Diabetes and the Risk of Heart Failure

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• Ventricular remodeling

The current American Heart Association heart failure classification schema designates the presence of diabetes mellitus as stage A heart failure, which raises the risk of developing stage B heart failure or asymptomatic left ventricular (LV) dysfunction. The present body of scientific evidence suggests that individuals with diabetes have a much higher risk for heart failure than those without diabetes.[1] Several clinical and experimental studies have shown that diabetes mellitus leads to functional, biochemical, and morphologic abnormalities of the heart, independent of promoting myocardial ischemia, and some of these changes happen earlier in the natural history of diabetes. In this review, the authors summarize some of the epidemiologic evidence that supports that diabetes is an independent risk factor for heart failure and promotes myocardial remodeling (a precursor of heart failure). The authors also provide a brief overview of the mechanisms (beyond ischemia) that lead to the development of heart failure in individuals with varying degrees of impaired glucose homeostasis (diabetes itself representing the most overt form of the spectrum of dysglycemic disorders).

INCIDENCE AND PREVALENCE OF DIABETES AND HEART FAILURE: 2 CONDITIONS INCREASING IN MAGNITUDE WORLDWIDE

Heart failure remains a major medical illness in individuals aged 65 years or more, with an estimated annual incidence of 10 per 1000.[2] At age 40 years, the lifetime risk of developing heart failure is about 1 in 5 for both men and women.[3] Similarly, prevalence and incidence of diabetes is increasing at an exponential rate, with an observed age-adjusted increase in incidence of 90% in the last decade.[4] Current estimated prevalence of diagnosed diabetes in the United States is approximately 7.8% for individuals older than 20 years, another 14.6% have undiagnosed diabetes, and nearly 37% have prediabetes. Each year, about 1.6 million cases of diabetes are newly diagnosed in the United States.[2] In addition, an estimated 23.1% of individuals aged 60 years or more have diabetes as assessed in the year 2007 by the National Health Interview Survey.[5] The estimated lifetime risk of developing diabetes ranges from 33% (men) to 39% (women), rivaling and exceeding that of heart failure.[6] Thus, diabetes and heart failure represent twin epidemics that pose a substantial population burden.

DIABETES AS AN INDEPENDENT RISK FACTOR FOR HEART FAILURE

More than a century ago, heart failure was noted to be a complication of diabetes.[7] In 1974, Kannel and colleagues[8] reported diabetes to be "another discrete cause of congestive heart failure" and postulated the mechanism as caused by small vessel disease or associated metabolic disturbances. These observations have been confirmed

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by several recent epidemiologic studies.[9] Data also support the hypothesis that individuals with diabetes who have poor blood glucose control are at much higher risk for heart failure.[10] In addition, other studies indicate that individuals without overt diabetes but who have insulin resistance[11] or have higher hemoglobin A1C values[12] (5.5%–6.0%) also incur greater risk for heart failure on follow-up.

Framingham researchers had estimated a 2-fold increase in risk of heart failure in men and about a 5-fold increase in risk in women with diabetes.[13] In fact, even in a cohort of postmenopausal women with prior history of coronary disease, diabetes was recognized to be the strongest predictor of heart failure.[14] Prevalence and incidence of diabetes among patients with heart failure is observed to be growing,[15,16] whereas mortality among those with heart failure with diabetes is also noted to be alarmingly high.[15,17]

DIABETES, IMPAIRED FASTING GLUCOSE, AND LV REMODELING

Individuals with diabetes frequently have echocardiographic evidence of LV remodeling; both increased LV mass and dilatation have been reported,[18] and these phenotypes are well-known predictors of heart failure in community studies.[19,20] Subclinical LV remodeling in diabetes is more prevalent in women.[21] These sex-related differences, with greater impact of dysglycemia in women, are also consistently seen among studies that observed that LV mass increases with worsening glucose tolerance and with greater insulin resistance.[22,23] More recently, longitudinal data from the Framingham cohort indicate that individuals with diabetes mellitus experienced greater age-associated increases in LV wall thickness and a lesser decrease in LV diastolic dimensions with increasing age.[24] In the Multi Ethnic Study of Atherosclerosis, researchers observed ethnicity-related variability in the prevalence of greater LV mass (in Hispanics and blacks), smaller LV end-diastolic volume, and reduced stroke volume (in whites, blacks and Chinese) in diabetic patients independent of the presence of subclinical atherosclerosis.[25] In addition, insulin levels and insulinlike growth factor 1 (IGF-1) are also associated with greater LV mass, although insulin resistance assessed by hemostasis model is related to LV remodeling in some[26–29] but not all studies.[23,30,31]

SYSTOLIC AND DIASTOLIC DYSFUNCTION IN DIABETES

Several studies have observed that individuals with diabetes have a greater risk of developing LV diastolic dysfunction.[32–35] Prior epidemiologic studies have observed higher prevalence and increased incidence of clinical heart failure among individuals with diabetes after controlling for other traditional risk factors.[15,36,37] Subclinical diastolic and systolic dysfunction progress to clinical heart failure[38] and are associated with greater cardiovascular mortality.[39] Researchers have also observed that factors associated with insulin resistance syndrome predate the development of LV systolic dysfunction by 2 decades, adjusting for ischemic heart disease and other risk factors.[40]

DIABETES AND VASCULAR STIFFNESS

Pulse wave velocity is a well-known indicator of target organ damage in patients with diabetes.[41] Higher peripheral pulse pressure is associated with a greater risk of subsequent cardiovascular disease events in the general population[42,43] and in high-risk patients with LV dysfunction.[44] In a recent meta-analysis, greater stiffness in large arteries was associated with higher cardiovascular events and all-cause mortality.[45] Vascular stiffness coupled with ventricular systolic stiffness is positively related with increase in age.[46] Furthermore, it is also evident that large artery compliance is reduced with age in patients with diastolic heart failure.[47] Aortic stiffness as measured by carotid-femoral pulse wave velocity increases in the presence of diabetes and also with age and obesity.[48] Researchers have observed that individuals with diabetes and diastolic dysfunction are prone to have ventricular and arterial stiffening beyond that expected because of aging or hypertension.[49] Although several studies have shown positive associations between diabetes, impaired fasting glucose, and lower large artery compliance,[50–52] a recent study suggested that only frank diabetes but not impaired fasting glucose increased aortic stiffness.[53] Some investigators have suggested that the impact of diabetes on vascular stiffness attenuates beyond age 65 years.[54] Of note, despite the lack of unanimous consensus regarding effect modification by age, most investigators agree that the evolution of the “diabetic heart” is mediated in part by altered ventriculovascular coupling.[52,55]

ASSOCIATION OF DIABETES WITH OTHER CLINICAL RISK FACTORS

Most established risk factors for atherosclerosis also increase the risk of heart failure.[56] As previously known, coronary disease is the most common cause of heart failure. In the presence of coronary disease, the risk of heart failure is