Review

Heart Failure as a Comorbidity of Diabetes: Role of Dipeptidyl Peptidase 4

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Heart failure is a primary cause of death worldwide, and it is notable that heart failure patients exhibit a high incidence of diabetes. On the other hand, comorbid diabetes significantly worsens the prognosis of heart failure, even independently of complicated coronary artery disease.

To date, heart failure caused by diabetes has been designated as “diabetic cardiomyopathy (DMC),” and a recent cohort study of the large-scale (1.9 million people) research platform of linked electronic medical records in UK (CALIBER registry) demonstrated that heart failure and peripheral arterial disease are the most common initial manifestations of cardiovascular disease in type 2 diabetes. The underlying pathophysiology has been characterized as microvasculopathy, myocardial hypertrophy, and cardiac fibrosis; however, these evidences are mostly obtained under a preclinical setting, and its clinical application on DMC in terms of its diagnosis and therapeutic intervention yet has reached practical. Our group has focused on and clarified the molecular mechanisms underlying DMC both in preclinical and clinical settings and has found the primary role of “dipeptidyl peptidase-4 (DPP4)” in the pathogenesis of diabetic microvasculopathy in the heart. Moreover, there are evidences implicating the potent role of circulating DPP4 activity in the diagnosis of diastolic heart failure. The present review aimed to review the current comprehension regarding diabetes and heart failure and discuss the therapeutic and diagnostic roles of DPP4.

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Key words: Diabetes, Heart failure, Dipeptidyl peptidase 4, Diabetic cardiomyopathy

DMC: Past and Present Concepts

The link between diabetes and HF was first documented in 1881^{1, 2)}, and the term DMC was coined in 1972³⁾. Case reports demonstrated the pathophysiological characteristics of the clinical entity such as “microvascular remodeling of coronary arteriole” and “enhanced cardiac fibrosis”^{3, 4)}. These early reports seemed to focus on the end-staged DMC of HF-REF with comorbid diabetic nephropathy and retinopathy.

In 2013, the ACCF/AHA and the ESC/EASD at last denoted the definition of DMC^{5, 6)} (it remains undetermined in Japanese guidelines). These guidelines define DMC as follows: “DMC is a clinical con-

dition diagnosed when ventricular dysfunction occurs in the absence of coronary atherosclerosis and hypertension”⁵⁾. However, this statement gives no concrete definition on the ventricular dysfunction and/or diabetic myocardial remodeling. In DMC, one of the most popular clinical conditions observed in DMC is diastolic dysfunction (HF-PEF)^{7, 8)}. Therefore, the terminology of DMC might be revised for reflecting each disease condition more accurately in terms of these clinical and pathological features.

Characteristics of the Diabetic Burdens on the Heart: Microvasculopathy, Myocardial Hypertrophy, Fibrosis, and Prothrombogenic Phenotype

Diabetes causes a wide variety of myocardial damages such as microvasculopathy, myocardial hypertrophy, fibrosis, and prothrombogenic phenotype via glucotoxicity and lipotoxicity^{7, 9, 10)}. The spa-

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tio-temporal relationship among these pathological changes in myocardial remodeling remains unclear. However, clinical evidence provided by UKPDS35 demonstrated that the incidence of macrovasculopathy was higher than microvasculopathy during HbA1C remains relatively low level^{5, 11}.

1. Microvasculopathy

In diabetes, both gluco- and lipo-toxicities are considered as a primary cause for increasing oxidative stress and chronic inflammation, leading to microvasculopathy^{5, 12, 13}. Interesting reports demonstrated that diabetic retinopathy predicts the incidence of HF¹⁴ and reflects diastolic cardiac dysfunction in diabetic patients^{15, 16}. Because the retina is the only window where one can observe microvascular damage in an extracorporeal fashion, retinopathy may thus represent vascular damage and injury not only in the eyes but also in other vital organs such as the heart in diabetic patients. Recently, Kawata *et al.* demonstrated that coronary flow reserve (CFR), which reflects coronary microvascular function, is associated with left ventricular diastolic dysfunction in patients with type 2 diabetes¹⁷. Furthermore, an interesting evidence demonstrated that those patients with retinopathy are prone to display diastolic left ventricular dysfunction¹⁵.

One of the primary mediators promoting microvasculopathy is the AGE/RAGE axis¹⁸. Notably, there is a novel link between the AGE/RAGE axis and DPP4¹⁹, a known inflammatory mediator^{20, 21} that is involved in the pathophysiology of cardiovascular diseases^{22, 23}. Diabetes enhances DPP4 activity^{24, 25} that links to the AGE/RAGE axis. Consistently, recent studies suggest that DPP4 inhibitors ameliorate macro-²⁶ and micro-vascular endothelial damage²⁴ in diabetes via its anti-inflammatory effects^{26, 27}.

2. Myocardial Hypertrophy

Myocardial hypertrophy is another feature of DMC that causes diastolic dysfunction as a typical cardiac dysfunction observed in diabetes. One of the primary factors causing its pathogenesis is hyperinsulinemia as well as impaired insulin signaling of the myocardium²⁸. Insulin is mitogenic and pro-survival under healthy circumstance, and it promotes hypertrophy in cardiomyocytes²⁹. Indeed, type 1 diabetic rodents generated by streptozotocin-induced insulin deficiency exhibits myocardial atrophy³⁰. The myocardium possesses an insulin receptor that determines its innate insulin signaling pathway connecting to metabolic³¹ and mitochondrial remodeling³¹⁻³³. It gains consensus that an abnormal excess of insulin signaling exerts vicious effects on the cardiovascular sys-

tem, primarily because of oxidative stress through mitochondrial dysfunction even independently of comorbid diabetes, which was elegantly demonstrated by the use of a pressure-overloaded HF model³⁴.

Another considerable pathology that could result in diabetic myocardial hypertrophy is cardiac steatosis³⁵⁻³⁷. Diabetes promotes dyslipidemia and myocardial metabolic remodeling through an increase in free fatty acids³¹ that causes an abnormal accumulation of large-sized lipids (e.g., triglyceride) into the cardiac cells in addition to the deposition of excess epicardial fat. The precise mechanisms underlying the myocardial accumulation of the lipids remain unknown; however, several clinical reports demonstrated that cardiac steatosis is observed even at the prediabetic state and causes diastolic dysfunction, and magnetic resonance spectroscopy is a good tool to detect abnormal TG accumulation in the heart^{38, 39}.

3. Increase in Cardiac Fibrosis

Cardiac fibrosis is another feature of diabetes. The impact of diabetes on cardiac fibrosis is presumably similar to the mechanism that is observed in diabetic nephropathy^{40, 41}. Four primary factors responsible for the cardiac fibrosis of DMC are as follows: First, the RAAS that activates TGF- β 1 pathway⁴⁰; second, the AGE/RAGE axis that suppresses collagen turnover via an abnormal crosslinking of collagen⁴²; third, hyperinsulinemia that impairs the differentiation of fibroblast progenitor cells⁴³; and fourth, dysregulation of extracellular matrix degradation⁴⁴.

Recently, we and others reported that DPP4 inhibitors attenuate myocardial fibrosis independently of diabetes. Interestingly, the DPP4 inhibitors have been reported to suppress renal and hepatic fibrosis^{45, 46}. Consistently with these notion, the DPP family (DPP8/9) has characteristics of a collagenase as well as a fibroblast activating protein (FAP)⁴⁷ and, likewise DPP8/9, DPP4 is reported to have an capacity for a collagenase.

4. Prothrombotic Phenotype

Abnormalities in platelet function are another cardiovascular risk observed not only in diabetes⁴⁸ but also in the prediabetic state⁴⁹. The primary cause of enhanced platelet aggregation observed in diabetes is hyperglycemia and hyperinsulinemia, leading to platelet activation and oxidative stress⁴⁸⁻⁵⁰. In addition to macrovascular thrombosis, microvascular thrombosis could occur in diabetes⁵¹. Therefore, the prothrombotic phenotype may link to an impaired coronary microcirculation and the resultant cardiac dysfunction^{7, 52, 53}. Collectively, potential benefits promoted

Fig. 1. DPP4 is a serine protease that ubiquitously expressed in the whole body. Table summarized various substrates of DPP4 that modulates cardiovascular pathophysiology.

by the administration of anti-platelet drugs are strongly expected for diabetic patients^{54, 55}. DPP4 per se possesses anti-thrombotic properties and may behave as an immobilized anti-coagulant on endothelial cells. Under nondiabetic conditions, ischemia/hypoxia induces the loss of coronary microvascular endothelial DPP4 expression and increased tissue factor expression in AMI⁵⁶.

Hemodynamic Characteristics Induced by Diabetes

Hemodynamic characteristics of DMC likely reflects the above four pathological changes. The hemodynamic changes observed in the diabetic heart occurs both in systolic and diastolic functions. As ample reviews have noted, all pathological changes of the diabetic heart cause a diastolic dysfunction^{5, 57}. Diabetes-induced systolic dysfunction has been clinically less popular, except for genetic cardiomyopathy that is caused by mitochondria disorders⁵⁸. However, several clinical studies have clearly shown the link between diabetes and systolic dysfunction under an asymptomatic state^{59, 60}. In a preclinical setting, hyperglycemia promotes systolic dysfunction in type 1 diabetic rodents³⁰. The cause of systolic dysfunction was explained because of cardiac negative remodeling induced by insulin deficiency and hyperglycemia-

induced impaired Ca^{2+} homeostasis⁶¹.

DPP4 Inhibition in Heart Failure: Friend or Foe?

DPP4 (DPP4/DPPIV/CD26) is a 110-kDa type II integral membrane glycoprotein that cleaves N-terminal dipeptides from peptides with preferably proline or alanine at the penultimate⁶². Interestingly, these substrates are bioactive peptides that regulate the cardiovascular system^{63, 64} (**Fig. 1**), and its activity level alters in response to the comorbid diseases. For instance, diabetes enhances membrane-bound type DPP4 activity^{24, 25}, which is suppressed by non-diabetic cardiac stress (**Fig. 2**)^{23, 24}. Therefore, DPP4 inhibitors and its major substrate incretin peptides are expected to play beneficial roles in various cardiovascular diseases. Indeed, preclinical evidences and phase-trials consistently proved their protective roles; therefore, the large-scale randomized studies were expected to provide any favorable results in terms of cardiovascular protection in diabetic patients, although these were intention-to-treat data obtained from these trials, which were designed as a safety test for antidiabetic remedies according to the recommendation stated by USFDA^{65, 66}. The year 2013 was a milestone year for the clinical aspects of the “diabetes-related heart failure” based on two important events: one was a major

Fig. 2. Alternative changes of cardiac DPP4 activity.

Cardiac DPP4 is expressed in capillary endothelial cells and its activity diversely changes. DPP4; Dipeptidyl peptidase, TAC; pressure-overload-induced heart failure.

revision of the clinical guidelines for heart failure with comorbid diabetes⁵), and the other was the unexpected increase in the incidence of HF observed in RCT for saxagliptin and placebo⁶⁷). In response to FDA's recommendation for the assessment of the cardiovascular safety of anti-diabetes remedies, the two trials enrolled T2DM patients with a high cardiovascular risk such as a history or risk of cardiovascular events in SAVOR-TIMI53⁶⁷) and a recent acute coronary syndrome event in EXAMINE⁶⁸). Both trials assessed non-inferiority for the risk of major adverse cardiovascular events. Indeed, these trials proved the safety of these "gliptins"; however, in saxagliptin arms, the unexpected increase in the incidence of heart failure was observed. The SAVOR-TIMI groups immediately published the subanalysis results regarding the increase in the incidence of heart failure and demonstrated the risk factors for heart failure as follows: past medical history of heart failure, CKD, aging, male gender, insulin use, and race (i.e., Caucasian). This paper also mentioned about its limitation that there was no increase in myocardial injury markers such as BNP and troponin I, and the underlying mechanisms remain uncertain⁶⁹). On the other hand, the subanalysis of the EXAMINE trial clearly demonstrated that there was no influence of the past history of heart fail-

ure on the incidence of heart failure, and they also consistently demonstrated that alogliptin had no effects on myocardial injury markers⁶⁵). Furthermore, the TECOS trial, another RCT of DPP4 inhibitor sitagliptin, revealed that DPP4 inhibition did not increase the risk of any cardiovascular diseases, including heart failure⁷⁰) (**Table 1** and **2**). Taken together, the unexpected risk of heart failure observed in the SAVOR-TIMI53 trial was presumably independent from the drug-class effect of DPP4 inhibitors. A further prospective study for the evaluation of the risk of heart failure induced by anti-diabetic remedies are awaited under consideration for the incidence of hypoglycemia, clinical report bias for the diagnosis of heart failure, and assessment of cardiac function.

Conclusion and Perspective

The last question is how we diagnose DMC? To date, no surrogate markers have gained consensus as a diagnostic tool for DMC, i.e., this is one of the critical causes why DMC has been a clinically uncommon diagnosis. Further basic and clinical evidences are needed to establish the diagnostic and therapeutic guidelines for DMC.

Table 1. Comparison of study characteristics of the recent randomized large cohort trials for DPP4 inhibitors.

	SAVOR-TIMI-53	EXAMINE	TECOS
Enrollment	16,492	5,380	14,724
Gliptins	Saxagliptin	Alogliptin	Sitagliptin
HbA1C(median%)	6.5 – 12%	6.5 – 11%	6.5 – 8%
Age (Median, y/o)	65	61	65
DM duration (year)	10.3	7.3	9.4
Hypertension (%)	82	83	86
Dyslipidemia (%)	71	N/A	77
Smoker (%)	N/A	14	11
Hx of HF (%)	13	28	18
Trial period (median)	2.1years	18 months	3 years

Table 2. Summary of the clinical outcomes of the recent randomized large cohort trials for DPP4 inhibitors.

Trial components	SAVOR-TIMI-53	EXAMINE	TECOS
Clinical outcomes			
CV death, nonfatal MI/ CAD	HR 1.00 (NS)	HR 1.00 (NS)	HR0.98 (NS)
Death from any cause	HR 1.11 (NS)	HR 0.88 (NS)	HR 1.01 (NS)
Hospitalization for HF	HR 1.27*	HR 1.19 (NS)	HR1.00 (NS)

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Conflict of Interest

Research grants from Daiichi-Sankyo, Astra Zeneca, Tanabe-Mitsubishi, (to YKB). Actelion, Astellas, Bayer, Boehringer Ingelheim, Chugai, Daiichi Sankyo, Dainippon Sumitomo, Eisai, Fuji Film RI, Kaken, Kowa, Kureha, Medtronic, Denso, Mochida, MSD, Novartis, Pfizer, Sanofi-Aventis, Schering-Plough, and Takeda (to TM). However, the research topics of these donation grants are not restricted. Lecturer's fee

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