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Diabetes, heart failure, and renal dysfunction: The vicious circles

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ABSTRACT

The prevalence of Type 2 diabetes mellitus (T2DM) has reached pandemic proportions. T2DM frequently causes macrovascular and/or microvascular pathologic changes and thereby increases the risks for the development of myocardial infarction, heart failure, stroke, renal failure, and reduced survival. This article describes the important interactions between T2DM, heart failure, and renal dysfunction, forming vicious circles. The interruption of these circles represents important therapeutic goals.

Contents

Introduction: the magnitude of the problem

Type 2 diabetes mellitus (T2DM), heart failure (HF), and diabetic kidney disease (DKD) are major pandemics of the twenty first century.[1] T2DM affects more than 400 million persons worldwide, with an estimated annual cost exceeding $1.3 trillion.[2] In the United States (U.S.), 25 million persons (10% of the adult population) are affected, with an annual estimated cost of $475 billion.[3] HF occurs in 42 million persons in the U.S.,[4] where it is the most frequent admission diagnosis in patients on Medicare. The lifetime risk of middle aged adults developing HF in North America has been estimated at 30%.[5] Chronic kidney disease is present in approximately 37 million Americans[6]; among these DKD is now the most frequent cause of chronic, end-stage renal disease and occurs in about half of all patients with chronic T2DM.[7] The prevalence of all three of these pandemics is rising as a consequence of the aging of the population, the increasing incidence of obesity, and moderate prolongation of survival of affected persons. Currently, this growth is especially rapid in developing countries. It is the purpose of this article to describe the vicious circles that connect T2DM with its two most important complications.

These three conditions often coexist, and each worsens the prognosis of the other two, setting up a series of vicious circles. (Fig. 1) For example, T2DM is a powerful risk factor for the development of HF (Fig. 1a)[8,9]; it is associated with a 2 to 4 times greater risk of the development of cardiovascular disease (CVD), which is responsible for about two-thirds of all deaths in patients with T2DM.[9,10] In the U.S., more than 40% of patients hospitalized for worsening HF have concurrent T2DM.[11] The combination of T2DM and left ventricular dysfunction is

Abbreviations: AGE, Advanced glycation end products; CVD, Cardiovascular disease; DCM, Diabetic cardiomyopathy; DKD, Diabetic kidney disease; HF, Heart failure; HFpEF, Heart failure with preserved ejection fraction; HFrEF, Heart failure with reduced ejection fraction; RAAS, Renin-angiotensin -aldosterone system; ROS, Reactive O_2 species; T2DM, Type 2 diabetes mellitus; U.S., United States.

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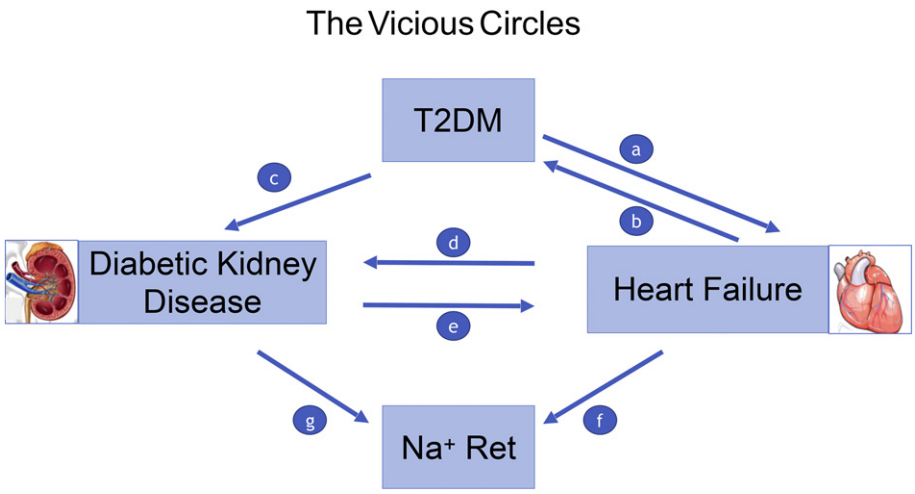

Fig. 1. The vicious circle: an overview. Type 2 diabetes mellitus (T2DM), heart failure (HF), and diabetic kidney disease (DKD). T2DM is a major risk factor for HF (a) and for DKD (c). HF can cause or intensify the severity of T2DM (b). Both T2DM (c) and HF (d) and can cause DKD. DKD can intensify HF (e). Both HF (f) and DKD (g) can cause sodium retention (Na^+ ret), pulmonary congestion, dyspnea and edema.

particularly dangerous, with high incidence of chronic disability and mortality.[10,12] In addition to the increase in HF attributed to T2DM, there is also evidence for the reverse, *i.e.* it is a "two-way street." (Fig. 1b) Thus, HF can play a causal role in the development of T2DM,[13] with advanced HF being associated with the development of marked insulin resistance.[14] Conversely, treatment of advanced HF with implantation of a left ventricular assist device has been shown to result in improved diabetic control.[15]

By definition, diabetes is the cause of DKD. (Fig. 1c) There is "cross-talk" between the failing heart and the failing kidney.[16] The combination of a lower cardiac output and an elevated renal venous pressure reduces renal blood flow. The upregulation of the sympathetic nervous system and the renin-angiotensin-aldosterone system (RAAS) in HF causes constriction of afferent glomerular arterioles, reducing glomerular filtration. The failing kidney in DKD may contribute to secondary hypertension and to anemia, thereby placing extra burdens on the failing heart. This bidirectional interaction between the heart and kidneys sets up an important vicious circle. (Fig. 1c and d) Both HF (Fig. 1f) and DKD (Fig. 1g) result in sodium retention which can be responsible for pulmonary congestion, dyspnea, and edema.

Disease mechanisms

The vicious circle between HF and T2DM is shown in Fig. 2, modified from Maack et al.[17] Central to the development of T2DM is insulin resistance (Fig. 2a), which is responsible for insulin hypersecretion (Fig. 2b). With progression, insulin secretion by the pancreas, while greater than normal, is insufficient to prevent hyperglycemia, signifying the presence of T2DM (Fig. 2c). Fig. 3 shows the relations between HbA1c and arterial pressure with adverse outcomes in patients with T2DM.[18] These include

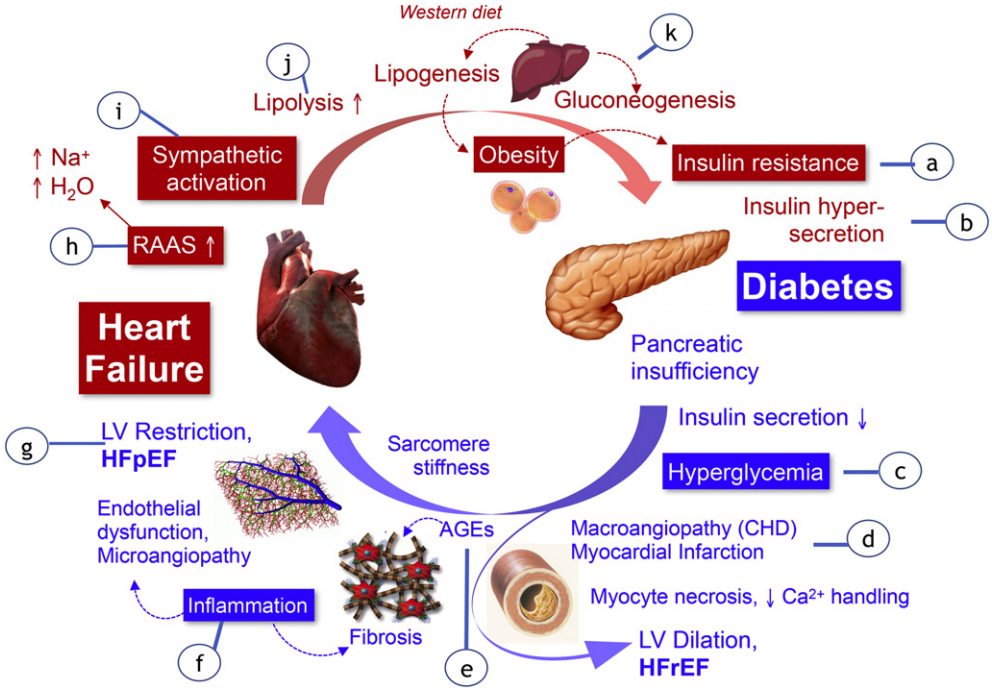

Fig. 2. The vicious circle between T2DM and Heart Failure. For explanation, see text. AGEs, advanced glycation end products; HFrEF, heart failure with reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; RAAS, renin-angiotensin-aldosterone system; LV, left ventricle. (Modified with permission from Maack C, Lehrke M, Backs J et al. Heart failure and diabetes: metabolic alterations and therapeutic interventions. Eur Heart J 2018;39:4243–4254).

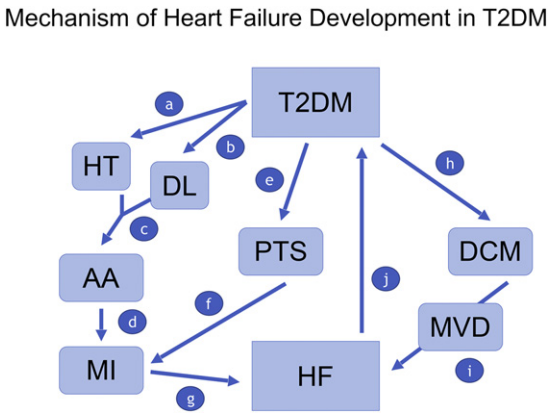

Fig. 3. Mechanism of heart failure development in T2DM, which is frequently associated with hypertension (HT,a) and dyslipidemia (DL,b). These and other risk factors are responsible for accelerated atherosclerosis (AA, c), which in turn is responsible for coronary artery disease. The latter interacts with the prothrombotic state (PTS, e) of T2DM to cause myocardial infarction (MI, d and f), which is responsible for HF with reduced ejection fraction. T2DM can cause diabetic cardiomyopathy (DCM, h), in which microvascular coronary artery disease (MVD, i), contributes to the development of heart failure with preserved ejection fraction.

vascular complications, which can be divided into two major categories[19]: The *macrovascular* complications include epicardial coronary artery disease, cerebrovascular disease, aortic and peripheral arterial disease (Fig. 2d); the *microvascular* complications include DKD, neuropathy, retinopathy,[20] and small vessel coronary disease. Many patients, especially those with longstanding T2DM, may have multiple vascular complications. Patients with microvascular complications are at increased risk of developing macrovascular complications, as well.[21,22]

Increased insulin resistance of cardiomyocytes reduces their glucose utilization and contributes to hyperglycemia. It also increases the uptake and metabolism of free fatty acids, which impairs the efficiency of cardiac contraction. When excessive, this uptake can lead to triglyceride storage in cardiomyocytes, causing lipotoxicity, a contributor to impairment of cardiac contractility.[23]

An important mechanism by which hyperglycemia is responsible for adverse clinical outcomes in T2DM is through the production of advanced glycation end products (AGE) (Fig. 2e), which act upon and activate a specific receptor, RAGE. This causes an accumulation of reactive O_2 species (ROS) which, in turn, trigger inflammation (Fig. 2f) in both the myocardium and the microcirculation. Oxidative stress and myocardial inflammation[24] can lead to myocyte apoptosis as well as mitochondrial dysfunction; the latter can reduce myocardial production of ATP, which may reduce the uptake of Ca^{++} by the sarcoplasmic reticulum of cardiomyocytes and thereby interfere with contraction.[25] AGEs can also lead to cardiac fibrosis, which causes myocardial stiffness and HF with preserved ejection fraction (HFpEF) (Fig. 2g). AGEs may also be responsible for endothelial dysfunction and microangiopathy.

The development of HF causes activation of two systems: 1) the RAAS (Fig. 2h), which causes retention of Na^+ and H_2O; and 2) the sympathetic nervous system (Fig. 2i), causing lipolysis (Fig. 2j), which when combined with a typical Western diet and obesity (Fig. 2k), can lead to insulin resistance (Fig. 2a), thereby completing the "vicious circle."

Heart failure

T2DM increases the risk of hospitalization or death secondary to HF both with reduced and with preserved ejection fraction.[26] Hypertension (Fig. 3a) and dyslipidemias (Fig. 3b) occur earlier, more frequently, and more severely in patients with T2DM, and play an important role in accelerating atherosclerosis (Fig. 3c), which is characterized by earlier and more extensive development of coronary artery plaques. Moreno et al. compared coronary atherectomy specimens obtained from patients with and without T2DM. The former showed greater contents of lipid, with larger infiltrates of macrophages.[27] Such plaques are at high risk of rupture and have been referred to as "vulnerable" plaques.

T2DM can also produce a prothrombotic state[28] (Fig. 3e), with hyperactive platelets,[29] and increases in coagulation factors including thrombin, and impaired fibrinolysis.[30] The combination of vulnerable plaques and the prothrombotic state enhance the risk of development of coronary thrombosis, acute myocardial infarction (Fig. 3d and f) and HF with reduced ejection fraction (HFrEF). Other important outcomes of accelerated atherosclerosis include chronic coronary artery disease, peripheral vascular disease, cerebrovascular disease, and stroke.

Diabetic cardiomyopathy (DCM)

T2DM is also responsible for molecular changes in myocardial structure and function that can cause DCM (Fig. 3h), a condition characterized by ventricular dysfunction in patients with T2DM in the absence of hypertension and coronary artery disease. The several mechanisms believed to play important roles in the genesis of DCM are shown in the Table 1. Seferovic and Paulus have described two phenotypes of HF resulting from DCM.[31] The first, myocyte death, causes left ventricular systolic dysfunction and HFrEF. The second, caused by coronary microvascular disease (Fig. 3i),[21,22] is a restrictive phenotype characterized by concentric left ventricular remodeling and diastolic dysfunction leading to HFpEF. More recently, depressed function of cardiomyocytes related to impaired mitochondrial Ca^{2+} has been implicated.[32] As pointed out above, the presence of HF intensifies the severity of T2DM (Fig. 3j).

As described above, T2DM can result in *de novo* HF, which can also worsen prognosis in patients with previously established HF. MacDonald et al[26] reported that both in the presence and absence of T2DM, HFrEF is associated with a greater risk of adverse outcomes than HFpEF. (Fig. 4) Also, importantly, T2DM was a powerful predictor of adverse outcomes, increasing the risk of cardiovascular death or hospitalization for HF, both in patients with HFpEF and with HFrEF. These adverse effects of T2DM were more profound in patients with HFpEF than in those with HFrEF.

Diabetic kidney disease

In 1972, Rubler et al. described a "new type of cardiomyopathy associated with diabetic glomerulosclerosis."[33] This condition, DKD, is a microvascular complication which frequently progresses to the need for dialysis or renal transplantation.[33] Next to CVD, DKD is the most common cause of death in patients with T2DM. The two major phenotypes of DKD and their prognostic importance are shown in Fig. 5.[34] Mortality is increased about fourfold in patients with albuminuria and preserved glomerular function, about fivefold in patients with impaired glomerular function without albuminuria, but about ten-fold in patients with the combination of impaired GFR and albuminuria.

T2DM and arterial hypertension play important roles in the development of DKD by causing glomerular hyperfiltration, glomerular

Table 1
Potential mechanisms of diabetic cardiomyopathy.

AGEs	Fibrosis
RAAS	Inflammation
Oxidative stress	Apoptosis/necrosis
Mitochondrial dysfunction	Autophagy
ER stress	Increased FA utilization
Impaired Ca2+ handling	Lipotoxicity

ER = endoplasmic reticulum; AGE = advanced glycation end product; RAAS = renin-angiotensin-aldosterone system; FA = fatty acids.
Modified from Bugger H, Abel ED. Molecular mechanisms of diabetic cardiomyopathy. Diabetologia 2014;57:660–671.

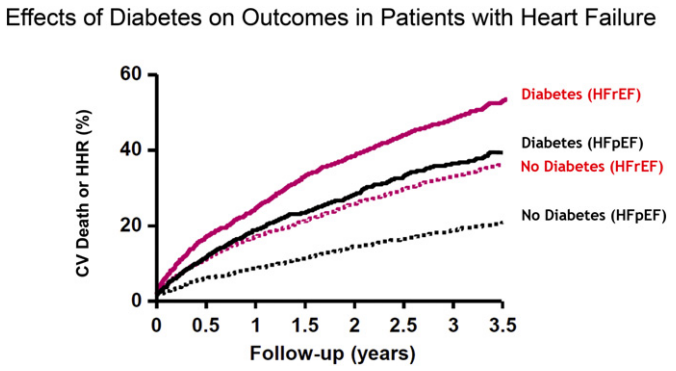

Fig. 4. Diabetes increases risk of hospitalization or death due to heart failure. In patients without diabetes, the risk of heart failure (HF) is higher in patients with heart failure with reduced ejection fraction (HFrEF) than in patients with heart failure and preserved ejection fraction (HFpEF). The presence of diabetes increases the adverse outcomes in both forms of heart failure. CV, cardiovascular; HHF, hospitalization for heart failure. (With permission from MacDonald et al. Eur Heart J 2008;29:1377–85).

hypertrophy, followed by expansion of the mesangium, and accumulation of extracellular matrix.[35,36] The latter can lead to a loss of podocytes, disruption of the mesangium (mesangiolysis), and glomerular fibrosis. Thus, another vicious circle is created whereby the combination of T2DM and essential hypertension leads to DKD, which may cause secondary hypertension and further impairment of renal function.

As is the case with other microvascular complications of T2DM, early and effective glycemic control reduces the likelihood of developing DKD. Hyperuricemia, which in some instances is secondary to renal dysfunction, can "feed" into this circle. Uric acid is pro-inflammatory, induces oxidative stress, and activates the RAAS.[37] Hyperuricemia is believed to increase the incidence and severity of DKD, which may, in part, be responsive to uric acid lowering.

Conclusions

The several vicious circles described herein are designed to help explain the natural progression of T2DM, with cardiovascular and renal complications the most frequent causes of disability and death. However, they also demonstrate a number of opportunities for intervention, thereby interrupting the vicious circles and improving clinical outcomes. For example, the importance of attaining an optimal lifestyle in preventing the progression and even reversing microvascular damage has already been mentioned. This approach can be extended to patients with pre-diabetes, which might prevent the development of T2DM. The rigorous control of hyperglycemia[38] is, of course, of enormous importance.

PCSK9 inhibitors added to HMG-CoA reductase inhibitors result in intensive reduction of low density lipoprotein cholesterol, which can delay or even prevent the development of accelerated atherogenesis in patients with T2DM.[39] Similarly, vigorous control of hypertension[40] may prevent ventricular hypertrophy and thereby limit both cardiac and renal damage. Potent antiplatelet agents and anticoagulants can overcome the prothrombotic state and improve the prognosis in patients who have experienced an acute coronary syndrome. Newer agents, such as the angiotensin receptor blocker neprilysin inhibitor, (sacubitril/valsartan),[41,42] when appropriately administered, improve the outcome of HFrEF in patients with T2DM. The sodium-glucose cotransporter 2 (SGLT2) inhibitors are also especially useful since in addition to reducing HgbA1c and arterial pressure, they reduce both cardiac and renal failure[33] and prolong life in patients with T2DM.[43,44]

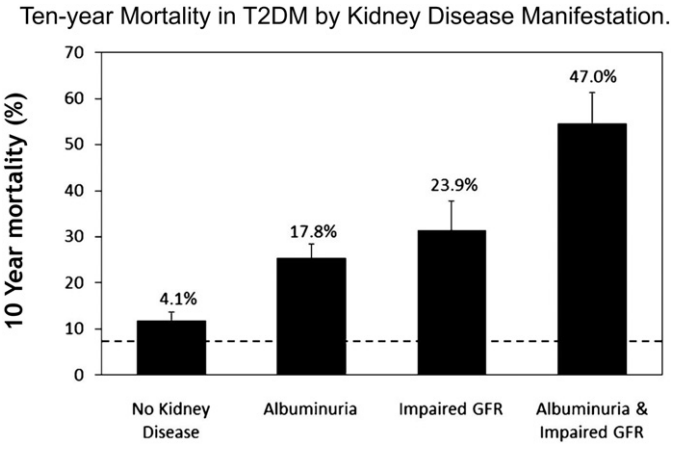

Fig. 5. The dashed line indicates mortality in persons without diabetes or kidney disease (the reference group). The numbers above the bars indicate excess mortality. GFR, glomerular filtration rate. (Reproduced with permission from: Afkarian MJ et al. Am Soc Nephrology 2013;24:302).

Declaration of Competing Interest

None related to this manuscript.

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