowledge of the impact of diabetes on the heart has expanded to address how the diabetes milieu alters the natural history and clinical presentation of heart disease, from the familiar conditions of coronary artery disease (CAD) and congestive heart failure (CHF) to the less familiar conditions of microangiopathy and autonomic dysfunction. In essence, the diabetic state accelerates most cardiac pathologies due to abnormalities in systemic and local vascular inflammation, endothelial and microvascular injury, altered thrombosis, autonomic nerve dysfunction, and likely membrane instability in nerves, smooth muscle, and endothelium. As we continue to learn from genome-wide analyses and functional genomics studies, the influence of genetic and epigenetic susceptibility is also likely important determinants of cardiac health in diabetes. A 2017 *Nature* article found that individuals who had genes known to increase risk of T2D also had an increased risk of heart disease. Furthermore, a new genetic loci, CCDC92, was identified that associated with both T2D and heart disease, implicating a shared pathway in the pathogenesis of these 2 diseases.[5] At this time, however, although multiple single nucleotide polymorphisms have been found to be associated with CVD in genetic association studies, usually their individual influence is small, and genetic contributions to CVD are poorly understood.[6]

In this concise review on pathogenesis of heart disease in diabetes, CVD is considered a class of distinct conditions that involve the heart and blood vessels, with each condition either presenting alone or, commonly, along with others due to overlapping pathophysiologic factors. Although the spectrum of CVD with increased prevalence in diabetes is broad, the authors highlight the pathogenetic factors that are known to contribute to the following conditions that present uniquely in diabetes and often overlap. These conditions include *atherosclerosis*, *microangiopathy*, *diabetic cardiomyopathy*, and *cardiac autonomic neuropathy* (**Fig. 1**). The "glucose hypothesis" linking hyperglycemia to cardiac abnormality is explored in this context, and the unique pathogenic factors are discussed for each condition. Subsequent articles in this issue address some of the conditions (eg, CHF) in more detail as well as the benefit of targeted therapeutic approaches to treat and/or prevent CVD in individuals with diabetes.

THE "GLUCOSE HYPOTHESIS" IN THE HEART

High glucose levels over time play an independent role in the development of CVD, although details on the importance of degree and duration of exposure to the severity of disease are less clear. Perhaps the best evidence of the link between hyperglycemia and cardiac dysfunction due to hyperglycemia is in studies of T1D, a "pure" insulin-deficient state. In one observational study of 20,985 individuals with T1D, each 1% increase in HA1c was associated with a 30% increase in risk of heart failure independent of other factors, including hypertension, smoking, and obesity. The "glucose hypothesis" linking high glucose to cellular damage is based on the concept that for many tissues in the body and/or under certain metabolic conditions, glucose transport across the cell membrane is unregulated by insulin and high glucose concentrations bombard cells with high intracellular glucose and glucose metabolites. These metabolites activate several accessory metabolic