

# Mechanisms underlying heart failure in type 2 diabetes mellitus

Johannes Gollmer, MD; Heiko Bugger, MD

Division of Cardiology, Medical University of Graz, Graz, Austria

Correspondence: Heiko Bugger, MD, Medical University of Graz, Division of Cardiology, Auenbruggerplatz 15, 8036 Graz, Austria

E-mail: heiko.bugger@medunigraz.at

**Abstract:** The prevalence of heart failure is markedly increased in individuals with diabetes mellitus. Numerous observational studies suggest that this increased risk for heart failure can be attributed to exacerbated vascular complications and the presence of increased risk factors in diabetic subjects. In addition, experimental studies revealed the presence of a number of distinct molecular alterations in the myocardium that occur independently of vascular disease and hypertension. Many of these molecular alterations are similarly observed in failing hearts of nondiabetic patients and have thus been proposed to contribute to the increased risk for heart failure in diabetes. The interest in understanding the underlying mechanisms of impaired cardiovascular outcomes in diabetic individuals has much increased since the demonstration of cardioprotective effects of SGLT-2 inhibitors and GLP-1 receptor agonists in recent clinical trials. The current review therefore summarizes the distinct mechanisms that have been proposed to increase the risk for heart failure in diabetes mellitus. ■ *Heart Metab.* 2019;80:37-39

**Keywords:** diabetes; heart failure; mechanism

## Introduction

The incidence of type 2 diabetes mellitus (DM) has rapidly increased in recent decades, and will soon affect more than 500 million individuals worldwide. In these individuals, the prevalence of heart failure with preserved (HFpEF) and reduced (HFrEF) ejection fraction is markedly increased, accompanied by an increased risk for hospitalization and mortality.<sup>1-3</sup> While the rate of heart failure hospitalization increases steeply in the 7<sup>th</sup> decade in nondiabetic subjects, this increase occurs 10 to 15 years earlier in diabetic individuals.<sup>2</sup> Underlying mechanisms for increased HF in DM include a more robust manifestation of cardiac and extracardiac macro- and microvascular complications, and also molecular and structural changes of the myocardium itself.

## Macrovascular and microvascular complications

Coronary artery disease (CAD) and myocardial infarction are the most common reasons for heart failure in Western countries, and far more prevalent in patients with DM than without DM. The risk of a diabetic individual without known CAD suffering myocardial infarction is equally high as in nondiabetic individuals with established CAD, thus highlighting the noxious influence of DM on pathogenesis and also acute complications of atherosclerosis in diabetic subjects.<sup>4</sup> In intravascular ultrasound trials, type 2 diabetic individuals had a smaller vascular lumen as well as increased plaque progression rate with greater plaque burden, although atherosclerosis-independent mechanisms may also contribute to increased risk for MI.<sup>5</sup> Furthermore, the clinical outcome in patients with DM seems to be impaired, as suggested by clinical trials in

different settings of CAD.<sup>6</sup> Complications in diabetes are mainly driven by the systemic metabolic alterations that include hyperglycemia, dyslipidemia, insulin resistance, and hyperinsulinemia. Glucose-induced protein modifications such as advanced glycation end products (AGE) and O-linked N-acetylglucosamine (O-GlcNAc) modifications, increased oxidative stress, the induction of chronic inflammation, and endothelial dysfunction not only lead to the progression of atherosclerosis and pronounced vascular calcification, but also to many of the other accompanying cardiovascular risk factors like arterial hypertension or chronic kidney disease (CKD).<sup>6</sup> Other mechanisms like chronic activation of the renin-angiotensin-aldosterone system (RAAS) or the sympathetic nervous system are further driving the progression of micro- and macrovascular complications.<sup>7</sup> Of note, some evidence exists to show that blood pressure goals are also more difficult to achieve in diabetic individuals and that these patients have worse cardiovascular outcome, regardless of the blood pressure values that were achieved.<sup>8</sup> CKD independently increases the risk of developing CAD, and guideline-directed therapy is less frequently achieved in patients with HF and CKD.<sup>9</sup>

### Molecular alterations in the diabetic myocardium

Structural and molecular alterations in the diabetic heart can also occur in the absence of CAD and hypertension, thereby contributing to a clinical phenotype frequently characterized by cardiac hypertrophy, impaired relaxation, and defects in systolic strain, also referred to as diabetic cardiomyopathy (DCM).<sup>10-12</sup> Increased fibrosis occurs as a consequence of increased hyperglycemia-induced modification of structural proteins and crosslinking of collagen molecules, as well as increased profibrotic signaling and impaired extracellular matrix degradation. DCM is also characterized by a proinflammatory state with increased expression of cell adhesion molecules, infiltration with leukocytes, and expression of proinflammatory cytokines. Alterations of myocardial energetics like increased fatty acid oxidation, impaired insulin-stimulated glucose uptake, mitochondrial dysfunction, and mitochondrial uncoupling contribute to myocardial energy depletion and impaired metabolic flexibility. Alterations in cytosolic and mitochondrial Ca<sup>2+</sup> handling, in particular impaired release and

uptake of Ca<sup>2+</sup> by the sarcoplasmic reticulum, may impair excitation contraction coupling and contractility. Diabetes also induces increased reactive oxygen species (ROS) production both within mitochondria but also in the cytosol by NADPH oxidases, thereby causing damage to lipids, proteins, and DNA. Oxidative stress, but also fibrosis and hypertrophy, are to some extent mediated by local and systemic activation of RAAS. More recently discovered dysregulated mechanisms proposed to contribute to DCM include removal of damaged cellular components (autophagy, mitophagy), or transcriptional (FoxO signaling, alternative splicing, micro-RNAs, epigenetics) and post-translational regulation (O-GlcNAcylation, protein deacetylation) of proteins, among others.<sup>13</sup> Given that many of these molecular mechanisms are altered in a similar fashion in systolic heart failure, a possible contribution to, or at least predisposition for, increased heart failure risk seems likely.

### Conclusions

Sufficient evidence exists to assume that the increased HF risk is related both to vascular complications but also to diabetes-induced molecular changes in the myocardium. The exciting recent finding that treatment with the SGLT-2 inhibitor dapagliflozin improved the composite end point of worsening HF or cardiovascular death both in diabetic and nondiabetic individuals with preexisting HF underscores a contribution of myocardium-specific mechanisms to HF in diabetic subjects that are independent of HbA<sub>1c</sub> lowering and that may overlap between diabetic and nondiabetic failing hearts.<sup>14</sup> Elucidating these as yet incompletely defined mechanisms of SGLT-2 inhibitors in further studies, combined with a better understanding of underlying mechanisms of HF, particularly including the role of myocardial energetics, should increase our understanding of increased HF risk in diabetic individuals and promote the development of new therapeutic avenues to improve outcomes in patients with DM. ■

**Disclosure/Acknowledgments:** *The authors have no conflict of interest to disclose.*

### REFERENCES

1. Bertoni AG, Hundley WG, Massing MW, Bonds DE, Burke GL, Goff DC, Jr. Heart failure prevalence, incidence, and mortality in the elderly with diabetes. *Diabetes Care*. 2004;27(3):699-703.

2. McAllister DA, Read SH, Kerssens J, et al. Incidence of hospitalization for heart failure and case-fatality among 3.25 million people with and without diabetes mellitus. *Circulation*. 2018;138(24):2774-2786.
3. Sarma S, Mentz RJ, Kwasny MJ, et al. Association between diabetes mellitus and post-discharge outcomes in patients hospitalized with heart failure: findings from the EVEREST trial. *Eur J Heart Fail*. 2013;15(2):194-202.
4. Nicholls SJ, Tuzcu EM, Kalidindi S, et al. Effect of diabetes on progression of coronary atherosclerosis and arterial remodeling: a pooled analysis of 5 intravascular ultrasound trials. *J Am Coll Cardiol*. 2008;52(4):255-262.
5. Schramm TK, Gislason GH, Kober L, et al. Diabetes patients requiring glucose-lowering therapy and nondiabetics with a prior myocardial infarction carry the same cardiovascular risk: a population study of 3.3 million people. *Circulation*. 2008;117(15):1945-1954.
6. Low Wang CC, Hess CN, Hiatt WR, Goldfine AB. Clinical update: cardiovascular disease in diabetes mellitus: atherosclerotic cardiovascular disease and heart failure in type 2 diabetes mellitus - mechanisms, management, and clinical considerations. *Circulation*. 2016;133(24):2459-2502.
7. Dunlay SM, Givertz MM, Aguilar D, et al. Type 2 Diabetes mellitus and heart failure, a scientific statement from the American Heart Association and Heart Failure Society of America. *J Cardiac Fail*. 2019;25(8):584-619.
8. Bohm M, Schumacher H, Teo KK, et al. Cardiovascular outcomes and achieved blood pressure in patients with and without diabetes at high cardiovascular risk. *Eur Heart J*. 2019;40(25):2032-2043.
9. House AA, Wanner C, Sarnak MJ, Pina IL, et al. Heart failure in chronic kidney disease: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. *Kidney Int*. 2019;95(6):1304-1317.
10. Rubler S, Dlugash J, Yuceoglu YZ, Kumral T, Branwood AW, Grishman A. New type of cardiomyopathy associated with diabetic glomerulosclerosis. *Am J Cardiol*. 1972;30(6):595-602.
11. Bugger H, Abel ED. Molecular mechanisms of diabetic cardiomyopathy. *Diabetologia*. 2014;57(4):660-671.
12. Jia G, Hill MA, Sowers JR. Diabetic cardiomyopathy: an update of mechanisms contributing to this clinical entity. *Circ Res*. 2018;122(4):624-638.
13. Gollmer J, Zirlik A, Bugger H. Established and emerging mechanisms of diabetic cardiomyopathy. *J Lipid Atheroscler*. 2019;8(1):26-47.
14. McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. *N Engl J Med*. 2019. In press.