Microvascular Disease and the Pathogenesis of Heart Failure in Diabetes: A Tiny Piece of the Tricky Puzzle

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Heart failure (HF) is estimated to affect globally more than 63 million individuals, 1–2% of the population in developed countries (1). The number of patients with HF is expected to rise in the future as a result of the aging of the population and the increased rate of common cardiovascular risk factors, such as hypertension, obesity, metabolic syndrome, and diabetes. In addition, HF has an important impact on costs for health care systems, especially in Western countries: in the U.S., the total medical costs for individuals with HF are supposed to rise from USD 20.9 billion in 2012 to USD 53.1 billion by 2030 (2).

Both type 1 and type 2 diabetes are leading causes of HF. The strong association between diabetes and HF was documented almost 50 years ago by the Framingham Heart Study, showing that diabetes was independently associated with a two- and fivefold increased risk of HF in men and women, respectively (3). HF in people with diabetes is known also as diabetic cardiomyopathy. This expression was created more than 40 years ago to describe a form of HF characterized by ventricular dysfunction in the absence of coronary artery disease and hypertension in people with diabetes (4). Presently the scenario is completely changed, and the term diabetic cardiomyopathy is used to define the augmented susceptibility to developing left ventricular dysfunction in people with diabetes (5).

Recent epidemiological data indicate that 10–15% of individuals with diabetes experience HF during their life, and 44% of patients hospitalized for HF are affected by diabetes (6). In addition, individuals with diabetes have a worse prognosis than individuals without diabetes with HF; in fact, they are at higher risk of sudden cardiac death and of rehospitalization for worsening HF (7). Interestingly, HF in people with diabetes is characterized by preserved systolic function, a condition defined as HF with preserved ejection fraction (HFpEF), whose prevalence among people with diabetes is ∼45%. Of note, the prognosis of HFpEF is poor and comparable to that of HF with reduced EF, with 1-year mortality ranging between 10% and 30% (8). In light of the rapid increase of diabetes prevalence and the strong association between diabetes and HF, understanding the pathogenic bases of HF in individuals with diabetes is one of the most important contemporary challenges to establishing the adequate strategies of cardiovascular prevention.

Development of HF in diabetes is a complex and multifactorial process that involves different mechanisms. These include the morphological and structural changes of the diabetic or prediabetic heart, abnormalities of myocardial substrate utilization, impaired mitochondrial oxidative capability and Ca^{2+} handling, lipotoxicity and glucotoxicity, impairment of the cardioprotective and cardioreparative processes, excess oxidative stress, impairment of autophagy control, uncontrolled activation of the endoplasmic reticulum, increased formation of advanced glycation end products, impairment of insulin signaling, low-grade chronic inflammation, chronic kidney disease, abnormalities of neurohormonal homeostasis, etc. (9) (Fig. 1). During the last two decades, it has emerged that coronary microvascular dysfunction plays a key role in the genesis of HF in people with diabetes (10–12). In this context, it has also been documented that additional manifestations of microvascular dysfunction, such as retinopathy or neuropathy, have been found to be associated with HF in unselected populations (13) as well as in individuals with diabetes (14).

Li et al. (15), in this issue of *Diabetes Care*, investigated the association between microvascular disease (MVD) and risk of HF. The authors analyzed the UK Biobank database, a large prospective cohort of middle-aged adults that recruited more than 500,000 individuals throughout the U.K. between 2006 and 2010. MVD was defined by the presence of retinopathy, peripheral neuropathy, and chronic kidney disease (CKD). Main results of the analysis support that the higher the burden of MVD (i.e., number of organs affected by MVD), the higher the risk of incident HF in people with both type 1 and type 2 diabetes, even if this association was

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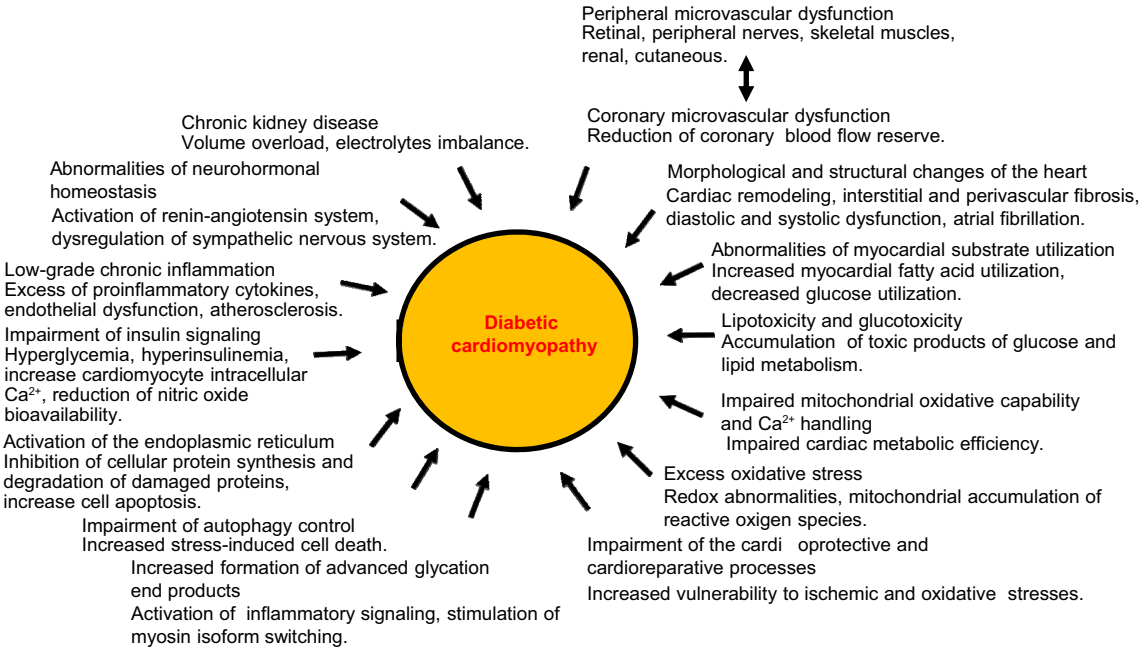

Figure 1—Principal mechanisms involved in the pathogenesis of diabetic cardiomyopathy.

more evident in individuals with type 1 diabetes. In particular, individuals with type 1 and with type 2 diabetes with three organs affected by MVD compared with those without any organ involved had a risk of incident HF of 11 and nearly 4 times higher, respectively.

Although these findings further confirm, using a larger sample size, previous data on type 2 diabetes, the real novelty is the description of the association between the clinical manifestations of MVD and incident HF in individuals with type 1 diabetes. In addition, in individuals with type 2 diabetes, the presence of MVD in a single organ seems to be weakly associated with incident HF. The strengths of these observations are related to the large sample size (>30,000 individuals) of the study and to the duration of the follow-up (>11 years). However, some limitations owing to the study design deserve equal appraisal. First, although a wealth of clinical parameters are provided at the inclusion of the individuals by the UK Biobank to support biomedical analysis focused on improving the prevention, diagnosis, and treatment of chronic disease, we lack any information related to the changes in these parameters over the follow-up and more; in particular, we are not informed about on-target primary or secondary preventive measures. Therefore, we do not know whether appropriate treatment of these individuals can positively modulate the risk of incident HF. The overall incidence of HF subtypes (e.g., HFpEF and HF with reduced EF), as well their incidences in type 1 and type 2 diabetes, is a missing crucial piece of information. Last, the inclusion of CKD among the MVD manifestations raises additional concern given its multifactorial etiology, which cannot be solely ascribed to the presence of MVD.

However, the crucial question raised by Li et al. (15) is what is the role of MVD as a determinant of HF in people with diabetes? It is reasonable to speculate that the clinical manifestations of MVD represent a surrogate of the coronary microvascular dysfunction, a well-known pathogenic mechanism of HF. In this regard, the burden of MVD could reflect the severity of coronary microvascular dysfunction and, consequently, the risk of HF. In this case it is possible to hypothesize the existence of a continuum of disease between the coronary and peripheral MVD. Alternatively, it is also reasonable to speculate that the burden of MVD reflects the severity of the diabetes-induced target organ damage. In this case it is reasonable to hypothesize that the burden of MVD is a hallmark of the functional impairment of the heart and consequently reflects the risk for HF. Studies in the future should clarify these issues and verify if MVD has similar relevance in the pathogenesis of HF in people with type 1 and type 2 diabetes.

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