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THE PRESENT AND FUTURE

STATE-OF-THE-ART REVIEW

Implications of Underlying Mechanisms for the Recognition and Management of Diabetic Cardiomyopathy

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ABSTRACT

Heart failure is a complex clinical syndrome, the incidence and prevalence of which is increased in diabetes mellitus, pre-diabetes, and obesity. Although this may arise from underlying coronary artery disease, it often occurs in the absence of significant major epicardial coronary disease, and most commonly manifests as heart failure with preserved ejection fraction. Despite epidemiological evidence linking diabetes to heart failure incidence and outcome, the presence of a distinct primary "diabetic" cardiomyopathy has been difficult to prove, because the link between diabetes and heart failure is confounded by hypertension, microvascular dysfunction, and autonomic neuropathy. Nonetheless, several mechanistic associations at systemic, cardiac, and cellular/molecular levels explain different aspects of myocardial dysfunction, including impaired cardiac relaxation, compliance, and contractility. This review seeks to describe recent advances and limitations pertinent to integrating molecular mechanisms, clinical screening, and potential therapeutic avenues for this condition.
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Diabetes mellitus (DM) may elicit symptoms of primary cardiac disease through 3 major mechanisms: coronary artery disease (CAD), cardiomyopathy, and cardiac autonomic neuropathy (1). Separately, DM can also contribute to other systemic cardiovascular symptoms through vascular disease and autonomic neuropathy. Although heart failure (HF) may arise from CAD, the most common causes are nonischemic. The connection between DM and HF was observed about 150 years ago, but the proposal of a distinct "diabetic cardiomyopathy" (DCM) is more recent (2). The clinical detection of DCM as a separate entity from the other comorbidities of diabetes in the clinical context is confounded by hypertension and atherosclerosis, but both preclinical models of diabetes (3) and epidemiological evidence (4,5) provide robust support for DCM.

EPIDEMIOLOGY OF DIABETES-ASSOCIATED HF

Epidemiological evidence indicates a strong association between DM and HF. The Framingham study documented a 2.4-fold increased incidence of HF in diabetic men and a 5-fold increase of HF in diabetic women (4). Indeed, in people with DM, HF is a more common initial presentation of cardiovascular disease (CVD) than is myocardial infarction (6). Incident HF has been studied in more than 8,000 patients with

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ABBREVIATIONS AND ACRONYMS

DCM = diabetic cardiomyopathy

DD = diastolic dysfunction

DM = diabetes mellitus

GLS = global longitudinal strain

HFpEF = heart failure with preserved ejection fraction

O-GlcNAc = β-N-acetylglucosamine

ROS = reactive oxygen species

SGLT2 = sodium/glucose cotransporter 2

DM in the Kaiser Permanente system. In type 2 DM, new-onset HF occurred in 30.9 per 1,000 person-years in subjects with DM and 12.4 per 1,000 in control subjects over 6 years of follow-up (5). The lower reported annual incidence of HF (0.2 per thousand) (7) and myocardial dysfunction (1 per 1,000) in type 1 DM (8) likely reflects the study of these in younger age groups. Nonetheless, subclinical evidence of diastolic dysfunction is observed in both types 1 and 2 diabetes, even in the absence of other comorbidities such as hypertension (9,10).

Insulin-resistant states, including obesity and pre-diabetes, have a 20% to 70% risk increment of HF (11). Most of these patients have heart failure with preserved ejection fraction (HFpEF), although there are groups with a preponderance of heart failure with reduced ejection fraction (HFrEF) (12). The myocardial changes associated with obesity are independent of hypertension, obstructive sleep apnea, and CAD. The roles of metabolic disturbances, activation of the renin-angiotensin-aldosterone and sympathetic nervous systems, and myocardial remodeling are similar to the mechanisms of LV dysfunction in DM (13).

Just as HF is common in DM, DM is highly prevalent in the large trials of HF that defined the current management algorithm, being reported in 25% to 40% of patients with HF (14). One-third of patients admitted with HF in the absence of a previous diagnosis of DM demonstrate DM or impaired glucose tolerance (14). Most of these published data do not distinguish HFpEF from HFrEF. Insulin resistance is common in HF, with DM documented in 30% of patients with HFpEF.

In addition to HF being among the most common complications of DM, it is also among the most serious. In a prospective study from the mid-1990s, the 1-year mortality of HF was 30% in people with DM, about 1.5-fold greater than in those without DM (15). In the CHARM (Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity) trial, DM associated with HFrEF had a mortality rate of 119 per 1,000 patient-years, compared with 59 per 1,000 patient-years in HFpEF (16), with respective HF admission rates of 155 and 117 per 1,000 person-years. Although HFpEF has a slightly more favorable prognosis than HFrEF, the degree of this differential may be because an ischemic etiology is more common in HFrEF, and the excess risk for mortality associated with diabetes is greater when HF is ischemic than when HF is nonischemic.

CONTRIBUTING MECHANISMS TO DIABETES-ASSOCIATED HF

Diabetic heart disease is a complex entity associated with multiple contributing mechanisms and consequent manifestations (**Central Illustration**). These are evident at the systemic, cardiac, and cellular/molecular levels (**Table 1**) (3,17–19). Each of these derangements predispose the diabetic heart to defects in myocardial function, including impairments in cardiac relaxation, compliance, and contractility.

HYPERGLYCEMIA. Both preclinical and clinical evidence point to a causal role for hyperglycemia in diabetes-associated HF (20). Diastolic dysfunction is correlated with the degree of hyperglycemia; furthermore, the amelioration of hyperglycemia blunts diabetes-induced diastolic dysfunction with concomitant attenuation of its known triggers (18,20). Epidemiological evidence indicates that each 1% increase in hemoglobin A1c (HbA1c) confers an 8% increased risk of HF (21). This association of hyperglycemia with HF is biologically plausible, as levels of glucose metabolites are associated with glucose-mediated modifications that affect cardiac pathology (17,22). Formation of advanced glycation end-products as a result of nonenzymatic glycation of proteins, lipids, and nucleic acids initiates inflammation with consequent apoptosis and fibrosis (17,23). Distinct from this process, the glucose metabolite β-N-acetylglucosamine (O-GlcNAc) (generated by the hexosamine biosynthesis pathway) attaches to a multitude of proteins (at serine and threonine residues, likely competing with phosphorylation at the same site on affected proteins) to alter their function (22,24). Although a multitude of proteins (likely >1,000) are susceptible to O-GlcNAc modification, several specific examples are likely key to the functional impairments in the diabetic heart. This includes O-GlcNAc modification of Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII), phospholamban and the myofilaments (22), which negatively affect cardiac contractility and relaxation. Moreover, multiple mitochondrial proteins are also highly susceptible to O-GlcNAc modification (25), which is likely detrimental to both mitochondrial metabolism and subsequently to cardiac function in the context of diabetes. Advanced glycation end-product and sustained O-GlcNAc modification of proteins are both detrimental routes of glucose metabolism in diabetes (17,18,22,24,25), incurring epigenetic changes and mitochondrial damage and, consequently, myocardial dysfunction.