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Diabetes and the Risk of Heart Failure

Ravi Dhingra, MD, MPH and

Instructor of Medicine, Section of Cardiology, Heart and Vascular Center, Dartmouth Hitchcock Medical Center, One Medical Center Drive, Tel. 603-650-6224, Fax. 603-650-0523, ravi.dhingra@hitchcock.org

Ramachandran S. Vasan, MD, DM, FACC, FAHA

Chief, Section of Preventive Medicine and Epidemiology, Dept. of Medicine Professor of Medicine, Boston University, School of Medicine, The Framingham Heart Study, 73 Mount Wayte Avenue, Suite 2 Framingham, MA 01702-5803, Tel. 508-935-3450. Fax. 508-626-1262. vasan@bu.edu

Synopsis

Prevalence of diabetes and heart failure are increasing exponentially worldwide. Diabetes is well-known to increase the risk of heart failure independent of other traditional risk factors and ischemia. Current evidence indicates the presence of several biochemical and molecular changes associated with diabetes that lead to diastolic dysfunction or AHA stage B heart failure. Some, if not all changes may also predate the development of frank diabetes. In this review, we present some of the epidemiologic evidence and a brief description of major mechanistic pathways which favor the development of heart failure in prediabetic and diabetic state.

Keywords

Diabetes mellitus; Heart failure; Prediabetic State; Ventricular Remodeling

Introduction

The current American Heart Association (AHA) 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 compared to those without diabetes.¹ Several clinical and experimental studies have shown that diabetes mellitus leads to functional, biochemical, and morphological abnormalities of the heart, independent of promoting myocardial ischemia, and some of these changes happen earlier in the natural history of diabetes. In the present review, we summarize some of the epidemiological evidence that supports that diabetes is an independent risk factor for heart failure, and promotes myocardial remodeling (a precursor of heart failure), and we also provide a brief overview of the mechanisms (beyond ischemia) that lead to the development of heart failure in individuals with varying degrees of

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Correspondence to: Ramachandran S. Vasan.

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impaired glucose homeostasis (diabetes itself representing the most overt form of the spectrum of dysglycemic disorders).

Incidence and Prevalence of Diabetes and Heart Failure: two conditions increasing in magnitude world-wide

Heart failure remains a major medical illness in individuals 65 yrs of age or older, with an estimated annual incidence of 10 per 1000.² At 40 years of age, 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 over 20 years of age, 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 US.² In addition, an estimated 23.1% of individuals aged 60 years of age or older have diabetes as assessed in the year 2007 by 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 et al reported diabetes to be "another discrete cause of congestive heart failure" and postulated the mechanism as due to small vessel disease or associated metabolic disturbances.⁸ These observations have been confirmed 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 Additionally, other studies indicate that individuals without overt diabetes but who have insulin resistance¹¹ or have higher hemoglobin A1C values¹² (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 5-fold increase 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 heart failure patients is observed to be growing^{15,16} whereas, mortality among heart failure patients with diabetes is also noted to be alarmingly high.^{15,17}

Diabetes, Impaired fasting glucose and left ventricular remodeling

Individuals with diabetes frequently have echocardiographic evidence of left ventricular (LV) remodeling; both increased left ventricular 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 diabetics

independent of the presence of subclinical atherosclerosis.²⁵ Additionally, insulin levels and insulin-like 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 left ventricular 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 failure³⁸ and are associated with greater cardiovascular mortality.³⁹ Researchers have also observed that factors associated with insulin resistance syndrome predates the development of LV systolic dysfunction by two 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 greater risk of subsequent CVD 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 increases with age and obesity.⁴⁸ Indeed, researchers have observed that individuals with diabetes and diastolic dysfunction are prone to get ventricular and arterial stiffening beyond that expected due to aging or on the basis of 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 ventriculo-vascular 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 etiology of heart failure. In the presence of coronary disease, the risk of heart failure is increased several fold among individuals with diabetes. It is conceivable that individuals with diabetes may have a decreased awareness of chest discomfort due to acute ischemia that could result in delay in seeking medical attention and consequently they may accrue greater myocardial damage. After myocardial infarction, ventricular remodeling may occur at a faster pace among diabetics, which greatly elevates the risk for development of overt heart failure.⁵⁷

Diabetes and Dyslipidemia

In general, individuals with diabetes who have insulin resistance also have higher circulating levels of triglycerides and lower HDL cholesterol concentrations, and commonly manifest the metabolic syndrome.⁵⁸ The metabolic syndrome is a predictor of future risk of cardiovascular disease.⁵⁹ Specifically, it is widely recognized that higher levels of small

dense LDL particles are a major contributor of increased risk for CVD in insulin resistant patients.⁶⁰ The association of different lipid fractions (especially the total-to-high density lipoprotein cholesterol ratio) with incident heart failure is not same as for incident atherosclerotic cardiovascular events.⁶¹ Evidence supports that higher triglycerides⁶² or higher non HDL cholesterol levels⁶³ increase the risk of developing heart failure, perhaps because presence of insulin resistance that predisposes to metabolic changes characterized by impaired myocardial fatty acid oxidation and greater uncoupling of mitochondrial proteins in the heart.⁶⁴ Thus, in an insulin resistant patient, myocardial glucose uptake is decreased.⁶⁵ Indeed, patients with nonischemic cardiomyopathy may still exhibit relatively preserved myocardial glucose uptake in presence of insulin sensitivity.⁶⁶ Another possible lipid fraction which could be associated in raising the risk for heart failure in diabetics is higher levels of lipoprotein (a).⁶⁷ Underexpression of peroxisome proliferator-activated receptor α (PPAR- α) increases glucose metabolism and prevents cardiac dilatation whereas its overexpression leads to severe cardiomyopathy. The multiple mechanistic steps implicating PPAR- α in the development of heart failure and the use of fibrates that act as agonists to PPAR- α in heart failure have been reviewed recently.⁶⁸

Diabetes and Hypertension

Individuals with hypertension are prone to develop clinical heart failure.⁶⁹ A study from human autopsies showed that the alterations in myocardial cells and capillaries in diabetics leading to ventricular systolic and diastolic dysfunction are more pronounced in individuals with history of hypertension.⁷⁰ Hypertensive patients with type 2 diabetes are observed to have higher LV mass, and LV hypertrophy compared to their normotensive counterparts with diabetes.^{26,71} Although intensive blood pressure control (systolic BP <120mmHg) with medications in patients with diabetes has not shown reduction in fatal or nonfatal cardiovascular events consistently in recent trials,^{72–74} prior observational data does demonstrate that lower blood pressure in diabetes generally is associated with lesser risk of cardiovascular disease.^{75–77} Recommendations from JNC 7 guidelines suggest treating patients with diabetes with a systolic BP goal of below 130 mm Hg.⁷⁸

Diabetes and Obesity

Framingham Heart Study data have shown a significant positive association of obesity with incident heart failure, independent of diabetes status.⁷⁹ In presence of insulin resistance, obesity is known to increase the free fatty acids use that further leads to decreased cardiac bioenergetic efficiency (cardiac work/myocardial oxygen consumption).⁸⁰ Among obese individuals with insulin resistance⁸¹ and those with frank diabetes, LV mass increase is potentiated,⁸² although some reports are inconsistent.³⁰

Mechanisms for diabetes associated heart failure risk

Insulin resistance and diabetes has considerable effect on myocardium.^{83,84} It is beyond the scope of this review to describe all molecular pathways which may act as a mediator for raising the risk of heart failure. There are several postulated mechanisms which may be responsible for causing diastolic and systolic dysfunction of heart in an insulin resistance patient or in overt diabetes. We describe briefly below some mechanisms that have been the focus of considerable research.

Metabolic derangements in diabetes

The basic metabolic defects in the diabetic patient include hyperglycemia, insulin resistance and increased circulating levels of free fatty acids. The inability of the myocardial cells to metabolize pyruvate in diabetes resulting in lipid accumulation in the myocardium and decrease in glucose uptake by the myocardial cells, a long-postulated mechanism for the

impact of diabetes on the heart.⁸⁵ Glucose uptake by myocardial cells is primarily determined by local concentrations of insulin and by the intensity of cardiac contraction.⁸³ However, the mechanisms by which free fatty acid metabolism and glucose oxidation are interrelated are quite complex.⁸⁶ Increased activation of different isomers of protein kinase C has been noted to play a role in inhibition of insulin secretion by free fatty acids.⁸⁷ On the other hand, hyperinsulinemia in diabetics is also associated with increased free fatty acids levels, elevated heart rate, and increased activation of sympathetic nervous system; all these factors subsequently lead to cardiac hypertrophy and intracellular accumulation of triglycerides. In presence of hyperinsulinemia and insulin resistance, the human heart has also been shown to reduce protein degradation, which may then promote myocardial hypertrophy.⁸⁸ Additionally, dyslipidemia and production of free radicals result in alteration of genetic transcription factors and coding, which subsequently alters the translation of nucleoprotein genes such as those in the renin-angiotensin system (RAS) and IGF-1. Increased expression of RAS genes promotes insulin resistance, whereas greater expression of the IGF-1 gene increases sensitivity of cardiac myocytes to calcium concentrations and increases myocardial contractility. IGF-1 also acts synergistically with angiotensin II in promoting cellular and myocardial hypertrophy.⁸⁹

In experimental models of diabetes⁹⁰ and glucose intolerance,⁹¹ increased collagen-bound advanced glycation end products (AGE) are recognized to promote ventricular hypertrophy by increasing myocardial collagen deposition and fibrosis. In clinical studies, serum levels of advanced glycation end products (AGE) are associated with greater diastolic dysfunction or ventricular stiffness.⁹² AGE and their potential role in increasing vascular stiffness in diabetic patients has also been postulated⁹³ and the existence of higher levels of AGE in diabetes has been known for several decades.⁹⁴ Additionally, besides the collagen binding effect, AGE also bind to the endothelial cells and promote oxidative stress.⁹³ Furthermore, up-regulation of soluble AGE receptor (sRAGE) is also postulated to promote vascular stiffness, and increases risk of incident cardiovascular disease and mortality in diabetes.⁹⁵ Of note, an AGE 'breaker' does attenuate diabetes-induced myocardial damage.⁹⁶

Oxidative Stress in diabetes

Hyperglycemia increases reactive nitrogen and oxygen species (ROS) production leading to increased glucose auto-oxidation, and cardiac lipid peroxidation that in turn promotes abnormal gene expression and altered the signal transduction leading to myocardial cell death.⁹⁷ In experiment studies, treatment with antioxidant protein (metallothionein) has been shown to reverse myocardial effects of diabetes in mice.⁹⁸ Furthermore, depressed expression of sarco(endo)plasmic reticulum Ca – ATPase (SERCA2) protein (resulting in decreased Na-Ca exchange leading to intracellular calcium overload) is another postulated mechanism that has been demonstrated in diabetic rats.⁹⁹ Several other mechanisms have also been proposed in addition to depressed SERCA2 expression in relation to impaired calcium metabolism in diabetes; these include reduced activity of ATPases, decreased activity of sarcoplasmic reticulum to take up Ca²⁺, and reduced activity of other exchangers such as Na²⁺ - Ca²⁺ pump.¹⁰⁰

Mitochondrial Dysfunction in diabetes

Studies over the last 3 decades have reported structural and functional mitochondrial alterations in diabetes.^{101–104} Most experimental studies have shown that these mitochondrial alterations eventually cause a reduction in ATP production by lower creatine phosphate activity,^{105,106} lower ATP synthase activity,¹⁰² and lower creatine-stimulated respiration,¹⁰⁷ which then promotes cardiac dysfunction. These results are supported by similar findings in human heart.¹⁰⁸ In addition, reactive oxygen species-mediated

mitochondrial uncoupling may also play a role in development of myocardial dysfunction in diabetes.⁸⁶

Autonomic Neuropathy in diabetes

Abnormal myocardial contractile response to exercise suggestive of impaired sympathetic innervation has been observed in type 1 diabetes.¹⁰⁹ This observation is further supported by the observed higher incidence of abnormal LV diastolic function by myocardial radionuclide imaging studies¹¹⁰ and by echocardiography¹¹¹ in diabetics with impaired autonomic responses. On the same note, presence of autonomic neuropathy in patients with diabetes also increases likelihood of having an abnormal radionuclide perfusion imaging study¹¹² and of manifesting LV diastolic dysfunction.¹¹³

Additionally, there are several other postulated mechanisms by which diabetes may cause cardiac dysfunction; these include increased activation of protein kinase C or upregulation of RAS, angiotensin II- or aldosterone-induced fibrosis, coronary vasomotor abnormalities,¹¹⁴ endothelial dysfunction,¹¹⁵ impaired angiogenesis with upregulation of microRNA¹¹⁶ and VEGF expression.¹¹⁷ A detailed discussion of these mechanisms is beyond the scope of the present review.

Conclusion

In summary, there is substantial and consistent evidence in the literature to indicate that diabetes is a premier risk factor for heart failure, independent of its association with ischemic disease. The most common abnormality observed in asymptomatic diabetics is LV diastolic dysfunction, likely resulting from greater LV myocardial and vascular stiffness. There is also growing evidence that some, if not all, of these structural and biochemical myocardial abnormalities start at the pre-diabetic stage. Further research is needed to identify more sensitive markers of early myocardial abnormalities in asymptomatic individuals with diabetes and to formulate strategies for reversing these subclinical abnormalities to lower the risk of heart failure on long-term follow-up.

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