Diabetes-Related Heart Failure
– Does Diabetic Cardiomyopathy Exist? –
Yasuko K. Bando, MD, PhD; Toyoaki Murohara, MD, PhD

As the link between heart failure (HF) and diabetes mellitus (DM) becomes unignorable, so the need is further increasing for pathological comprehension: What is “diabetic cardiomyopathy (DMC)”?

In response to current concern, the most updated guidelines stated by the ACCF/AHA and by the ESC/EASD take one step further, including the definition of DMC, although it is a matter yet to be completed. For more than 40 years, coronary artery disease and hypertension have been considered as the main causes of diabetes-related cardiac dysfunction. HF was originally considered as a result of reduced left ventricular ejection fraction (HF-REF); however, it has been recognized that HF symptoms are often observed in patients with preserved EF (HF-PEF). DMC includes HF with both reduced and preserved entities independent of coronary stenosis and hypertension. Cardiologists are thus facing a sort of chaos without clear guidelines for the “deadly intersection” of DM and HF. Today, the increasing interest and concern have caused DMC to be revisited and the first step in controlling the chaos around DMC is to organize and analyze all of the available evidence from preclinical and clinical studies. This review aims to illustrate the current concepts of DMC by shedding light on the new molecular mechanisms. (Circ J 2014; 78: 576–583)

Key Words: Diabetes mellitus; Heart failure; Pathology; Remodeling

“Heart failure and diabetes: a deadly intersection”: this exaggerated but impressive phrase was stated in the joint symposium at EASD 2013 organized by the ESC. It is becoming more obvious that cardiac dysfunction is a major comorbidity of diabetes mellitus (DM) and vice versa. Indeed, the most updated guidelines stated by the ACCF/AHA and by the ESC/EASD devote a specific section to DM and heart failure (HF) in which the term of “DMC” has at last appeared. There is no doubt that hypertension (HT) is a “class-A criminal” in the etiology of HF (Figure 1). Meanwhile, HT and DM closely complicate each other. Activation of the renin-angiotensin-aldosterone system (RAAS) in HT causes insulin resistance. Indeed, the evidence that RAAS blockers reduce the incidence of DM also support the causal link between the RAAS and DM.

One of the great clinical concerns for managing HF with DM is the undetermined goal of blood glucose with regard to preventing myocardial remodeling and future decompensation of HF. Another issue is the difficulty in specifying diabetic cardiac remodeling, presumably because of the lack of diagnostic criteria and tools, including biomarkers, based on evidence with a broad consensus. Not only the famous phenomenon of “silent myocardial ischemia” in diabetic patients suffering coronary artery disease, but diabetic cardiac remodeling also progresses asymptomatically but significantly enough to elevate the high-sensitivity troponin-T level. Microvascularopathy is a primary feature of diabetic myocardial remodeling, but no surrogate could directly monitor the disease progression. Furthermore, the term DMC is a matter of debate because DMC has been originally specified only for HF-REF patients, although the current diagnostic criteria for DMC include HF-PEF. Thus, increasing interest and concern have been focused on the causal link of DM to HF and cardiologists are contrarily confused how to cross the “deadly intersection” between DM and HF. Cardiologists frequently see diabetic patients and try to provide the best care for prevention of cardiovascular events when the guidelines have yet to be finalized worldwide. This review provides current perceptions of DMC for a better understanding of its molecular mechanism and the potential therapeutic options.

Historical Background of DMC
An increase in the number of publications concerning DMC reflects the rising interest in the topic (Figure 2). The link between DM and HF was first documented in 1872. At that point, the pathological entity of DMC was characterized as “microvascular remodeling of coronary arterioles” and “enhanced cardiac fibrosis”. Epidemiologic evidence demonstrating an association of HF with DM became evident with the Framingham study. Those early reports seemed to focus on HF-REF with comorbid diabetic nephropathy and retinopathy. For typical instance, Hamby et al made a detailed comparison of the base-
Figure 1. Overview of the clinical course of heart failure and its risk factors*: ref. 3 **ref. 4.

Figure 2. Exclusive increase in the number of publications on diabetic cardiomyopathy "DMC". Search engine powered by Pubmed. Notable events are indicated with arrows. †Year of the first report presenting the link to DMC.
Figure 3. Summary of pathological mechanisms of diabetic cardiomyopathy (DMC) and expected therapeutic interventions (listed in green square).

Figure 4. Pathologic cardiac remodeling and tissue hypoxia in the diabetic heart. These are typical immunohistochemical images representing pathologic cardiac remodeling observed in diabetes (streptozotocin-induced diabetic rodents heart). The diabetic heart shows loss of capillary density (CD31 staining; green dots in upper panels) and resultant tissue hypoxia (Hypoxprobe-1 staining; green spots in lower panels). Data are summarized in the bar graphs (changes in capillary density (Upper) and those of hypoxprobe-positive area (Lower), respectively). *P<0.05, **P<0.01.
line characteristics of idiopathic cardiomyopathy, of which patients diagnosed with DMC were younger (46±10.1 years old) and had a high incidence of familial history of DM (68.8%). suggesting the DMC as denoted in the primary era might indicate genetic and orphan cases.

**Terminology of DMC**

To the best of our knowledge, the term DMC is used less commonly and unofficially at the clinical level, especially among diabetologists who may have much less chance of managing HF patients. Indeed, DMC has been a matter of debate, presumably because of its difficulty and the ambiguity in making the diagnosis; concretely speaking, one could diagnose DMC exclusively in a retrospective manner based on autopsy or exclusion diagnosis. In 2007, an excellent review entitled “Diabetic cardiomyopathy revisited” was published and it highlighted the underlying molecular mechanisms of DMC, but could not contribute to uniting the diagnostic and therapeutic criteria. In 2013, guidelines from both the ACCF/AHA and the ESC/EASD officially denoted the definition of DMC.

The ESC/EASD guideline defines DMC as “…a clinical condition diagnosed when ventricular dysfunction occurs in the absence of coronary atherosclerosis and hypertension”. This statement does not give a concrete definition of “ventricular dysfunction”. Because we now recognize the clinical condition of HF-PEF, which is highly complicated by DM, the definition of DMC might need to be revised to more accurately reflect its disease condition. For instance, DMC could be specifically defined as HF–REF with DM independent of coronary artery disease and HT as the primary causes of systolic dysfunction.

**Diabetes and Obesity: Are They “Two Sides of the Same Coin”?”**

Obesity is the major risk for insulin resistance and its relationship to type 2 DM could be compared to the “the two sides of the same coin” in terms of metabolic disorder (Figure 3). Obesity is also a risk for HF, presumably through hyperleptinemia, which causes insulin resistance. On the other hand, there is the conflicting evidence known as the “obesity paradox”, indicating the negative correlation between increased BMI and the incidence of cardiovascular events, including HF. Recent reports state the possible cause of this paradox might be misreading of high BMI regardless body fat composition. However, there is clear evidence demonstrating the existence of the obesity paradox in Japanese HF patients. Further study is awaited.

**Four Major Burdens on the Heart Born of Diabetes: Microvasculopathy, Myocardial Hypertrophy, Fibrosis, and Thrombotic Risk**

Diabetes causes vasculomycardial damage, including microvasculopathy, myocardial hypertrophy, fibrosis, and thrombotic risk via glucotoxicity and lipotoxicity. It remains unclear whether these pathological changes occur simultaneously. However, it is noteworthy that clinical evidence provided by the UKPDS35 study demonstrated that the incidence of microvasculopathy was higher than microvasculopathy while HbA1C remains at a relatively low level. Regarding the sequence between fibrosis and microvasculopathy, a previous report concerning the spatiotemporal changes in myocardial remodeling observed in hypertrophic cardiomyopathy (HCM) suggests a clue. That report observed coronary microvascular remodeling more frequently when the coexisting myocardial fibrosis was less extensive, indicating the possibility that cardiac microvasculopathy might precede the onset of fibrosis.

**Microvasculopathy**

In DM, both gluco- and lipotoxicities are the primary causes of increasing oxidative stress and chronic inflammation, leading to microvasculopathy. One of the primary mediators promoting microvasculopathy is the AGE–RAGE axis. Of note, there is a novel link between the AGE–RAGE and dipeptidyl peptidase 4 (DPP4), a known inflammatory mediator, involved in the pathophysiology of cardiovascular disease. Diabetes enhances DPP4 activity, which links it to the AGE–RAGE axis. Consistently, recent studies suggest that DPP4 inhibitors ameliorate macro- and microvascular endothelial damage in DM via antiinflammatory effects. Interestingly, there is a report demonstrating that diabetic retinopathy predicts the incidence of HF, and also reflects diastolic cardiac dysfunction in diabetic patients. Because the retina is the only extracorporeal “window” onto microvascular damage, retinopathy may thus represent vascular damage not only in the eyes but also in other vital organs such as the heart in diabetic patients.

How does microvasculopathy cause cardiac dysfunction? The key evidence is reduced coronary microcirculation leading to chronic myocardial ischemia, which is induced by lack of compensatory angiogenesis in response to myocardial remodeling (Figure 4). In contrast to the case of physiological cardiac hypertrophy, namely athlete’s heart, pathological cardiac remodeling develops because of the lack of a sufficient level of compensatory angiogenesis related to the underlying diseased angiogenic potential observed with HT and DM, leading to subsequent diastolic dysfunction.

**Myocardial Hypertrophy**

Myocardial hypertrophy is another typical feature of DMC. One of the primary causes is comorbid hyperinsulinemia. Insulin is mitogenic and pro-survival under healthy circumstances and promotes hypertrophy of cardiomyocytes. Indeed, type 1 diabetic rodents generated by streptozotocin-induced insulin deficiency exhibit myocardial atrophy. The myocardium has insulin receptors that determines its innate insulin signaling connected to metabolic and mitochondrial remodeling. It is gaining consensus that abnormal insulin signaling has a vicious cycle on the cardiovascular system primarily through oxidative stress from mitochondrial dysfunction even independently of comorbid DM, which was elegantly demonstrated in a pressure-overloaded HF model.

Another considerable pathology of diabetic myocardial hypertrophy is cardiac steatosis. Diabetes promotes dyslipidemia and myocardial metabolic remodeling through an increase in free fatty acids, which causes abnormal accumulation of triglycerides (TG) and lipid intermediate ceramide in the myocardium, in addition to deposition of excess epicardial fat. This phenomenon remains uncertain; however, several clinical reports have demonstrated that cardiac steatosis, even in the prediabetic state, causes diastolic dysfunction and magnetic resonance spectroscopy is a good tool for detecting abnormal TG accumulation in heart.

**Cardiac Fibrosis**

Cardiac fibrosis is another feature of DMC. The effect of DM on cardiac fibrosis is presumably similar to the mechanism observed in diabetic nephropathy. Four primary factors...
responsible for the cardiac fibrosis of DMC are as follows: (1) the RAAS, which activates the Transforming growth factor beta (TGF-β) pathway;\(^2\) (2) AGE–RAGE axis, which suppresses collagen turnover via abnormal crosslinking of collagen;\(^6\) (3) hyperinsulinemia, which impairs differentiation of fibroblast progenitor cells;\(^6\) and (4) dysregulation of extracellular matrix degradation because of hyperglycemia.\(^6\)

**Thrombotic Risk**

DM alters hemostasis, platelet activity, and vascular endothelial function, which together contribute to the development of a characteristic prothrombotic state.\(^16\) In particular, abnormal platelet function is observed not only with DM,\(^6\) but also in the prediabetic state.\(^19\) Both hyperglycemia and hyperinsulinemia could cause enhanced platelet aggregation via promotion of abnormal platelet activation and oxidative stress.\(^6\)–\(^70\) Collectively, potential benefits of antiplatelet drug therapy are strongly expected for diabetic patients;\(^6\) however, the JPAD trial demonstrated that aspirin had no benefit in the primary prevention of cardiovascular events in Japanese diabetic patients.\(^72\)

In addition to macrovascular thrombosis, microvascular thrombosis could occur with DM.\(^73\) Therefore, the thrombotic risk in DM may be linked to impaired coronary microcirculation and the resultant cardiac dysfunction.\(^15,16,74\) Of note, there has been little evidence regarding the effect of antithrombotic treatment on HF with DM.

**Hemodynamic Characteristics Induced by Diabetes**

The hemodynamic characteristics of DMC likely reflects the 4 pathologic changes. The hemodynamic changes observed in the diabetic heart occur in both systolic and diastolic function. Ample reviews have focused on the diastolic dysfunction in DM.\(^2,14,75\) In contrast, DM-induced systolic dysfunction has been clinically less common, except for genetic cardiomyopathy caused by mitochondria disorders such as Friedreich’s ataxia.\(^76\) However, recent clinical studies have clearly shown the link between DM and systolic dysfunction in the asymptomatic state.\(^77,78\) In the preclinical setting, hyperglycemia promotes systolic dysfunction in type 1 diabetic rodents.\(^72\)

The cause of systolic dysfunction can be explained by cardiac negative remodeling induced by insulin deficiency and hyperglycemia-induced impairment of Ca\(^{2+}\) homeostasis.\(^79\) Of note, this systolic impairment is elicited more than 3 months after induction of hyperglycemia (unpubl. observation).

**How Cardiologists Manage Diabetic HF**

**Medication**

The 2013 ESC/EASD joint guideline regarding glucose-lowering medication is as follows: “the cardiovascular risk burden is not eradicated by intensive glycemic control associated with optimal multifactorial treatment, mechanism-based therapeutic strategies are needed”. Thus, there has been no direct recommendation regarding therapy.\(^2\)

However, this guideline gave an important commentary to clarify the existing confusion for HF patients regarding the use of metformin, which improves gluconeogenesis via activation of AMP-kinase and is recommended by diabetologists worldwide as a first-line medication.\(^2\) The guideline noted the safety and benefit of metformin based on the evidence that metformin ameliorates myocardial infarction size and prognosis.\(^80\) In contrast, the use of thiazolidine was not warranted in view-point of potential risk for congestive HF. Further evidence and deeper insights will be necessary. The guideline emphasizes the use of RAAS inhibitors for diabetic HF, presumably because of the pivotal role of the RAAS in the pathophysiology of both HF and DM (Figure 3).\(^8\) The guideline also recommends the use of β-blockers, in particular for diabetic HF-REF, based on the nested interpretation of large randomized clinical studies but with a caution for comorbid renal dysfunction.

**Candidates for Diagnostic and Predictive Surrogates**

Because any diagnostic surrogate of the inflammatory and oxidative stress markers for DMC remains unknown, this review limitedly focuses on the popular surrogates at the present moment.

**HbA1C**

To monitor the diabetic condition, HbA1C is the most popular among all physicians including cardiologists; however, there exists controversy regarding HbA1C as a predictor of cardiovascular events, including HF. For instance, the UKPDS study demonstrated that the risk of myocardial infarction was 2- to 3-fold higher than the microvascular endpoint at near-normal concentrations of updated mean HbA1c, whereas in the highest category of HbA1c concentration (>10%), the risks were of the same order.\(^31\) Moreover, based on the results of the ARIC study, HbA1C values show a J-shaped association with the incidence of HF.\(^83\) Furthermore, the prediabetic state has been demonstrated to increase the risk for HF,\(^82,83\) but we need to carefully interpret these results because the data were obtained under medical control with earlier generations of antidiabetic remedies such as sulfonylurea or insulin, which is apt to promote unfavorably progressive hypoglycemia. Collectively, the predictive role of HbA1C in the incidence of HF remains a matter of debate.

**Postprandial Glucose Level**

The vicious effect of chronic hyperglycemia on heart should be monitored.\(^14\) Among the indices of glucose metabolism, what is a better tool than HbA1c for monitoring glucotoxicity with respect to predicting HF? Ample evidence consistently shows that postprandial hyperglycemia (especially 2h after a meal), not the fasting glucose, predicts all-cause mortality.\(^2,84,85\) Furthermore, recent reports demonstrate the link between HF and postprandial dysglycemia\(^86,87\) as well as hyperinsulinemia.\(^82\) Collectively, as an alternative measure, postprandial blood glucose could be counted as a good surrogate for monitoring both glycemic control as well as the future incidence of HF.

**BNP**

The choice of B-type natriuretic protein (BNP) for monitoring DMC is an issue of debate because of the ‘natriuretic handicap’, which was demonstrated in prior evidence indicating that individuals with obesity, metabolic syndrome, and insulin resistance seem to have lower plasma BNP levels indicating that individuals with obesity, metabolic syndrome, and insulin resistance seem to have lower plasma BNP levels than their lean counterparts.\(^88\) The mechanism of this “handicap” was based on preclinical evidence obtained from BNP-transgenic mice; that is, the BNP cascade regulates muscle mitochondrial biogenesis and fat oxidation, which is suppressed by obesity and glucose intolerance.\(^89\) Further study is needed to reach consensus on its pathophysiology.

**Circulating DPP4**

DPP4 is a serine protease that truncates various bioactive peptides and mediates inflammatory responses.\(^90,91\) It exhibits 2 isoforms, a soluble-type and membrane-bound-type, and recent preclinical and clinical evidence suggests that the soluble form of DPP4 positively correlates with cardiac dysfunction.\(^41,92,93\) Because chronic inflammation could be counted as the primary pathophysiology of HF,\(^15\) the role of DPP4 as another surrogate marker for predicting progression of pathological myocardial remodeling via chronic
inflammation could be promising.

**Diabetic Autonomic Nerve Disorder in Heart: The Last Untouched Black Box**

DM promotes autonomic disorder that is strongly linked to cardiovascular disease, including arrhythmia. Lastly, we would like to discuss diabetic cardiac autonomic neuropathy (CAN).

CAN results in tachycardia, exercise intolerance, postural hypotension, and cardiac systolic and diastolic dysfunction. CAN increases with age, poor glycemic control, and probably the duration of DM. The enhanced sympathetic activity at the onset of CAN would stimulate the RAAS, which not only increases the hemodynamic stress from sodium retention and peripheral vasoconstriction but also promotes pathological myocardial remodeling. At a more advanced stage of CAN, peripheral vasoconstriction but also promotes pathological myocardial remodeling.

There are various diagnostic procedures for CAN, such as SPECT and PET; however, spectral analysis of heart rate variability seems to be the primary technique because of its low cost and good intra-individual reproducibility. Nevertheless, any efficacious medication for CAN is undetermined; thus, diabetic CAN in cardiovascular disease is the last black box left untouched.

**Conclusions and Perspectives**

To allow cardiologists to “negotiate the intersection at DM and HF with safety”, diagnostic and therapeutic guidelines are desirable. More evidence based on ample clinical trials is needed to establish guidelines fulfilling these requirements. Furthermore, additional needs should be considered exclusively for Asian patients who exhibit unique characteristics of impaired insulin excretion (ie, poor pancreatic β-cell function) compared with Caucasians. Lastly, a more intimate joint academic network between diabetology and cardiology may be desirable.

**Acknowledgments**

We sincerely thank Dr Toshimasa Shigeta and all of laboratory colleagues for his/her great contribution to the project of diabetes-related heart failure. This work was supported by the Japanese Society for the Promotion of Science Grant-in-Aid for Scientific Research (no. 23591080 to YKB and no. 20249045 to TM), grant support by the Suzuki Memorial Foundation (to YKB), Nagoya University Sentan Iryou Kenkyu Shien (to YKB and TM), a research grant (Jyutaku Kenkyu-hi) from Daiichi-Sankyo, Nagoya University, and grant support by the Suzuken Memorial Foundation (to YKB), Nagoya University Sentan Iryou Kenkyu Shien (to YKB and TM), grant support by the Suzuken Memorial Foundation (to TM), a research grant (Jyutaku Kenkyu-hi) from Daiichi-Sankyo, Nagoya University Sentan Iryou Kenkyu Shien (to YKB), and no. 20249045 to TM), grant support by the Suzuken Memorial Foundation.

**Conflict of Interest**

Lecturer’s fee from Daiichi-Sankyo, MSD, and Dainippon Pharmaceutical (to YKB) and lecturer’s fees from Daiichi Sankyo, Novartis Pharma, Pfizer, and Takeda (to TM).


