



REVIEW ARTICLE

What's new in heart failure in the patient with type 2 diabetes?☆



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Abstract Type 2 diabetes mellitus (T2DM) is considered an independent risk factor of heart failure (HF). It has been observed that diabetics have a higher risk of heart failure than non-diabetics. However, many aspects are still unknown; for example, the existence of a particular myocardiopathy common to T2DM, the pathogenesis of the HF associated with T2DM that is still not sufficiently clear, its role in the prognosis of HF, or the influence of anti-diabetic treatments on the outcome of the HF. An attempt is made in this review to summarize all those findings that have been published in the past 5 years as regards this interesting question, placing special emphasis on those questions still unresolved.

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¿Qué hay de nuevo en insuficiencia cardiaca en el paciente con diabetes tipo 2?

Resumen La diabetes mellitus tipo 2 (DMT2) es considerada un factor de riesgo independiente para insuficiencia cardiaca (IC). Se ha visto que los diabéticos tienen un riesgo mayor de IC que los no diabéticos. Sin embargo, muchos aspectos son aún desconocidos, por ejemplo la propia existencia de una miocardiopatía propia de la DMT2, la patogénesis de la IC relacionada con la DMT2 que tampoco está suficientemente aclarada, su papel en el pronóstico de la IC, o la influencia de los tratamientos antidiabéticos en la evolución de la IC. En esta revisión intentaremos resumir todos aquellos hallazgos que han sido publicados en los últimos 5 años en relación con esta interesante cuestión, haciendo especial hincapié en aquellas cuestiones no resueltas.

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Introduction

Type 2 diabetes mellitus (T2DM) is one of the non-communicable diseases representing the greatest threat to public health, both because of its prevalence and increasing incidence and because most diabetic patients are at risk of suffering and dying from cardiovascular disease (CVD). Thus, T2DM is considered to be an independent risk factor for atherosclerotic cardiovascular disease and, of course, also for heart failure (HF). Diabetic women have been found to have a five times greater risk of HF than non-diabetic women, and this risk is 2.4 times greater in males.^{1–3} Different factors may explain this, such as the fact that T2DM is often associated with high blood pressure (HBP) and, thus, to increased cardiovascular complications such as CVD or the subsequent development of HF.⁴ In Spain, a recent study conducted in the Basque Country showed a 73.7% prevalence of HBP in T2DM. On the other hand, the prevalence of chronic diseases related to diabetes such as ischemic heart disease was 11.5%, while the prevalence rate of heart failure was 4.3%.⁵ There are however many unknown aspects, such as the possible existence of a T2DM-induced cardiomyopathy, a proposal based on post-mortem findings, or the demonstration of the presence of systolic and diastolic dysfunction in patients with T2DM. The pathogenesis of this disease has also not been fully elucidated, and its role in HF prognosis and the potential impact of antidiabetic treatment on the course of HF are also far from clear.¹

This review will try to summarize all the findings reported over the past five years related to this interesting question, with special attention being paid to pending issues.

Methods

A literature search was conducted of relevant computer databases in the field of health, the most important being MEDLINE (through PubMed). All studies published from January 1, 2010 to February 1, 2015 were examined as the basis for this review. Search criteria included the terms *heart failure*, restricted to *MESH major topic* or *title and abstract*, and *type 2 diabetes mellitus*, also restricted to *MESH major topic* or *title and abstract* combined with the *AND* operator.

The search encompassed clinical trials, meta-analyses, and reviews, as well as clinical practice guidelines; studies not written in English, German, French, or Spanish were excluded. Of the 83 studies selected, articles that did not provide new responses were finally excluded at the author's discretion, in an attempt to select those studies which were considered to be the most relevant or to have the greatest practical implications.

Once the studies had been reviewed, this review was divided into sections devoted to HF prevention in T2DM, the pathophysiology of HF in T2DM, the prognostic role of T2DM in HF, and the impact of T2DM therapy on HF (Tables 1 and 2).

Prevention of heart failure

More intensive blood glucose control has been shown to decrease the risk of microvascular disease in patients with T2DM, but it has not been shown to be associated with a reduction in the risk of macrovascular events. It is

Table 1 Key new findings in the prevention of HF associated with T2DM.

The risk of HF in T2DM is associated with U-shaped HbA1c levels (higher and lower HbA1c levels are related to a greater risk of HF) ⁶
The risk of HF is not significantly different in diabetics on intensive blood glucose control and those on standard treatment ⁷
Intensive treatment of CVRFs associated with T2DM significantly increases exercise capacity in patients with HF, while standard treatment decreases exercise capacity ⁸

Table 2 Recent key findings in the pathophysiology of HF associated with T2DM.

Autonomic neuropathy may play a role as a link between T2DM and the occurrence of HF ⁹
Diastolic dysfunction occurs in more than 50% of patients with T2DM and mainly correlates with diabetes duration, HbA1c levels, and the presence of obesity and diabetic microangiopathy ¹⁰
Independent predictors of asymptomatic LV dysfunction in T2DM include advanced age and the presence of valve calcifications and signs of concentric LV remodeling ⁴

also known that poor blood glucose control is associated with an increased risk of HF, but it is not known whether improved blood glucose control decreases that risk. Thus, for example, a U-shaped association of the risk of HF with glycosylated hemoglobin (HbA1c) levels has recently been reported, so that the highest and lowest HbA1c levels are related to a greater risk of HF.⁶

This question was analyzed in a recent meta-analysis to find out whether intensive blood glucose control decreased the incidence of fatal or nonfatal HF. For this purpose, the authors analyzed a total of 37,229 patients from eight randomized clinical trials followed up for 2.3–10.1 years. A total of 1469 events were found (55% in the group on intensive T2DM treatment). No significant difference was found between the risk of HF for patients with intensive blood glucose control and those on standard treatment (OR: 1.20; 95% CI: 0.96–1.48). The only finding was that intensive blood glucose control with thiazolidinediones increased the risk of heart failure.⁷

An additional pending issue is whether intensive and global control of cardiovascular risk factors (CVRFs), as compared to standard control, may contribute to the prevention of HF in patients with T2DM. This issue was analyzed in a recent study by Ofstad et al. This study enrolled 100 patients with ≥ 1 CVRF who were randomized to two arms (intensive vs standard management of overall CVR). The ability to prevent HF was assessed through improvement in left ventricular function, as measured by echocardiography and the results of a stress test. Stress capacity, as measured by ergometry, significantly increased in patients on intensive treatment and decreased in those on standard treatment ($p=0.014$). There were no significant changes between the groups in the echocardiographic parameters tested.⁸

Pathophysiology of heart failure

What are the mechanisms by which metabolic changes lead to HF and other cardiac changes such as atrial fibrillation (AF)? Autonomic neuropathy of diabetic patients, with its attendant cardiovascular implications, could be a potential link. Negishi et al. investigated this hypothesis. For this purpose, they explored the association between heart rate recovery (HRR), as a sign of autonomic neuropathy, and the occurrence of HF or AF. An analysis of the correlation between HRR and new onset HF and AF was conducted in 914 patients with T2DM but no known heart disease after a follow-up period of 7.8 years. The authors showed that HRR was an independent predictor for HF and AF, as well as a prognostic factor. The association was independent of other relevant factors, such as left atrial volume index, and of other markers of abnormal cardiac structure and function. All the above findings suggest that autonomic neuropathy plays a role in metabolic changes in T2DM and the subsequent development of HF.⁹

On the other hand, as already known, in hypertensive patients asymptomatic LF dysfunction usually precedes HF. Does this situation occur in patients with T2DM? Diastolic dysfunction is very common in patients with diabetes. It has been reported in more than 50% of them, and has been correlated to diabetes duration, HbA1c levels, and the presence of obesity and diabetic microangiopathy.¹⁰ However, there are pending issues which have been addressed in different studies, as will be seen below.

Does LV dysfunction lead to HF in diabetic patients? With which factors is it associated? In an attempt to resolve these questions, From et al. identified all diabetic patients in Olmsted County, Minnesota, U.S.A. who had undergone echocardiography with an evaluation of diastolic function by tissue Doppler. The primary endpoint was the development of heart failure (HF). Twenty-three percent of a total of 1760 patients had diastolic dysfunction. The five-year cumulative probability of HF development in these patients was 36.9%, as compared to 16.8% in patients with no diastolic dysfunction ($p = 0.001$). On the other hand, diabetic patients with diastolic dysfunction had a significantly greater mortality rate than those with no diastolic dysfunction. This association was independent of the presence of high blood pressure, coronary artery disease, or other echocardiographic parameters.⁴

Faden et al. also attempted to answer these questions. They reported the prevalence and the factors associated with this condition in patients with T2DM based on a detailed echocardiographic assessment. Asymptomatic LV dysfunction was detected in 68% of all patients recruited ($n = 386$). Sixteen percent of these patients had isolated diastolic dysfunction, while 25% had concurrent systolic and diastolic dysfunction. As regards the characteristics of patients with asymptomatic LV dysfunction, these were older and had lower glomerular filtration rates, higher HbA1c and C-reactive protein levels, greater LV mass and relative wall thickness, and a prevalence of valve calcifications. A multivariate analysis showed that independent predictors for this condition were advanced age and the presence of valve calcifications and signs of concentric LV remodeling.¹¹

Ayalon et al. investigated whether preclinical left ventricular diastolic dysfunction could occur independently of

LVH in metabolic syndrome (MS). For this, they recruited 90 consecutive patients with MS and no cardiovascular disease and 26 controls (with no risk factors for MS and a mean age of 43 years). In an age- and sex-adjusted analysis, after performing echocardiography with tissue Doppler (which allows for a detailed analysis of the presence of LV diastolic dysfunction), patients with MS were seen to have a greater left atrial (AL) diameter and LV mass and a lower E/A ratio and mean e' (both of which are parameters related to the presence of diastolic dysfunction) ($p < 0.001$). Most interestingly, this association continued to be significant after adjustment for blood pressure values, the use of antihypertensive medication, and the body mass index. Moreover, after adjusting for LV mass, MS continued to be independently associated with a greater LA diameter, a lower E/A ratio, and a lower mean value of the e' wave ($p \leq 0.01$). These differences, and more specifically those in e' wave measurements, were more marked at younger ages ($p = 0.003$). The authors concluded that MS is associated with preclinical LV diastolic dysfunction, which is independent of LV mass. These data suggest that MS may lead to the development of diastolic dysfunction through mechanisms other than hypertrophy. As these differences are more marked at younger ages, an early modification of dietary and lifestyle habits should be recommended.¹²

An additional issue of interest is when these changes in cardiac geometry leading to remodeling, LV dysfunction and, finally, HF start to occur. Do they occur in the early stages? In an attempt to answer this question, Shah et al. assessed the impact of obesity and obesity-related T2DM on cardiac remodeling and systolic and diastolic function in adolescents and young adults. Using echocardiography, they compared the cardiac structure and function of a group of adolescents and young adults with normal weight, obesity, and obesity-associated diabetes. The results of this study showed remodeling in 16% of obese subjects and in 20% of patients with diabetes-related obesity, as compared to <1% of subjects with normal weight ($p < 0.05$). Since adults with diastolic dysfunction have a greater risk of developing HF, these results suggest that adolescents with T2DM and obesity may be at greater risk of the early development of HF.¹³

An additional question that may be posed in the light of the results available is whether this change is due to the presence of obesity or whether T2DM also plays a role. In this regard, in a recent report Ofstad et al. analyzed echocardiographic parameters, including the evaluation of diastolic dysfunction by tissue Doppler, in 100 patients with T2DM but no HF and 100 non-diabetic controls matched by age, sex, body mass index, and systolic BP. Patients with T2DM had greater concentric hypertrophy and relative LV wall thickness. The T2DM group also showed lower E/A ratios, shorter deceleration times, and higher E/e' ratio values, among other diastolic dysfunction parameters. These differences were statistically significant for all parameters. The authors concluded that, as compared to non-diabetic obese subjects, obese diabetics had more advanced subclinical impairment in diastolic function.¹⁴

What is the basis for this relationship? What are the mechanisms leading from diastolic dysfunction to HF? In an attempt to answer this question, Abdulghani et al. recently reported the results of a study addressing these issues. These authors selected 65 patients with no coronary stenosis >30%

and categorized them as patients with T2DM (19) and non-diabetic subjects (46), the latter in turn being categorized as prediabetics (30) or controls (16). All study subjects underwent cardiovascular magnetic resonance imaging. LV mass was seen to be greater in diabetic patients as compared to both non-diabetic subjects ($p=0.01$) and prediabetic subjects ($p=0.02$). The LV torsion angle was greater in diabetics as compared to non-diabetic subjects ($p=0.047$), and the myocardial perfusion reserve was lower in diabetics as compared to non-diabetic subjects ($p=0.01$), amongst other parameters. The authors concluded that patients with T2DM have greater LV mass and LV torsion and a lower myocardial perfusion reserve, which suggests a potential link between coronary microvascular disease and the presence of cardiac dysfunction in diabetes.¹⁵

Are there other mechanisms leading to these changes? Expansion of the myocardial extracellular matrix and a reduction in coronary flow reserve are known to occur in patients with T2DM with no heart failure or coronary artery disease. Since aldosterone is involved in the pathophysiology of cardiac fibrosis and vascular lesion, Rao et al. attempted to assess the extent to which aldosterone is associated with extracellular matrix expansion and decreases coronary flow reserve in T2DM. For this, they recruited patients with T2DM with no evidence of coronary artery disease, in whom cardiac resonance and PET parameters were assessed in addition to clinical and laboratory parameters. In the 53 patients with T2DM enrolled, extracellular matrix expansion, but not coronary flow reserve, was seen to significantly correlate to 24-h urinary aldosterone excretion and to increased angiotensin II-stimulated aldosterone production, with 24 h urinary aldosterone excretion being the greatest predictor of extracellular matrix expansion. These results suggest that aldosterone may play a role in myocardial remodeling in the early stages of T2DM.¹⁶

Unresolved issues also exist in more advanced HF stages. One of these relates to circulating lipid levels and myocardial lipid contents, which are usually increased in T2DM. This may cause lipotoxicity that compromises left ventricular function and aggravates heart failure. To clarify this issue, Nielsen et al. investigated the relationship between circulating lipid levels, myocardial lipid contents, and cardiac function, as well as the acute cardiac effects of high versus low levels of circulating free fatty acids and triglyceride levels in patients with T2DM and HF. In this study, conducted on 18 patients, myocardial lipid contents correlated to triglyceride levels ($p=0.003$) and to free fatty acid levels ($p=0.001$), and these inversely correlated to left ventricular ejection fraction ($p=0.004$). The intravenous administration of free fatty acids caused no differences in exercise capacity and peak oxygen consumption between the study groups (medium or low high levels). These findings appear to suggest that patients with T2DM and HF are able to adapt to short-term extreme changes in circulating lipid substrates, showing no acute lipotoxicity.¹⁷

Type 2 diabetes mellitus as a prognostic factor for heart failure

T2DM is a common comorbidity in patients with HF and may worsen HF prognosis in these patients as compared to

non-diabetic patients. Thus, for example, a 45.3% prevalence of T2DM has been reported in patients admitted to hospital for HF.¹⁸ In this same study, after adjustment for baseline characteristics, T2DM was significantly associated with greater overall mortality (RR: 1.54; 95% CI: 1.20–1.97; $p<0.001$) and more readmissions (RR: 1.46; 95% CI: 1.18–1.80; $p=0.001$).

Does this deleterious impact on prognosis also occur in patients with HF with a preserved ejection fraction (HF-PEF)? The results of a post hoc analysis of the study Phosphodiesterase-5 Inhibition to Improve Clinical Status and Exercise Capacity in Heart Failure with Preserved Ejection Fraction (RELAX-HF) have recently been reported. The purpose of this analysis was to characterize the clinical characteristics, exercise capacity, and prognosis of patients with HF-PEF depending on the coexistence of T2DM. The analysis, conducted on 216 patients with stable HF, included, in addition to the clinical data, echocardiographic, cardiac MRI, biomarker, exercise test, and clinical event data. As compared to non-diabetic patients ($n=123$), diabetic patients with HF-PEF ($n=93$) were younger, more obese, and more frequently males, and had a greater prevalence of high blood pressure, renal impairment, lung disease, and vascular disease ($p<0.05$ for all). Diabetic patients had higher levels of uric acid, C-reactive protein, galectin-3, carboxy-terminal telopeptide of type I collagen, and endothelin-1 ($p<0.05$). Diabetic patients also had greater ventricular hypertrophy, but with systolic and diastolic ventricular function parameters similar to non-diabetic subjects, with the sole exception of a trend to higher LV filling pressures (expressed as a greater value of the E/e' ratio) in diabetic patients. Diabetic patients had poorer maximal (maximal oxygen consumption) and submaximal (distance walked in 6 min) exercise capacity ($p<0.01$). Diabetics also had more frequent hospital admissions for HF in the year preceeding the study (47% vs 28%, $p=0.004$) and a higher incidence of hospitalization for cardiac or renal causes six months after recruitment (23.7% vs 4.9%, $p<0.001$). The authors concluded that patients with HF-PEF and T2DM were at a higher risk of hospital admission and had less exercise capacity. The reason for this may be that they have greater multimorbidity and left ventricular hypertrophy, and inflammatory, pro-oxidative, and vasoconstricting activation which, amongst other factors, may contribute to this poorer prognosis.¹⁹

Treatment of type 2 diabetes mellitus and heart failure

HF is no exception to the uncertainty regarding the potential effects of antidiabetic drugs on CVDs. It appears that metformin, a routinely used drug, may be safe in patients with T2DM and HF, and it has even been reported to have beneficial effects.^{20,21} However, both thiazolidinediones and sulfonylureas have been associated with an increased risk of HF in recent meta-analyses.^{22,23}

One of the most controversial aspects in this regard is the role of dipeptidylpeptidase-4 inhibitors (DPP-4 inhibitors) in patients with HF, for which conflicting data have been reported. The only data currently available from clinical trials come from the SAVOR-TIMI study, a cardiovascular safety study of saxagliptin in patients with T2DM. This study was

conducted in 16,492 patients with T2DM and CVD or CVRFs who were randomized to saxagliptin or placebo, in addition to adequate treatment for all of their CVRFs, and were followed up for a mean of 2.1 years. The study showed no CVD increase or decrease, but the hospitalization rate for HF was increased.²⁴ A recent analysis of admissions for HF in this clinical trial showed that the risk of hospital admission for HF in patients treated with saxagliptin occurred in the first 12 months of treatment. It was also shown that patients with a greater risk of hospitalization for HF had prior HF, elevated baseline levels of brain natriuretic peptide (BNP), or chronic kidney disease. However, patients treated with saxagliptin who did not have these risk factors showed no increase in the relative risk of hospitalization for HF as compared to placebo-treated patients.²⁵

The data available for DPP-4 inhibitors are inconclusive. Thus, while one meta-analysis has related the long-term use of DPP4 inhibitors to a 15% increase in HF,²⁶ this conclusion is not supported by other studies. Thus, for example, an analysis of the US prescription register examined new antidiabetic prescriptions in almost 80,000 patients and compared those treated with and without DPP-4 inhibitors, finding no increase in the risk of hospitalization for HF.²⁷

Additional studies are therefore needed to explore the mechanisms that may explain the increased risk of hospital admission for HF found in some studies. It should be kept in mind, for example, that the enzyme DPP-4 does not only act on GLP-1, but also has an inhibitory effect on bradykinin and substance P (both of which are vasodilators). Thus, a recent study showed that the concomitant inhibition of ACE (which also inhibits substance and bradykinin) and DPP-4 increases substance P levels, causing sympathetic stimulation secondary to vasodilation.²⁸ It has also recently been seen that the effect of corin and DPP-4 on the metabolism of ProBNP 1–108 (inactive) to BNP 1–32 (active) and BNP 3–32 (active) is deficient in patients with HF. The role played by DPP-4 inhibitors if they are also added in this context is therefore unknown.²⁹ However, it is known that DPP-4 inhibitors have a beneficial effect at myocardial level in animal models, decreasing stiffness and improving LV function.³⁰

Due to all of these uncertainties, the decision to choose a given antidiabetic drug should usually be based on an assessment of the balance between the potential benefit for decreasing microvascular complications by improving blood glucose control and any potential adverse events, including hypoglycemia, or on whether hospitalization for HF is indicated.¹ Lifestyle changes leading to a healthy dietary pattern and the practice of exercise, which have already been shown to decrease the incidence of both T2DM and BNP levels, will continue to be of particular relevance.^{31,32}

Conflicts of interest

The authors state that they have no conflicts of interest.

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