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REVIEW

Impact of Sex and Diabetes in Patients with Heart Failure

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Abstract

Purpose of review Heart failure (HF) is a complex clinical syndrome with a growing global health burden. This review explores the intersection of HF, diabetes mellitus, and sex, highlighting epidemiological patterns, pathophysiological mechanisms, and treatment implications.

Recent findings Despite similar HF prevalence in men and women, diabetes mellitus (DM) appears to exert a more pronounced impact on HF outcomes in women. Pathophysiological differences involve cardiovascular risk factors, severe left ventricular dysfunction, and coronary artery disease, as well as hormonal influences and inflammatory markers. Diabetic cardiomyopathy introduces a sex-specific challenge, with women experiencing common adverse outcomes related to increased fibrosis and myocardial remodeling. Treatment strategies, particularly sodium-glucose cotransporter 2 inhibitors, exhibit cardiovascular benefits, but their response may differ in women.

Summary The link between HF and DM is bidirectional, with diabetes significantly increasing the risk of HF, and vice versa. Additionally, the impact of diabetes on mortality appears more pronounced in women than in men, leading to a modification of the traditional gender gap observed in HF outcomes. A personalized approach is crucial, and further research to improve outcomes in the complex interplay of HF, diabetes, and sex is needed.

Keywords Sex · Diabetes · Heart failure · Prognosis, gender

Introduction

Heart failure (HF) is a multifaceted clinical syndrome that poses a significant and growing health burden worldwide. Age-adjusted occurrence of HF appears to be decreasing in developed nations, likely indicating improved cardiovascular disease management. However, the overall incidence is on the rise due to population aging [1].

Sexual differences in HF have been increasingly recognized, as emerging evidence highlights differences in the clinical presentation, response to treatment, and overall prognosis between men and women. Diabetes mellitus (DM) also seems to influence men and women with HF differently [2]. This manuscript aims to delve into the intricate dynamics of how sex and DM collectively affects the course of HF, shedding light on the underlying mechanisms, clinical implications, and potential avenues for personalized care.

Epidemiology

The relation between HF and diabetes is common and bidirectional, and its impact is well assessed in current European Society of Cardiology guidelines [1, 3]. Diabetes has a significant impact on the development of HF, as a risk factor for coronary artery disease [4]. Also, several epidemiological studies have indicated a heightened risk of HF associated with prediabetes, suggesting age-adjusted hazard ratios ranging from 1.2 to 1.7 [5, 6]. An increased risk of HF in patients with metabolic syndrome has also been described [7]. HF risk is lower in individuals with prediabetes compared to those with diagnosed diabetes [5]. Compared to those without diabetes, diabetics have an almost 2.5-fold higher HF risk [8, 9]. Furthermore, gestational diabetes, a condition specific to women, has also been linked to a future risk of HF, even after adjusting for postpartum diabetes and other risk factors [10].

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On the other hand, the prevalence of diabetes and prediabetes ranges between 25 to 40% in patients with HF [11–13]. Prevalence of HF is similar in men and women, increasingly exponentially with age [1], however, DM is more present in women than in men with HF, and it is a marker of poor prognosis, adversely affecting long term survival and risk of hospitalization in patients with acute and chronic HF [2, 14]. Newly diagnosed diabetes has been associated with a 5.3 times higher risk of all-cause mortality compared to the normoglycemic reference group in both men and women [12, 15••]. Diabetes seems to increase the risk of mortality by 32% in the presence of ischemic heart disease [16].

The impact of diabetes in mortality seems to be higher in women than in men with HF (Fig. 1).

In a retrospective cohort study, based on the Spanish National Hospital Discharge Database which included 28,894 individuals, women with diabetes had higher in-hospital mortality compared to men with diabetes, potentially influenced by factors such as age, anemic syndrome, chronic renal dysfunction, dementia, and depression [15••]. A parallel association has been identified in patients with ischemic heart disease, suggesting that diabetes may elevate in-hospital mortality to a greater extent in women compared to men [17•]. In a study with 3,162 HF hospitalizations, diabetes was associated with an increase in the composite event of mortality and HF readmission in the overall population. The hazard ratios were 1.3 for the total population, males, and females. However, after adjusting for potential confounders, DM retained its independent predictor status for composite events only in the total population (hazard ratio 1.2) and in females (hazard ratio 1.4) [18]. A large metanalysis including 47 cohorts and over 12 million patients found that the excess risk of HF associated with diabetes was significantly higher in women than in men (risk ratio 2.0 in women versus 1.7 in men) [19]. This stronger association between diabetes and worse outcomes in women than in men with HF has been reported also in clinical trials [2, 20, 21].

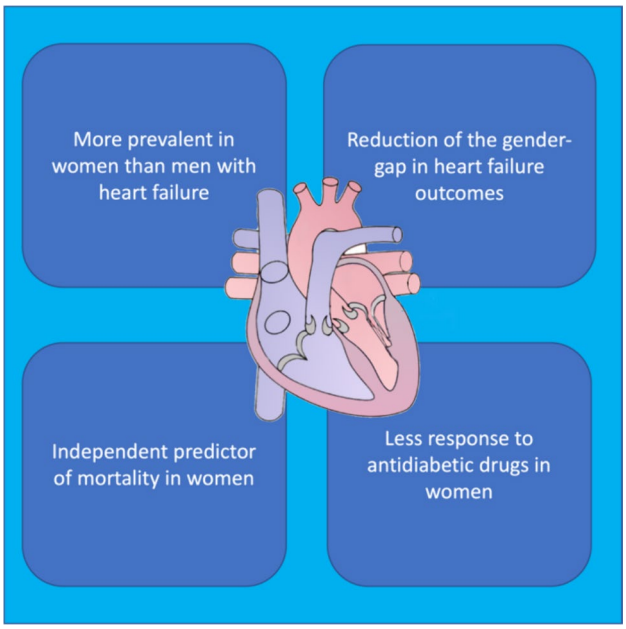

Fig. 1 Original figure illustrating the impact of diabetes mellitus in patients with heart failure and its variations according to sex

Pathophysiology

The reasons why women with diabetes and HF face a higher risk of mortality compared to men are not fully understood. The main possible factors are summarized in Fig. 2.

One possible explanation is that women with diabetes may have clusters of cardiovascular risk factors, that, together, could amplify the overall risk of developing cardiac-related complications [21]. In fact, women with HF and diabetes tend to have more severely impaired left ventricular function than men [18]. In addition, diabetes appears to have a more significant impact on coronary artery disease in women. Women with diabetes exhibit more extensive and severe coronary atherosclerosis than men. Importantly, this phenomenon cannot be solely attributed to the correlation with other traditional risk factors [22]. An increased incidence of lethal myocardial infarction in women has also been described [23].

Fig. 2 Original conceptual diagram showing a summary of various pathophysiological mechanisms contributing to excess mortality in women with diabetes and heart failure

Left ventricular hypertrophy and diastolic disfunction may also have a role in this poorer prognosis as they are more prevalent in women [24–26]. In subjects without HF, women typically have smaller left ventricular mass and ventricular size compared to men. However, with age, there is an increase in left ventricular mass among women and a decrease among men. Additionally, when there is injury or an increased workload on the heart, women tend to develop greater concentric hypertrophy of the left ventricle compared to men [27]. This concentric hypertrophy in women, with less apoptosis and cellular death lead to a more impaired diastolic function and higher filling pressures, whereas in men an eccentric pattern is predominant as cellular apoptosis occurs more frequently [28–30]. This diastolic disfunction with myocardial hypertrophy is, in addition, the hallmark of diabetic cardiomyopathy, as DM affects multiple mechanisms that contribute to myocardial stiffening [31]. It has also been reported that women with DM exhibit worse diastolic function than men with diabetes, which correlates to the extent of microvascular disfunction. This suggests a specific microvascular pattern linked to sex in diabetes, implying a potential connection between coronary microvascular and cardiac diastolic dysfunction [32].

Estrogens and androgens play crucial roles in cardiac function, influencing factors such as myocardial structure, contractility, and response to injury [33]. Androgens, such as testosterone, have been associated with increased contractility, left ventricular mass and cardiac fibrosis [34]. They can also contribute to vasoconstriction in blood vessels, whereas in the kidney they increase glomerulosclerosis and renin levels, potentially contributing to adverse remodeling [35]. Estrogens are generally considered cardioprotective, exhibiting anti-inflammatory and vasodilatory effects, and potential benefits in myocardial structure and function [36]. They are also linked to a reduction in glomerulosclerosis and a decrease in renin [37]. The interplay between these hormones also contributes to sex-specific differences in HF presentation and outcomes, and this relationship is also influenced by the presence of diabetes. Women with diabetes have less ability to convert androgen to estrogen due to a decrease of aromatase activity in the ovary [38]. Menopause, when coupled with diabetes, may amplify the risk of cardiovascular events [39]. This might be related with the increased risk of coronary artery disease seen in diabetic women.

Also, biomarkers related to inflammation and remodeling like C-reactive protein, which are significantly lower in women, increase relatively more in women than in men with diabetes [40]. Moreover, the levels of adiponectin, a protein associated with anti-inflammatory effects, show a relatively greater decrease in women compared to men across individuals with normal glucose tolerance, prediabetes, and type 2 diabetes [41]. This increased inflammatory stress in diabetic women might explain, at least in part, their comparatively elevated risk of cardiovascular disease.

The Sex-Gap in HF

Most studies analyzing the impact of sex in quality of life in HF show a poorer quality of life in women than in men [42, 43]. This is probably related to the greater prevalence of comorbidities in women, in which diabetes plays a major role [44]. However, despite women often presenting with more pronounced symptoms and reporting a lower quality of life, research consistently indicates a more favorable prognosis for women compared to men. A recent study involving contemporary HF trials revealed that, even after adjusting for powerful prognostic variables such as N-terminal pro B-type natriuretic peptide, women maintained a lower risk of mortality compared to men [42]. The adjusted risk of death from any cause was found to be 32% lower in women, a more significant difference than observed in prior analyses. Women also showed a consistent lower risk for both first and subsequent admissions, suggesting a nuanced pattern in hospitalization outcomes [42]. A post-hoc analysis of Vericiguat Global Study in Subjects With Heart Failure With Reduced Ejection Fraction (VICTORIA) trial also showed an improved prognosis in women despite being prescribed less aggressive background HF therapy compared to men [45]. Similar findings were also described in the Registrational Study With Omecamtiv Mecarbil [AMG 423] to Treat Chronic Heart Failure With Reduced Ejection Fraction (GALACTIC-HF) trial, in which a 20% less risk of cardiovascular death, HF event, and all-cause death was found in women [46].

However, the introduction of diabetes as a comorbidity modifies this sex-related gap. An analysis of 41,900 patients from the Meta-Analysis Global Group In Chronic Heart Failure (MAGGIC) found that the presence of diabetes attenuated the lower risk of death associated with female sex, suggesting that diabetes modified the relationship between sex and mortality [2]. Among patients with diabetes, there was no significant difference in the risk of death between men and women, irrespective of ejection fraction. However, in patients without diabetes, men had a higher risk of death compared to women, regardless of ejection fraction. This sex-related gap reduction has also been described in patients with ischemic heart disease, in which the presence of diabetes had a stronger association with mortality in women than in men [47].

Diabetic Cardiomyopathy

Even in the absence of coronary artery disease, hypertrophy or valvular heart disease, impaired myocardial function has been observed in diabetics, indicating the existence of a condition termed diabetic cardiomyopathy, in which sex is also an important factor [13].

The finding of myocardial dysfunction in patients with diabetes dates back to 1954, when the termed diabetic cardiomyopathy was proposed by Lundbeek, and confirmed 20 years later at autopsy by Rubler [48, 49]. While the idea of treating diabetic cardiomyopathy as a distinct condition solely linked to diabetes has faced scrutiny and is currently a topic of debate, research involving diabetic patients indicates the existence of a distinct cardiac dysfunction. The pathophysiology of this dysfunction appears unique, differing from that seen in other conditions and presenting as a complex systemic phenomenon [50•]. Initially, diabetes was thought to cause a dilated-phenotype cardiomyopathy, however, recent data confirm a more restrictive phenotype in which the typical patient is to be an elderly woman with a small left ventricular cavity, preserved ejection fraction, elevated left-ventricle filling pressures and enlarged left atrium [51, 52]. Some theories have considered this restrictive phenotype as an early stage of disease, in which its development would lead to a dilated and reduced ejection fraction phenotype, however, other believe that diabetic cardiomyopathy causes two independent phenotypes [53, 54]. Myocardial dysfunction in diabetes is thought to arise from various factors such as lipotoxicity, the deposition of advanced glycation end-products in microvasculature, reduced microvascular density (rarefaction), and autoimmune responses. These mechanisms collectively contribute to the development of myocardial fibrosis and/or hypertrophy, which are considered the characteristic features of this disease [55, 56].

When patients with diabetic cardiomyopathy have been studied according to sex, women seem to be more likely to experience negative outcomes compared to men. In a study of 100 patients with diabetic cardiomyopathy, female sex was an independent predictor of functional deterioration and cardiovascular events with an odds ratio of 3.6 [57, 58]. The process of myocardial remodeling takes place as diabetic cardiomyopathy develops, involving heightened fibrosis which results in increased stiffness of the myocardium [59, 60]. Research indicates more extensive myocardial remodeling and fibrosis in women with HF compared to men. Specifically, women with diabetes have greater cardiac hypertrophy, myocardial wall thickening, and an increase in left ventricular mass [61].

Treatment

A substantial body of evidence suggests that most HF drugs apply equally to individuals, whether they have diabetes or not. However, only some antidiabetic drugs reduce cardiovascular events, as sodium-glucose cotransporter 2 inhibitors, that decrease the risk of major cardiovascular events and HF hospitalizations [3, 62, 63]. The response to these drugs may be weaker in women. In previous metanalyses a significant reduction in major adverse cardiac events was seen in men but not in women [64], and the HF benefit is also less pronounced in women [65••]. In the case of glucagon-like peptide-1 receptor agonists, metanalysis data suggest a reduction in the risk of cardiac events in men and women, but without a relevant incidence in HF incidence [64].

Several sex-related variations have been observed in drug effects. There are gender differences in body composition, hormonal levels, and pharmacodynamics and pharmacokinetics [66]. For instance, women tend to experience a more significant prognostic advantage from angiotensin-receptor blockers [66]. On the other hand, the positive impact of sodium-glucose cotransporter 2 inhibitors on outcomes is mainly influenced by a decrease in HF-related hospitalizations [65••] and women tend to face a higher likelihood of recurrent HF-related hospitalizations compared to men [67–69].

Conclusions

Epidemiological evidence establishes a bidirectional relationship between HF and diabetes, with diabetes significantly increasing the risk of HF and vice versa. The impact of diabetes on mortality appears to be more pronounced in women than in men, modifying the traditional gender gap observed in HF outcomes. Further research, with a focus on sex-specific responses and inclusion of more women in HF clinical trials is needed.

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Declarations

Competing interests The authors have no relevant financial or non-financial interests to disclose.

Human and Animal Rights This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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