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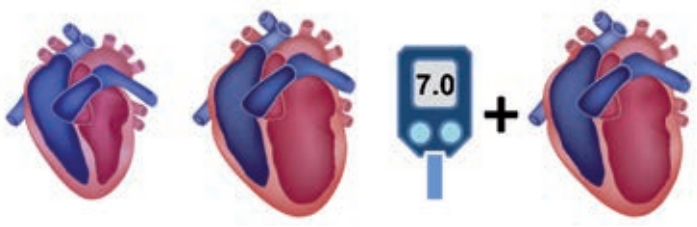

Heart failure in patients with diabetes

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Heart and Metabolism

Heart and Metabolism a Servier publication

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Aim and Scope *Heart and Metabolism* is a journal published three times a year, focusing on the management of cardiovascular diseases. Its aim is to inform cardiologists and other specialists about the newest findings on the role of metabolism in cardiac disease and to explore their potential clinical implications.
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Diabetes and heart failure – a challenging combination

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Diabetes mellitus and heart failure (HF) often coexist, and together, their effects on clinical outcomes are compounded. On the one hand, diabetes is an independent risk factor for developing heart failure, with a twofold increased risk in men, and a fivefold increased risk in women. On the other hand, in patients with heart failure, diabetes mellitus is highly prevalent, being present in 25% of chronic heart failure cases, and 40% of acute heart failure cases. The latter is especially so in heart failure with preserved ejection fraction. Individually, heart failure has a poorer prognosis than diabetes mellitus, and should therefore be the priority in terms of treatment. In this issue of *Heart & Metabolism*, the intimate relationship between diabetes and heart failure is explored, with a special focus on their changing epidemiology, the mechanisms underlying diabetes with concomitant heart failure, the effect of antidiabetic drugs on heart failure risk and other cardiovascular outcomes, and the diagnosis and management of patients with diabetes and HF.

Gierula and Kearney (p 4) open the issue with a description of the changing epidemiology of diabetes and HF, highlighting the epidemic of diabetes which is sweeping the world, especially in developing countries. Concurrent with this is an increased prevalence of HF, given that diabetes is the major risk factor for developing HF, either as a complication of coronary artery disease, or as the clinical entity of diabetic cardiomyopathy. Chandramouli and Lam (p 8) highlight the changing epidemiology and increased prevalence and burden of diabetes, obesity, and HF, which has taken place in Asia over the past few decades, in parallel with the significant economic growth and urbanization in this part of the world. Emerging data has shown that over half of Asian patients with HF have concomitant diabetes, and of special interest is that diabetic Asian patients with HF have a lower BMI, more comorbidities, earlier onset of HF, worse quality of life and clinical outcomes, when compared with their Western counterparts. This difference in clinical phenotype is likely to impact on the patient response to therapies, which may therefore need to be tailored to the unique Asian phenotype of diabetes and HF.

Diabetic cardiomyopathy refers to the presence of structural or functional abnormalities of the myocardium in diabetic patients which are not fully explained by other factors such as coronary artery disease or hypertension. As a clinical entity, it is often challenging to diagnose and manage. Wheatcroft (p 13) reviews the role of cardiac imaging modalities, echocardiography, and cardiovascular magnetic resonance for diagnosing diabetic cardiomyopathy, and Gollmer and Bugger (p 37) provide an overview of the mechanisms underlying diabetic cardiomyopathy. The metabolic perturbations underlying diabetes and HF and their interplay are reviewed by Karwi and Lopaschuk (p 32). They propose targeting myocardial energy metabolism by optimizing cardiac energy substrate reference, as a potential therapeutic approach to im-

prove patient outcomes. The challenges with managing diabetic patients with ischemic HF are highlighted in a case report by Magaña Serrano (p 28), who proposes a personalized approach to treating patients with concomitant diabetes and HF.

In recent times, several landmark clinical outcome studies have been published reporting beneficial effects of new antidiabetic drugs on cardiovascular outcomes in diabetic and more recently nondiabetic patients at risk of cardiovascular disease. These trials are reviewed in the next article, by Bell (p 18) who highlights the cardiovascular benefits of sodium/glucose linked transporter-2 inhibitors (SGLT2is) and glucagon-like peptide-1 receptor analogues (GLP-1RA). Particularly interesting are the beneficial effects of the SGLT2i, dapaglifozin, which was recently shown to reduce HF hospitalization in both diabetic and nondiabetic patients with HF with reduced ejection fraction. Further studies are needed to understand the mechanisms underlying the beneficial effects of these antihyperglyaemic agents on cardiovascular outcomes. Finally, the cardiovascular, kidney, and retinal complications of diabetes are well known. Kovalik (p 23) provides an overview of less well-known musculoskeletal, neuropathic, and skin complications of diabetes, which are often difficult to manage and treat.

In summary, in this issue of *Heart & Metabolism*, we aim to highlight the increasingly important and global problem of diabetes with concomitant heart failure, and we discuss the challenges of diagnosing and managing these two common medical conditions when they occur in combination. ■

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Original Article

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Changing epidemiology in patients with heart failure

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Abstract: Heart failure (HF) and type 2 diabetes mellitus (DM) are current global epidemics with increasing prevalence that show no signs of slowing down. Of particular concern is the burden that both of these disorders place on individuals and society as a whole. Individually, both are expensive in resources, have high mortality rates, and cause significant reductions in quality of life. However, 30% to 45% of patients with HF have DM, and DM is an independent risk factor for the development of progressive HF and cardiovascular death, complicating management for physicians and further raising pressures on health and social care systems. Breakthroughs in the medical management of DM and HF have reduced mortality rates, meaning that the current epidemic is largely fueled by increased prevalence of the two disorders. Of particular concern is the rise of DM in developing countries, as these areas of the world become more prosperous, with the trappings of Western civilization rapidly infiltrating their cultures. Subsequent declines in physical activity and increased consumption of refined foods, drastically removed from indigenous eating habits, are resulting in DM sweeping the globe. ■ *Heart Metab*. 2019;80:4-7

Keywords: diabetes mellitus; epidemiology; heart failure; heart failure with reduced ejection fraction; heart failure with preserved ejection fraction

Introduction

The prevalence of type 2 diabetes mellitus (DM) and heart failure (HF) have reached epidemic proportions, generating major challenges to health and social care systems globally.[1,2] Both conditions are associated with reduced quality of life, frequent hospitalization and are leading causes of mortality. An epidemic can reflect increased incidence, increased survival leading to increased prevalence, or both factors combined. In the case of HF and DM both increased incidence and survival have contributed to the rise in both of these disorders; it is estimated that 38 million people in the world are affected by HF,[2] and figures from the International Diabetes Foundation (IDF) indicate that in 2017 425 million adults were living with DM - a figure projected to rise to 629 million by 2045.[3]

It is becoming increasingly understood that HF is not an independent pathology, but rather a heterogeneous group of conditions presenting with the classic symptoms of the HF syndrome: fatigue, breathlessness, and edema. Historically HF has been viewed as a failure of left ventricular (LV) contractile function, with reduced left ventricular ejection fraction (LVEF) being used to define systolic dysfunction, assess prognosis, and select patients for therapeutic interventions.[4] However, it is now well established that HF can occur in the presence of normal or near-normal LVEF: this HF with preserved ejection fraction EF (HFpEF) now accounts for a substantial proportion of clinical cases of HF.[5,6]

HF is frequently accompanied by a number of comorbid conditions, complicating management for physicians and contributing to worsening morbidity and mortality. These comorbidities include, but are not limited to, renal disease, obesity, anemia, and type 2 diabetes mellitus (DM). DM is an independent risk factor for the development of progressive HF and cardiovascular death,[7-10] and is present in 30% to 45% of people with existing HF,[11] which, when combined with alarming projections for future prevalence,[3] implicates DM as perhaps the most important comorbidity of all in HF.

Type 2 diabetes mellitus

Traditionally viewed as a disease of affluent Western society, DM has now spread to all four corners of the globe, and there are now more people living with type 2 diabetes in developing societies than in industrialized nations.[12] It is estimated that the number of adults with DM in the world increased from 108 million in 1980 to 425 million in 2017,[3,12] with growth and aging of the world population, the global obesity epidemic, and the success of cardiovascular risk management and treatment being key factors in this meteoric rise.[13,14] The spread of the DM epidemic to the developing world adds a further challenge to health care systems already under strain from contending with communicable diseases.[1] Inadequate prevention strategies, delayed diagnosis, and substandard aftercare of people with diabetes raises the risk of developing future complications such as ischemic heart disease (IHD), [8] further increasing the burden on societies lacking sufficiently funded health care systems.

Heart failure with reduced ejection fraction

Arising as a consequence of a number of conditions impacting on LV function, including coronary artery disease, valvular heart disease, and hypertension, heart failure with reduced ejection fraction (HFrEF) remains a major cause of death and disability worldwide.[2] The second half of the 20th century saw little change in the incidence of HFrEF among men, a drop of one third in incidence among women and a one third decline in mortality following the onset of HF in both sexes.[15] Despite positive trends in mortality, HFrEF remained deadly: 50% of patients given a diagnosis of HFrEF in the 1990s, when annual incidence in North America was around half a million cases, were dead at 5 years.

Continued advancements in our understanding of the underlying pathophysiology of HFrEF led to developments in pharmacological treatment,[16-19] and device therapy[20,21] which, when combined with improved post-myocardial infarction survival rates[22] resulted in the first decade of the 21st century witnessing a simultaneous reduction in cardiovascular mortality and HFrEF incidence.[23-25] However, conflicting data from a recent population-based study in the United Kingdom raises cause for concern. From 2002 to 2014, the incidence of HF decreased by 7% from 358 to 332 per 100 000 person-years). But, the number of individuals with a new diagnosis of HF increased by 12%, from an estimated figures of 170 727 in 2002 to 190 798 in 2014, largely attributed to ageing and increases in population. This was accompanied by a 23% increase in the absolute number of patients with HF in the UK, a rise from 750 127 in 2002 to 920 616 equates to a 23% increase in prevalence over this period.[24]

Heart failure with preserved ejection fraction

The ongoing change in the HF landscape is also influenced by a higher proportion of diagnoses being attributed to HFpEF.[5,26] Understanding the epidemiology of HFpEF has been challenging due to the heterogeneity of underlying etiology and pathophysiology, making diagnosis difficult.[27,28] Despite this there is general consensus that prevalence of HFpEF is increasing.[28] A review of 31 studies conducted from 1970 to 1995 HF found between 13% and 74% (median 40%) of patients investigated for HF had HFpEF,[29] and following this 12 studies published from 1998 to 2003, found the prevalence of HFpEF to be between from 40% to 71% (mean 54%).[6,30] As of yet no therapeutic intervention has proven to be effective in HFpEF[31-34] consequently, this increased prevalence is unlikely to change in the near future. Alongside an emphasis on multiple phenotypes of HFpEF, there is a growing consensus about HFpEF being more of a systemic disease with adverse consequences in multiple organs than one involving exclusively the heart.[35] A number of studies have suggested that DM is an important risk factor for all-cause mortality in patients with HFpEF[9,36,37] identifying the presence of DM as an important phenotype of HFpEF, which may have implications for therapeutic strategies.

Conclusion

Both DM and HF represent a significant problem for society; individually both are expensive of resources and are leading causes of morbidity and mortality, but as comorbidities they result in significantly worse outcomes for an increasing number of people who suffer from both conditions. Advancements in medical therapy have shifted the landscape of both DM and HF: favorable impacts on mortality have the challenging effect of increased health care utilization, which is increasingly becoming a problem in countries with less developed and under resourced health care systems. The problems presented by DM and HF are too great for the scientific community to handle on their own; whilst emerging nations cannot be deprived of their chance to develop financially and socially, there is a desperate need for higher-level intervention, to ensure that the necessary education on lifestyle management is delivered to stem the tide of this deadly duo. ■

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Original Article

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"Glocalization" of concomitant heart failure and diabetes in Asia

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Abstract: Asia has witnessed significant economic growth and urbanization in the past few decades. In parallel, this has increased the burden of diabetes, obesity, and heart failure (HF). Emerging data has shown that between 40% and 57% of Asian patients with HF have concomitant diabetes. Compared with their Caucasian counterparts, Asian patients with HF have a threefold higher burden of diabetes, are a decade younger, have a lower body mass index, and have greater comorbidity burden. In Asia, there are important differences in clinical correlates and left ventricular remodeling patterns associated with diabetes between HF with reduced ejection fraction (HFrEF) and HF with preserved ejection (HFpEF). Irrespective of the HF subtype, diabetes portends worse quality of life and clinical outcomes. Simultaneously, evidence for a lean diabetic phenotype in HF is accumulating in this region. Given the rich ethnic and regional diversity in Asia, one size certainly does not fit all here. Tailoring therapies and public health policies which cater to these distinct Asian phenotypes is essential for strategic management of concomitant diabetes and HF. This review will explore the epidemiology, clinical correlates, and the unique characteristics of concomitant diabetes in both HFrEF and HFpEF in Asia, with emphasis on the lean diabetic phenotype of HF. ■
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Keywords: Asia; Asian; heart failure; HFrEF; HFpEF; lean diabetes

Introduction

Asia is the most diverse continent,with a "jambalaya" of ethnosociocultural aspects. The tiger economy of Asia has fueled rapid urbanization and epidemiological shifts in the last few decades. This in turn has escalated the prevalence of metabolic syndrome and diabetes in this region. More than half of the global diabetes population (4.7 billion)[1] now resides in Asia, with South-East Asia ranking the highest (78 million).[2] Heart failure (HF) is a common complication in patients with diabetes.[3-6] Among Asian patients with HF, concomitant diabetes portends the worst clinical outcomes, for both HF with preserved ejection fraction (HFpEF) and HF with reduced ejection fraction (HFrEF),[3-6] with key differences in both HF subtypes.[6] Simultaneously, evidence for a lean diabetic phenotype in HF, which has no proven therapy, is accumulating from this region. The management expenditure of diabetes is expected to escalate to $802 billion by 2040.[7] This poses tremendous economic strain on the health care systems across Asia, which are traditionally tailored to be acute, rather than chronic care, models.

This review examines the unique characteristics of concomitant diabetes in HFrEF and HFpEF in Asia, with emphasis on the lean diabetic phenotype.

Epidemiology of diabetes with heart failure in Asia

Population-based data on concomitant diabetes and HF from Asia is scarce. Regional registries of HF patients in Asia have documented a remarkably high prevalence of diabetes in 34% to 47% Asia-wide, with the exception of Japan and Korea.[8] The Asian Sudden Cardiac Death in Heart Failure (ASIAN HF) Registry (11 Asian regions: Taiwan, China, Hong Kong, India, Thailand, Japan, Korea, Singapore, Malaysia, Indonesia, and the Philippines) reported a striking 42.5% prevalence of diabetes among patients with HF, with a threefold higher risk of developing diabetes among those from higher- (vs lower-) income countries (Singapore, Taiwan, South Korea, Hong Kong, Japan).[9] Compared with White Europeans with HF, South-East Asians have a ~threefold higher prevalence of diabetes (57% vs 24%).[3] Patients with HFpEF (ejection fraction [EF]>50%) had a higher prevalence of diabetes (45.0% vs 40.2%) than HFrEF (EF<40%).[6] *Table I* summarizes key findings among HFrEF and HFpEF patients with diabetes.

Given the sociocultural diversity and diasporic nature of this region, regional and ethnic heterogeneities are rather distinct. The prevalence of diabetes among HF patients is highest in Singapore (58.2%), followed closely by Hong Kong (56.9%), and lowest in China (22.8%).[6] Patients with HF from South East Asia (Thailand, Malaysia, Philippines, Singapore, and Indonesia) and North-East Asia (South Korea, Japan, Taiwan, Hong Kong, China) have the highest (49.3%) and lowest (31.8%) prevalence of diabetes, respectively.[9] Key ethnic differences in HF patients are also noted, with diabetes being least prevalent among Westerners (29.3%), followed by Japanese/Koreans (34.1%), Chinese (42.3%), Indians (44.2%), and most prevalent among Malays (51.9%). Among HF patients, Malay women and Indians with comorbidities (coronary artery disease and hypertension) are particularly at greater risk of developing diabetes.[5]

Comorbidities

Despite a younger age (62 vs 77 years) and lower degree of obesity (19.5% vs 24.8%), there is greater comorbidity burden among Asian patients with HF, compared with their Caucasian counterparts.[3,10] Chronic kidney disease (CKD), hypertension, and coronary artery disease are more common among diabetic patients with HFrEF and HFpEF, compared with nondiabetics of both HF subtypes.[6] Microvascular complications (nephropathy, neuropathy, retinopathy) in diabetes were more prevalent in HFpEF than HFrEF (20% vs 27%) but was similarly associated with worse composite (adjusted hazard ratio [aHR], 1.35, 95% CI, 1.04-1.76) outcomes in both HF subtypes ($P_{interaction}$= 0.112).[11]

Cardiac structural and function changes

Among Asian patients with HF, diabetes is associated with adverse cardiac remodeling (smaller left ventricular [LV] volumes and greater diastolic dysfunction [higher E:e' ratio]), compared with those without diabetes.[6] Diabetes was predominantly associated with preserved LV wall thickness and eccentric hypertrophy among patients with HFrEF, but with increased LV wall thickness and concentric hypertrophy in HFpEF.[6] Intriguingly, among Asian women with HFrEF, diabetes is associated with more concentric remodeling than in men.[4] Differences in diabetes-related remodeling mechanisms could potentially differ between both HF subtypes.[12,13] In HFrEF, diabetes causes increased apoptosis accompanied by fibrosis. In HFpEF, diabetes could potentially cause cardiomyocyte hypertrophy and stiffness following hyperinsulinemia and endothelial dysfunction owing to coronary microvascular disease.[12] Indeed, having a greater number of microvascular complications among HF patients with diabetes is associated with higher LV filling pressures in both HF subtypes, but was also associated with reduced and increased LV hypertrophy in HFrEF and HFpEF, respectively.[11]

Clinical and patient-related outcomes

In both HF subtypes in Asia, diabetes was associated with worse outcomes at 1 year, with 27% and 22% greater adjusted risks of HF rehospitalization and composite outcomes *(Table I).*[6] Diabetes was associated with a 37% higher univariate risk for all-cause mortality, which was attenuated with multivariable adjustment,[6] possibly attribut-

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able to a short follow-up period.[14] Diabetes also portends worse composite outcomes among women with HFrEF in Asia, despite similar prevalence in both sexes *(Table I).*[4] Whether these sex differences also translate to HFpEF remains to be investigated.

Antidiabetic medication and HF outcomes

Prescription patterns of antidiabetic medications among patients with HF varies vastly across Asia. Metformin was most the commonly used in Asia, except in Japan and China,[15] the latter being possibly related

	HFrEF with diabetes (vs HFrEF without diabetes, where appropriate)	**HFpEF with diabetes** (vs HFpEF without diabetes, where appropriate)	**References**
Prevalence of diabetes (%)	40.2	45.0	6
Age (y)	61.9 (10.9)	69.4 (10.8)	6
Men (%)	75.6 - 78.2	50.3	6
Duration of diabetes (y)	9.8 (8.2)	12.0 (8.3)	6
Average BMI (kg/m^2)	25.5 (4.9)	28.4 (6.1)	6
Under- or normal weight*%	31.9	16.8	6
Obesity*%	28.1	49.4	6
Microvascular disease (neuropathy, retinopathy, and nephropathy)%	20	27	11
Correlates of diabetes	Older age, higher BMI, Indian and Malay ethnicity, middle-high income countries, presence of comorbidities (obesity, chronic kidney disease, hypertension, coronary artery disease, prior stroke, peripheral arterial disease), absence of atrial fibrillation	Higher BMI, Malay ethnicity, high-income countries, presence of comorbidities (chronic kidney disease, hypertension, coronary artery disease, microvascular disease [neuropathy, retinopathy and nephropathy])	3, 5, 6
DM medications	Metformin (most common, in absence of renal contraindication), sulfonylurea, insulin, and a dipeptidyl peptidase-4 inhibitor	Metformin, sulfonylurea, insulin, and a dipeptidyl peptidase-4 inhibitor	6, 15
HF medications	Less likely on MRA and RAASi more likely to be on diuretics or β-blockers	Less likely on MRA more likely to be on diuretics or β-blockers	6, 15
LV remodeling	Preserved LV wall thickness smaller LV end diastolic and systolic volumes higher E:e' ratio eccentric hypertrophy	Thicker left ventricular wall smaller LV end diastolic and systolic volumes higher E:e' ratio concentric hypertrophy	4, 6
Quality of life	Worse quality of life with diabetes	Worse quality of life with diabetes; Greater differences in patients with and without diabetes in HFpEF more than in HFrEF	6
Clinical outcomes	Worse 1-year outcomes in both HF subtypes (pooled analysis): all-cause mortality (adjusted hazard ratio [aHR] 1.08 95% CI 0.87-1.35, *P*=0.473), cardiovascular mortality (aHR 1.07 95% CI 0.83-1.36, *P*=0.603), composite outcomes (all-cause mortality/HF hospitalization) (aHR 1.22 95% CI 1.05-1.41, *P*=0.011), HF hospitalization (aHR 1.27 95% CI1.05-1.54, *P*=0.014) $P_{interaction}$ HF subtype and diabetes >0.05 for all		6
Sex differences	Among diabetic women (vs diabetic men): - similar prevalence of diabetes (42 vs 43%) - diabetes at a lower BMI (≥23 vs ≥27.5 kg/m^2) - Greater CKD burden (odds ratio: 1.85 vs 1.32) - Greater concentric remodeling - Worse composite outcomes (aHR 1.79 vs 1.32)	Not available	4

Table I *Key findings of concomitant diabetes among heart failure patients in Asia. BMI, body mass index; CKD, chronic kidney disease; DM, diabetes mellitus; HFrEF, heart failure with reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; LV, left ventricle; MRA, mineralocorticoid receptor antagonist; RAASi, renin-angiotensin-aldosterone system inhibitors. *WHO-recommended Asian cutoffs <18.5, 18.5-23.0, 23.0-27.5, ≥27.5 kg/m^2 for underweight, normal, overweight, and obese respectively*

to the high risk of lactic acidosis in their older patient population.[16] Paradoxically, prescription of sulfonylureas and dipeptidyl peptidase-4 (*DPP-4*) *inhibitors* were common, despite low trial evidence.[15] A number of cardiovascular outcome trials (Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes [EMPA-REG OUTCOME], Canagliflozin Cardiovascular Assessment Study [CANVAS] Program, Dapagliflozin Effect on CardiovasculAR Events [DECLARE-TIMI]) and real-world data [CVD-REAL 2], which included Asian countries, have evidenced that sodium glucose cotransporter 2 inhibitors (SGLT2is) reduce cardiovascular outcomes among diabetic patients with established cardiovascular disease.[17-19] Despite these promising results, the usage of SGLT2is is limited in Asia due to the high associated costs. Of note, appreciable ethnic differences with regards to SGLT2is also exist in published SGLT2i trials. The point estimates for Asians (HR 0.68, 95% CI: 0.48-0.95) and Caucasians (HR 0.88, 95% CI: 0.74-1.04) appeared lower than for blacks (HR 1.48, 95% CI: 0.80-2.02) in EMPA-REG OUTCOME.[19] Conversely, the point estimates for blacks (HR 0.45, 95% CI: 0.19-1.03) and Caucasians (HR 0.84, 95%CI: 0.73-0.96) appeared lower than for Asians (HR 1.08, 95% CI: 0.72-1.64) in CANVAS.[17] Notably, EMPA-REG OUTCOME, CANVAS, and DECLARE-TIMI only had 21%, 13%, and 13% Asians, respectively.[17-19] Therefore, further trial evidence on SGLT2i and a more feasible cost structure are needed for Asian patients with diabetes.

Lean-diabetic phenotype in Asia

Emerging data from the region has highlighted a *sui generis* lean diabetic phenotype among Asian patients with HF. Our rhetorical understanding of diabetes stems from lifestyle changes associated with urbanization and genetic predisposition causing higher prevalence in obesity, glucose intolerance, and subsequently insulin resistance. Lean diabetes occurring among normal or underweight individuals has challenged this conventional paradigm. Population studies from developing nations have evidenced an early age of onset, lack of ketosis upon withdrawal of insulin among malnourished individuals with poor socioeconomic status.[2,20] Compared with Europeans, Indians had strikingly higher prevalence and a three- to fourfold higher risk of diabetes without a corresponding higher risk of being overweight/obese.[21]

Accumulating evidence of lean diabetes among patients with HF is emerging from Asia.[3] In a cross-sectional comparison of Asian and white patients with HF, Asians patients had threefold higher prevalence of diabetes, despite lower body mass index (BMI).[3] The higher burden of diabetes persisted across all BMI categories in Asian patients with HF, including lean and normal BMI categories. Obesity was not as strongly related to diabetes among Asians, compared with whites (odds ratio [OR]: 1.82 vs 3.45).[3] When Asian patients with HF were naturally clustered based on comorbidities, the lean diabetic cluster was associated with the worst quality of life and composite outcomes, with 79% greater risk of hospitalization and mortality at 1 year, compared with young patients with HF.[3,22] Of note, Asian women with HF are more prone to be diabetic at a lower BMI (≥23 vs ≥27.5 kg/m^2), compared with men with HF.[4] Among asymptomatic (without HF) Chinese patients with diabetes, subclinical cardiac remodeling and systolic dysfunction occurred at much lower glycemic cutoffs (compared with universal), and to a more pronounced extent in those who were lean (BMI<23kg/m^2).[23]

Hypotheses surrounding the lean diabetes phenotype include maternal and fetal malnourishment, poor insulin secretion, and unfavorable fat distribution.[3,7] In a population-based study, glucose intolerance in adults was associated with low birth weight at infancy till 2 years of age and subsequent accelerated increase BMI during childhood till adulthood.[24] Mechanistically, a lower number of pancreatic β-cells at birth and poor insulin secretory capacity have also been implicated in lean diabetes. This is in contrast to the poor insulin action suggested in diabetics with higher BMI,[25] suggesting that lean diabetes is potentially a sharp variant of the conventional obesity-related diabetes. Further, Asians are also predisposed to visceral/abdominal fat deposition. A recent study comparing body composition between various ethnicities identified South Asians to have the least favorable body composition (greater visceral and pericardial fat) and adipokine profile compared with others (Whites, Chinese-Americans, African-Americans, and Latinos).[26] This has even prompted the International Diabetes Federation to decide on lower waist circumference cutoffs to diagnose metabolic syndrome in Asians.[27] However, these theories await investigations in HF populations.

Conclusion

Asia harbors the majority of the world's concomitant DM and HF population. Until recently, our knowledge about these coexisting conditions in this region was rather limited. Asian patients with HFrEF and HFpEF are laden with a huge burden of diabetes at a young age, have a high prevalence of comorbidities, and are associated with worse outcomes. In addition to the important ethnic and regional differences, the unique lean diabetic phenotype in this region makes management of these conditions more challenging. Much as we have begun to recognize and appreciate these unique Asian HF and diabetes phenotypes, this evidence merely serves as a maiden voyage for more warranted, deeper explorations to better understand the pathology. ■

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Original Article

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Diagnosing diabetic cardiomyopathy

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Abstract: Diabetic cardiomyopathy reflects the presence of structural or functional abnormalities of the myocardium in an individual with diabetes which are not fully explained by other factors known to cause myocardial dysfunction. Diabetes promotes a range of molecular and cellular changes leading to left ventricular concentric hypertrophy, fibrosis, abnormal perfusion, lipid deposition, altered metabolism, diastolic dysfunction, and later progression to systolic dysfunction. Diagnosis of diabetic cardiomyopathy requires identification of such pathological features whilst at the same time excluding other causes of left ventricular dysfunction. In this article, available modalities which can contribute to a diagnosis of diabetic cardiomyopathy are discussed. In most cases a diagnosis of diabetic cardiomyopathy can be reached by echocardiography or cardiac magnetic resonance imaging to detect structural and functional myocardial changes, with computed tomography coronary angiography being employed to exclude obstructive coronary artery disease which could account for left ventricular dysfunction. ■ *Heart Metab*. 2019;80:13-17

Keywords: cardiac computed tomography; cardiac magnetic resonance imaging; coronary artery disease; diabetes; echocardiography; heart failure

Introduction

Heart failure is common in patients with diabetes, with prevalence at least twofold higher in subjects with diabetes than in those without.[1,2] Unrecognized left ventricular dysfunction may affect over one quarter of patients with type 2 diabetes.[3] In some patients with diabetes, left ventricular dysfunction is attributable to other conditions including hypertension or coronary artery disease, but in others diabetes itself is thought to the be the cause.

What is diabetic cardiomyopathy?

The term "Diabetic cardiomyopathy" was first used by Rubler et al in 1972 to describe post-mortem histological findings in hearts from individuals with diabetes and heart failure who did not have coronary artery disease, hypertension, or valvular heart disease.[4] Despite subsequent research to better understand the mechanisms and clinical features of myocardial disease in the presence of diabetes, a consistently applied definition to identify a distinct cardiomyopathic process in diabetes is lacking. Recently Lee et al proposed a pragmatic definition of diabetic cardiomyopathy which will be used here – "cardiac abnormalities not wholly explained by other cardiovascular or non-cardiovascular causes and likely to be due to diabetes."[5]

The factors which underpin myocardial dysfunction in diabetes are described in detail elsewhere in this issue of *Heart & Metabolism*. However, diagnosis is founded on the basis that diabetic cardiomyopathy comprises structural, functional, and molecular alterations which can be assessed using appropriate imaging or biomarkers.[6] At the structural level, diabetes causes increases in left ventricular wall thickness and mass leading to concentric hypertrophy. Diffuse myo-

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cardial fibrosis and deposition of triglycerides lead to expansion of the extracellular matrix. Functional alterations in the early stages of diabetic cardiomyopathy include diastolic dysfunction and altered indices of myocardial deformation, whilst metabolic alterations reflect deposition of lipids and changes in substrate utilization. Over time, diabetic cardiomyopathy is thought to progress to left ventricular dilatation, eccentric remodeling, and systolic dysfunction.[7,8] Some observers, however, believe these "restrictive" and "dilated" phenotypes do not represent successive stages of diabetic cardiomyopathy but evolve independently depending on the type of diabetes and the presence of obesity.[9]

Diagnosis of diabetic cardiomyopathy

A pragmatic approach to diagnosing diabetic cardiomyopathy, summarized in *Figure 1*, first requires identification of structural and functional abnormalities indicative of myocardial dysfunction, and second exclusion of other conditions, in particular obstructive coronary artery disease, which could contribute to impaired cardiac performance. In most cases a diagnosis of cardiomyopathy can be reached by noninvasive cardiac imaging. Exclusion of concomitant obstructive coronary disease can be achieved by coronary imaging with computed tomography or by ruling out ischemia by stress imaging. Roles for circulating biomarkers and assessment of myocardial metabolism are still emerging and not yet in routine clinical use.

There are no universally accepted diagnostic criteria for diabetic cardiomyopathy. In the absence of clinical studies assessing the accuracy of diagnostic techniques specifically in individuals with diabetic cardiomyopathy, diagnosis is reliant on information extrapolated from studies carried out in the broader population with diabetes.

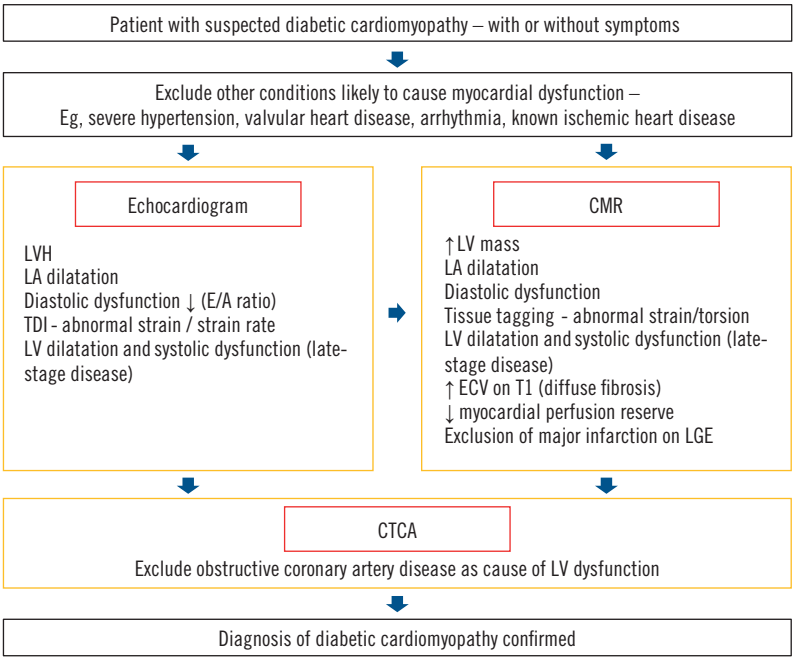

Figure 1 *Proposed algorithm for the diagnosis of diabetic cardiomyopathy. Selection of echocardiography or CMR is dependent on local resource availability. The presence of concentric left ventricular hypertrophy and diastolic dysfunction are characteristic of early-stage disease. Abnormal strain indices, including reduced longitudinal contractility and impaired systolic circumferential strain, are common in diabetes-related myocardial dysfunction. In established diabetic cardiomyopathy, raised extracellular volume on T1 CMR imaging indicates the presence of diffuse fibrosis. In late-stage disease, left ventricular dilatation and systolic dysfunction may be observed, although it is important to exclude a causative role for hypertension and obstructive coronary disease in such cases. E/A, ratio of E-wave to A-wave velocity on trans-mitral Doppler; ECV, extracellular volume; CMR, cardiovascular magnetic resonance; CTCA, computed tomography coronary angiogram; LA, left atrium; LGE, late gadolinium enhancement; LV, left ventricle; LVH, left ventricular hypertrophy; TDI, tissue Doppler imaging*

Echocardiography

Two-dimensional (2D) Doppler echocardiography is the gold-standard tool to identify structural and functional cardiac abnormalities in the evaluation of patients with suspected myocardial dysfunction. Comprehensive evaluation by conventional echocardiography allows the detection of multiple alterations associated with diabetic cardiomyopathy, including left ventricular hypertrophy, left atrial enlargement, and diastolic or systolic left ventricular dysfunction. Echocardiography also allows the exclusion of cardiac valve disease and assessment of regional left ventricular wall motion abnormalities which may indicate underlying coronary artery disease. Impaired left ventricular relaxation, characteristic of diastolic dysfunction, is identified by alterations in pulse-wave transmitral Doppler which are observed in over 50% of patients with asymptomatic type 2 diabetes and normal left ventricular systolic function.[10] Tissue Doppler imaging (TDI) allows detection of

diastolic dysfunction with increased confidence, especially in people with normal E:A ratio (pseudo-normalized pattern) on transmitral Doppler. Using a combination of transmitral Doppler, Valsalva maneuver, and TDI, diastolic dysfunction was detected in 75% of asymptomatic, normotensive patients with diabetes mellitus.[11] Speckle-tracking to assess mechanical deformation (strain) can detect early changes in patients with diabetes with subclinical disease and correlates with the diabetes duration.[12] In the long term, abnormal longitudinal strain predicts adverse ventricular remodeling and impaired prognosis.[13,14] Stress echocardiography, employing pharmacological or treadmill stress, can exclude significant coronary disease, although this may be confounded in diabetes by the presence of microvascular dysfunction. In patients with known or suspected coronary disease, the prognostic value of stress echocardiography is similar in patients with and without diabetes,[15] although this has not been evaluated in the setting of diabetic cardiomyopathy.

Cardiovascular magnetic resonance imaging

Cardiovascular magnetic resonance (CMR) imaging delivers higher spatial resolution than echocardiography and provides accurate assessment of cardiac structure, left ventricular mass, and systolic and diastolic function. Effects of diabetes on myocardial perfusion may be assessed both in absolute terms and as myocardial perfusion reserve.[16] Assessment of myocardial deformation by tagged imaging or feature tracking facilitates detection of altered myocardial strain or torsion which develop early in diabetic cardiomyopathy and are associated with abnormal myocardial perfusion reserve.[17] CMR can readily exclude regional myocardial changes, including infarction and inducible myocardial ischemia, which allows ischemic-myocardial dysfunction to be identified. This is important as almost one third of patients with diabetes had CMR evidence of previously unrecognized myocardial infarction in a study of older adults.[18] A major advantage of CMR in diagnosing diabetic cardiomyopathy is its ability to detect diffuse myocardial changes such as fibrosis. Late-gadolinium enhancement can identify focal areas of fibrosis, whereas T1 mapping allows identification of the diffuse myocardial pathology characteristic of diabetic cardiomyopathy. In subjects with diabetes, an increase in extracellular volume on T1 mapping, indicative of extracellular matrix expansion due to myocardial fibrosis, is highly suggestive of later-stage diabetes-related myocardial dysfunction and is associated with increased mortality and heart failure hospitalization.[19] CMR assessment of myocardial structure and function can be further augmented by detection of increased triglyceride deposition (myocardial steatosis) and altered myocardial metabolism by MR spectroscopy.[20,21] Using this approach, subclinical changes in subjects with diabetes have been shown by CMR to include concentric left ventricular (LV) remodeling, higher myocardial triglyceride content, impaired myocardial energetics, and impaired systolic strain.[22]

Cardiac CT

Multislice cardiac computed tomography (CT) provides information on ventricular volumes and ejection fraction, but its greatest utility is in exclusion of obstructive coronary artery which could account for left ventricular dysfunction by CT coronary angiography.[23] Although yet to be investigated in the context of diagnosing diabetic cardiomyopathy, CT coronary angiography is associated with improved clinical outcomes in comparison with functional stress testing in patients with diabetes, suggesting that it should be used more widely in this setting.[24] In subjects with suspected diabetic cardiomyopathy, CT findings should be evaluated together with other imaging modalities (echocardiography or CMR) to allow coronary disease to be interpreted in the context of regional myocardial dysfunction.

Nuclear imaging

Gated single photon-emission computed tomography (SPECT) facilitates the simultaneous evaluation of left ventricular function and myocardial perfusion. SPECT is widely used globally for the assessment of myocardial ischemia and a normal result has a high negative predictive value for cardiac events in patients with diabetes and known or suspected coronary artery disease.[25] However, the low spatial resolution of SPECT limits identification of subendocardial ischemia and reliance on detecting regional difference in perfusion diminishes its utility as a diagnostic test in patients with diabetes, who are more prone to diffuse coronary disease or microvascular dysfunction. Posi-

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tron emission tomography (PET) has the advantage of providing quantitative assessment of myocardial perfusion. Coronary vasodilator dysfunction detected by PET is a powerful predictor of cardiac mortality in patients with diabetes.[26]

Biomarkers

Although a wide range of cardiac biomarkers indicative of myocardial disease has been described in patients with diabetes, none has yet reached clinical use to diagnose diabetic cardiomyopathy. Elevated brain natriuretic peptide (BNP) concentration correlates with left ventricular dysfunction and can be employed to screen asymptomatic individuals[27] but does not discriminate the underlying cause. In contrast, a network analysis of patients with acute heart failure identified a panel of biomarkers which were differentially modified by the presence or absence of diabetes, including markers of inflammation (TNFR-1a, periostin), cardiomyocyte stretch (BNP), angiogenesis (VEGFR, angiogenin), and renal function (NGAL, KIM-1).[28] Further research is needed to identify and validate biomarkers specific for the pathological changes underlying diabetic cardiomyopathy.

Conclusions

The approach to diagnosing diabetic cardiomyopathy in individual cases is likely to depend on the local availability of imaging modalities. Concentric left ventricular remodeling and diastolic dysfunction are characteristic of early-stage diabetes-related myocardial dysfunction, particularly in the presence of reduced longitudinal contractility and impaired systolic circumferential strain on strain imaging. Diffuse fibrosis, resulting in increased extracellular volume on CMR, is suggestive of later-stage disease. With wide availability and its established role as a first-line investigation for suspected left ventricular dysfunction, echocardiography lends itself to most commonly be used to detect diabetic cardiomyopathy. Increasing availability of cardiac CT allows noninvasive coronary angiography to be employed to exclude significant coronary artery disease as a cause of myocardial dysfunction. Where available, CMR is the most powerful diagnostic tool for diabetic cardiomyopathy and allows multiparametric assessment of myocardial morphology, fibrosis, perfusion, and function. ■

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Original Article

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Antihyperglycemic drugs that improve cardiovascular outcomes and a model of diabetic cardiomyopathy

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Abstract: Recent cardiovascular outcome trials (CVOTs) have transformed the landscape for the management of type 2 diabetes mellitus. In a remarkably short period of time, national and international guidelines have been overhauled to reflect the remarkable cardiovascular benefits of sodium/glucose linked transporter-2 inhibitors (SGLT2is) and glucagon-like peptide-1 receptor analogues (GLP-1RA) in mitigating cardiovascular risk. Both SGLT2is and GLP-1RAs remain second-line to metformin, reflecting the historical importance of this biguanide antihyperglycemic. In this review, these three very different antihyperglycemics are discussed in the light of CVOT data and of the preclinical data revealing remarkable pleiotropic signaling effects of these drugs. A model of diabetic cardiomyopathy is discussed, and the points of contact that these therapeutic interventions have upon this model may of help in understanding how each can be best targeted in this complex pathophysiological disease process. ■ *Heart Metab*. 2019;80:18-22

Keywords: cardioprotection; diabetic cardiomyopathy; GLP-1 receptor agonist; metformin; SGLT2 inhibitor; type 2 diabetes mellitus

Introduction

Since the late 19th century, diabetes mellitus has been recognized as an important cardiovascular risk factor in the development of atherosclerosis.[1,2] Because elevated blood sugar is a principal diagnostic feature of this complex disease, unsurprisingly it was hoped that the control of circulating glucose would improve cardiovascular outcomes in diabetic patients. However, the reality of this approach has not been as rewarding as might have been wished, with generally neutral, or even adverse, cardiovascular outcomes observed. However, cardiovascular outcome trials (CVOTs), mandated by medicine regulators in both the United States and in Europe, have recently revealed two disparate classes of therapies for the use in type 2 diabetes (T2DM) with a significant and unexpected cardiovascular benefit: the sodium-glucose linked transporter inhibitors (SGLT2is) and the glucagon-like peptide-1 receptor agonists (GLP-1RA).

Metformin: the bedrock of contemporary diabetic management

The cornerstone of current T2DM management is the biguanide, metformin, an insulin sensitizer. In many respects, metformin could be regarded as the prototyp-

ical cardioprotective antihyperglycemic medication. In the UKPDS 34 study,[3] metformin was compared with both the then standard of care (predominantly diet control) and an "intensive blood-glucose control" group in overweight patients with T2DM. This latter drug-control group used either sulfonylureas or insulin to more effectively lower circulating glucose levels. Interestingly, while reductions in blood sugar were not maintained by any of the drug therapy regimens over the duration of 10-year follow-up, metformin, nonetheless, significantly improved cardiovascular outcomes. The incident rate of nonfatal and fatal myocardial infarction/sudden cardiac deaths separated from the control group after approximately 1 year, and by 10 years, patients on metformin had a significant 39% risk reduction (*P*=0.010) compared with patients in the control group[3] *(Figure 1).* In contrast, this composite end point was not significantly improved by "intensive medical therapy" with sulfonylurea or insulin (*P*=0.11).[3]

Recent meta-analyses (encompassing 40 trials and 1 million patients) suggest that the extent of the cardiovascular benefits of metformin seen in the UKPDS study is greater than that seen in contemporary practice; however, the protection appears robust and significant: comparison of metformin versus non-metformin revealed a significant reduction of cardiovascular mortality with an adjusted hazard ratio of 0.81 (95% CI of 0.79-0.84, *P*<0.00001).[4]

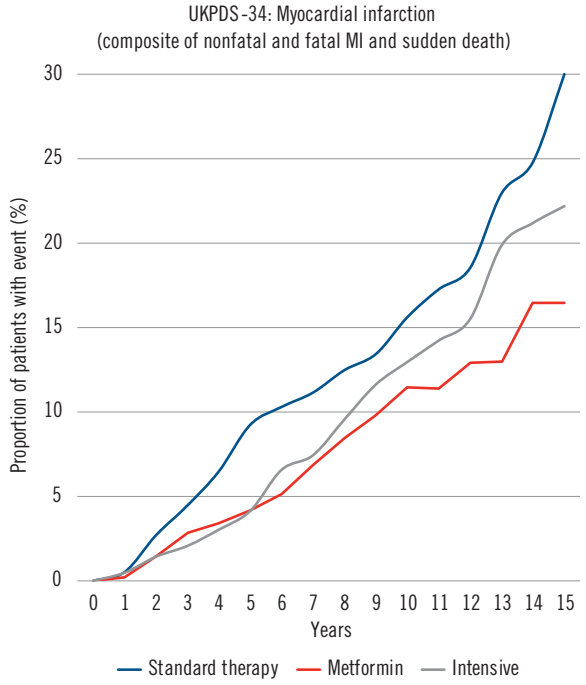

Figure 1 *Positive cardiovascular impact of metformin monotherapy upon myocardial infarction (a composite of nonfatal and fatal and sudden death) in the UKPDS 34 study. Compared with diet control (standard therapy), metformin led to a significant reduction of myocardial infarction, whereas there was no significant benefit with intensive therapy with either sulfonylureas and/or insulin, after median 10 year follow-up. Figure adapted from UKPDS 34.*[3]

The mechanism of this cardioprotective benefit has been extensively studied, with well-supported literature demonstrating the pleotropic effects that metformin has upon cell survival signaling (for example, 5' adenosine monophosphate-activated protein kinase (AMPK)[5] and endothelial nitric oxide synthase (eNOS) activation, see ref 6.

Metformin has thus been shown to have direct cardioprotective properties and, in historical and contemporary practice, to attenuate cardiovascular mortality.

SGLT2 inhibitors

The SGLT2is ameliorate hyperglycemia by inhibiting renal reabsorption of glucose via the renal SGLT2 transporter, which are responsible for 90% of normal reabsorption in the proximal tubule, thus promoting glucosuria and reduction of circulating glucose. Concomitant with glucosuria are natriuresis, osmotic diuresis, weight reduction (significant calorific loss) and mild ketosis. Empagliflozin, in the EMPA-REG OUTCOME study,[7] revealed a significant cardiovascular outcome benefit in patients with high-risk and established cardiovascular disease. Particularly impressive are their ability to reduce hospital admissions with heart failure, an observation that has been also been seen in other drugs within this class, canagliflozin and dapagliflozin (CANVAS[8] and DECLARE-TIMI 58[9]) and most recently confirmed in the prospective dapagliflozin heart failure study (DAPA-HF).[10] What is particularly remarkable regarding these therapies is the rapidity of the divergence of the survival curves – evident within just weeks of initiation of therapy. Thus, cardiovascular outcome benefits are unlikely to be related to attenuation of arterial atherosclerosis. Moreover, there is no difference in the rates of myocardial infarction during the relatively short duration of follow-up of these investigations. The cardiovascular mortality benefit therefore appears to be through benefits derived through heart failure and perhaps also improved survival from myocardial ischemia.

The mechanism of the cardioprotection stemming from SGLT2 inhibition has been the subject

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of intense research, and currently remains unclear. The reduction in the rates of hospitalization for heart failure may well have its foundation upon the diuretic and natriuretic effects of these drugs with concomitant benefits upon ventricular pre- and afterload. However, the evolution of the diabetic cardiomyopathy (DMCM) through left ventricular hypertrophy and heart failure with preserved ejection fraction (HFpEF) and concluding with a dilated cardiomyopathy and heart failure with reduced ejection fraction (HFrEF, *Figure 2)* is a complex pathophysiological process,[11,12] one in which SGLT2is may interact. Indeed, SGLT2is appear to have a positive impact upon left ventricular mass in the earlier phases of DMCM and improved ventricular performance (reviewed in ref 13). The ventricular remodeling and progression from HFpEF to HFrEF appear to be characterized by ischemic heart disease and ischemia/reperfusion injury,[11,12] and this too represents a target for SGLT2is.

EMPA-REG, CANVAS, and DECLARE were not studies designed to look at myocardial infarction (the number of fatal myocardial infarcts were very low, even within the high-risk population recruited into EMPA-REG). However, preclinical studies have revealed that SGLT2 inhibition does significantly reduce myocardial infarct size.[14-16] This is surprising: SGLT2 is not widely expressed in man, and there is negligible SGLT2 expression in the heart.[17] Remarkably, SGLT2i cardioprotection is independent of diabetic or glycemic status, and mediated through cytoprotective signaling: explanted hearts remain protected when perfused, ex vivo, following oral SGLTi administration.[14] This memory effect may be through the recruitment of cell-survival kinases, through Jak-STAT[15] or AMPK signaling[16] and the bolstering of cellular antioxidant defences.[16] In contrast, cardioprotection against heart failure may be mediated through preferential metabolism of β-hydroxybutyrate (augmented by SGLT2i therapy)[18] or through sodium/calcium exchange inhibition,[19] to attenuate adverse calcium accumulation.

With emerging evidence to suggest that SGLT2is may have benefits in all patients, irrespective of diabetic status,[10] the restriction of SGLT2i to patients with diabetes may change. DAPA-HF is the first heart failure study to demonstrate that SGLT2i is equally beneficial in both diabetic and nondiabetic patients, and this study will be joined by a number of heart failure trials that are due to report in the near future, including the EMPEROR-Reduced and EMEROR-Preserved studies.[20]

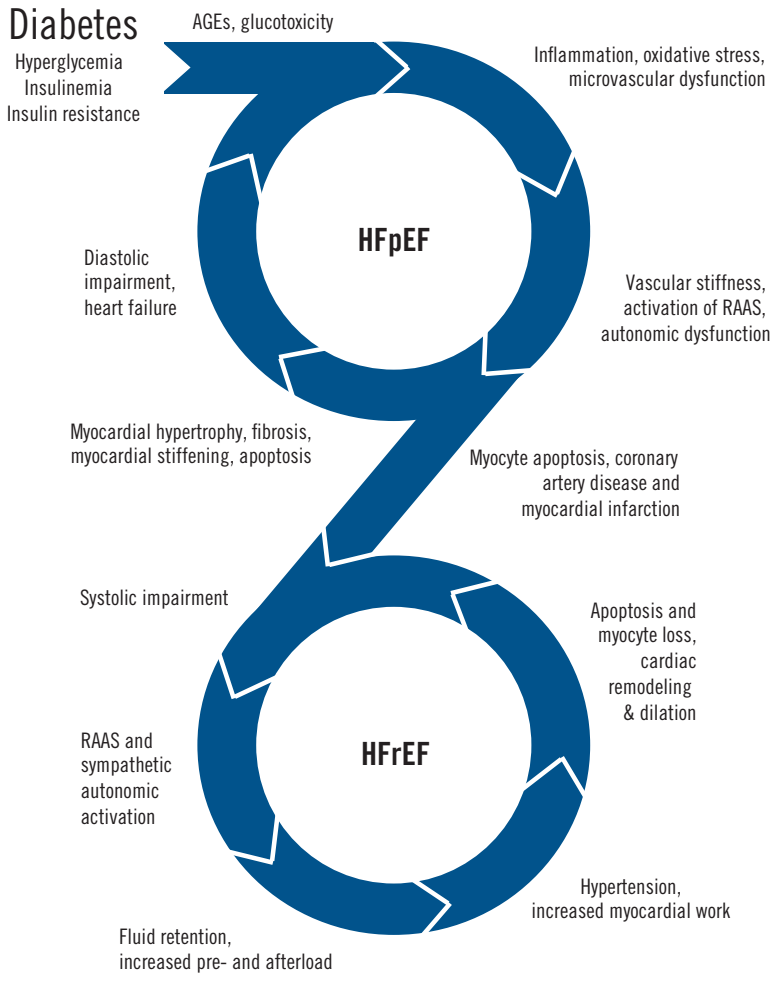

Figure 2 *A proposed model of diabetic cardiomyopathy. Diabetes and its consequences of hyper-insulinemia and insulin resistance leads to the initial insult upon the cardiovascular system. This initiates a self-sustaining loop of injury, characterized by vascular injury, hypertension, increased afterload, and myocardial hypertrophy and subsequent diastolic impairment and myocardial fibrosis. As this becomes symptomatic, these features characterize heart failure with preserved ejection fraction (HFpEF). Over time, the sustained strain and injury upon the left ventricle leads to myocyte loss through apoptotic cell death, which, in combination with the development of coronary atherosclerosis and ischemic heart disease and the initiation of a second self-sustaining loop of heart failure with reduced ejection fraction (HFrEF) and the characteristic late-phase dilated cardiomyopathy. AGE, advanced glycation end products; RAAS, renin-angiotensin-aldosterone system*

Glucagon-like peptide-1 receptor agonists

Synthetic analogues of the incretin hormone, GLP-1, glucagon-like peptide receptor agonists (GLP-1RAs) are predominantly injectable antihyperglycemics, although oral formulations of this class of drug are now emerging. GLP-1RAs stimulate insulin release from pancreatic islet cells to regulate glucose concentration, reduce glucagon secretion, alter gut motility, satiety, and lipid metabolism, and thus can lead to reduction of body weight.[21] These properties alone should have a positive impact upon the cardiovascular risk profile, but their benefit is likely to extend beyond their impact upon their canonical role.

The GLP-1RAs are either GLP-1- or Exendin-based (with modification to promote half-life), and it is interesting to note that GLP-1RAs based upon native GLP-1 (liraglutide, semaglutide, and albiglutide) have an advantageous impact upon cardiovascular outcomes. LEADER,[22] SUSTAIN-6,[23] and HARMONY[24] respectively revealed significant reductions in MACCE in patient populations at high risk of developing cardiovascular complications. In contrast to the SGLT2 inhibitors, the time to separation of the survival curves was longer and there was no positive signal in terms of heart failure (noninferior to placebo); indeed the benefits of GLP-1RAs appear to be mediated by the reduction of atherosclerosis-related cardiovascular events (myocardial infarction and stroke).[25]

Unlike SGLT2, GLP-1 receptors are widely expressed in man, including the heart.[26] Exogenously administered GLP-1 reduces infarct size in rodent models through cytoprotective signaling, involving post-receptor cAMP and cGMP activation,[27] Akt, Erk1/2, p70S6K, and AMPK signaling and inhibition of proapoptotic signaling.[28,29] The atherosclerosis benefits of these drugs may be mediated through a beneficial impact upon lipid profiles[30] and augmented endothelial nitric oxide.[31]

Thus, the characteristics of GLP-1-based receptor agonists are different from those seen with SGLT2i, which raises the intriguing possibility that the two classes of therapy may have additive benefits, particularly in patients with established coronary or cardiovascular disease.

An emerging paradigm of cardiovascular disease management in diabetes

Cardioprotection in T2DM has many facets, but evolution and progression of DMCM is a central feature *(Figure 2).* In the model presented, almost any intervention designed to mitigate hyperglycemia should slow the progression of HFpEF that characterizes early and intermediate phases of DMCM. Drugs with pleiotropic effects upon pro-survival cell signaling (eg, metformin, SGLT2i, GLP-1-based GLP-1RAs) may help prevent progression into late-phase DMCM, HFrEF, through attenuating apoptotic myocyte loss and abrogating ischemia/reperfusion injury from ischemic heart disease. Moreover, GLP-1RAs may have help ameliorate atherosclerotic progression to reduce ischemic events whereas SGLT2is may help offload and diurese, thus mitigating excess pre- and afterload and injurious cardiac decompensation. This model may be helpful in developing new therapeutic strategies in diabetes and supports triple therapy with metformin, SGLT2i, and GLP-1RA – a combination that deserves further investigation.

In summary therefore, building on the foundations of metformin therapy, there are two new classes of glucose-controlling therapies, SGLT2i and GLP-1RA, that each possess remarkable cardiovascular benefits. SGLT2is are clearly beneficial in mitigating heart failure, whereas GLP-1RA may help attenuate atherosclerosis. In clinical practice, the combination of these therapies that appear to have disparate targets may provide the optimum outcomes for diabetic and potentially also for nondiabetic patients, an effect that may have little to do with glucose levels, but through metabolic modulation and recruitment of cellular signaling to promote cellular survival. ■

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Original Article

Heart Metab. 2019;80:23-27

Complications of diabetes: beyond the heart, kidneys, and eyes

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Abstract: Diabetes is a leading global health problem. Clinicians and most patients are aware that diabetes can lead to complications in the heart, kidneys, and eyes. Given the high morbidity and mortality, much effort is made to screen for and treat these complications. Other organ systems can also be affected by diabetes. The pathogenesis and risk factors for developing these other complications does not always match those for heart, kidneys, and eyes. Additionally, treatment for these other complications is often limited or absent. Here we will review some of the major musculoskeletal, neuropathic, and skin complications linked to diabetes. ■ *Heart Metab*. 2019;80:23-27

Keywords: autonomic; complication; diabetes; musculoskeletal; neurologic; skin

Overview

Diabetes is a growing worldwide health problem. The disease leads to complications across multiple organ systems. Clinicians taking care of patients with diabetes worry most about increased risk for cardiovascular disease, renal failure, and vision loss. Reducing these risks involves reducing blood sugar levels and controlling blood pressure, as well as lipid-lowering therapy. This treatment strategy highlights the role of metabolic dysregulation and/or inflammation in pathogenesis of these diabetes complications.

Many other organ systems can be affected by diabetes. In this review we will summarize some of the major musculoskeletal, neuropathic, and skin complications linked to diabetes *(Table I, Figure 1).* The pathogenesis for these other complications is less understood but likely includes factors such as fibrosis, hypercoagulability, and ischemia in addition to metabolic dysregulation. Treatment of these complications is often either absent or less effective.

Musculoskeletal complications

Fibrosis is a prominent feature of the musculoskeletal complications of diabetes.[1-4] The fibrosing conditions are characterized by increased swelling, inflammation, and reduced mobility of the involved joints. Fibrosis is thought to begin with glycosylation of connective tissue components leading to activation of fibroblasts and inflammatory mediators. Fibrosis is most noted in the shoulder and hands:

- Frozen shoulder, also known as adhesive capsulitis, presents with pain and limited mobility of the joint and often affecting both shoulders
- Limited joint mobility, also known as cheiroarthropathy (cherio = hands in Greek), usually involves the hands. The tissue over the dorsum of the hands develops a waxy and/or stiff appearance. Joint mobility is decreased, especially flexion of the metacarpal-phalangeal (MCP) and proximal interphalangeal (PIP) joints. The disease is usually painless
- Dupuytren's contracture appears with increased frequency in patients with diabetes. The condition is associated with other chronic diseases, and smok-

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ing is a risk factor. There is fibrosis of the palmar aponeurosis that leads to flexion contractures of one or several digits.

- Trigger finger involves fibrosis and/or inflammation of a finger's flexor tendon and its sheath. This leads to "locking" of the involved finger in a flexed position.

Other musculoskeletal manifestations of diabetes are more related to inflammation, microvascular changes, and alterations in nerve function. These processes affect the spine, legs, and feet:

- Neuropathic arthropathy, also known as Charcot's joint, affects the bones of the ankles and feet. Changes in nerve function alter the biomechanics of walking, leading to bone microfractures. Altered autonomic activity disturbs blood flow and contributes to increased bone resorption. The initial phase of the disease is characterized by warmth, swelling, and erythema of the foot. Progressive destruction of the joints occurs with collapse of the arch, leading to the rocker-bottom deformity
- Diffuse idiopathic skeletal hyperostosis (DISH) involves calcification of tendons and ligaments. The disease primarily affects the thoracic and lumbar spine. Patients report stiffness, reduced range of motion, and sometimes pain. Diagnosis is made by x-ray imaging
- Muscle infarction is a rare condition which presents with pain and swelling of a muscle group, typically thigh or calf. The disease is relatively rare and specific for diabetes. Vascular changes, hypercoagulability, and inflammation are all thought to be contributing factors.

Neuropathic complications

Neuropathy is present in up to half of all patients with diabetes. Prevalence increases with increasing duration of diabetes.[5] The pathogenesis is poorly understood. Microvascular dysfunction, altered neuronal metabolism, and direct toxic effects of glucose have all been proposed as mediators of damage. The disease is notable for attacking primarily sensory neurons. The neuropathy syndromes are classified as distal symmetric polyneuropathy, various focal neuropathies, and autonomic neuropathy.

Symmetric polyneuropathy is the most common type of diabetic neuropathy. It is characterized by loss of sensation in the distal extremities (glove and stocking distribution). About 50% of patients report pain sensation described as "burning." Diagnosis is made based on clinical exam findings which include loss of pinprick, temperature, vibration, and proprioception. Diminished ankle reflexes frequently accompany distal neuropathy. Treatment is not very effective and is based on use of anticonvulsants (ie, pregabalin, valproate), antidepressants (amitriptyline), and opioids.[6]

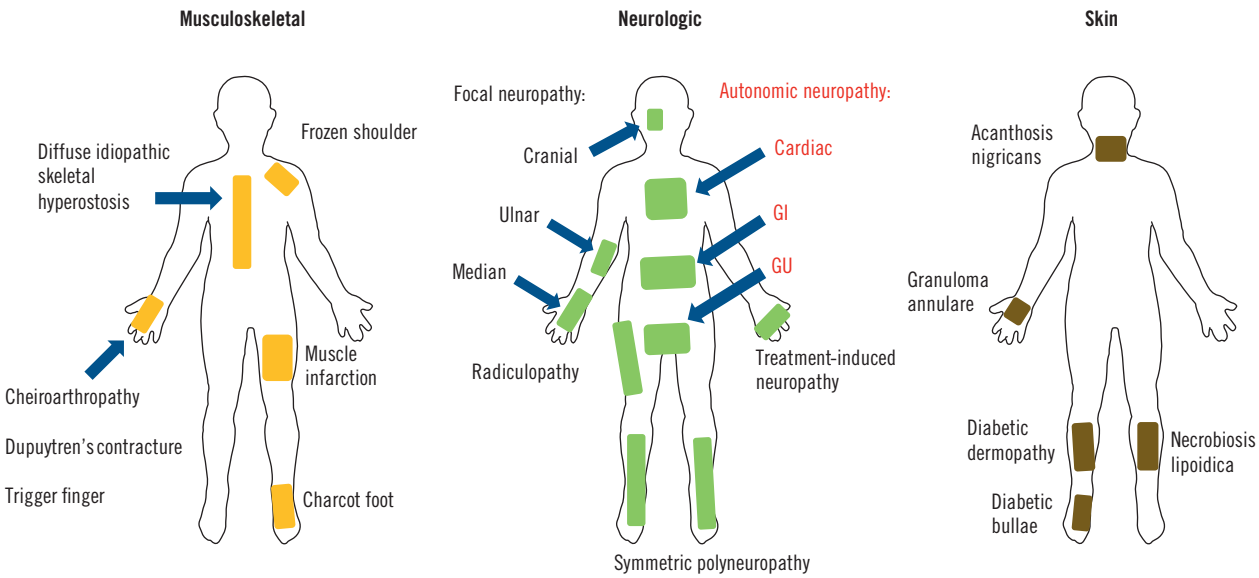

Figure 1 *Complications of diabetes.The figure highlights some of the organ systems and anatomic locations affected by diabetes. Left, musculoskeletal complications associated with diabetes. Middle, neurologic complications. Right, skin complications.*
Adapted from ref 5: Feldman EL, Callaghan BC, Pop-Busui R, et al. Diabetic neuropathy. Nat Rev Dis Primers. *2019;5:41.*

Focal neuropathy (polyradiculopathy, mononeuropathy, mononeuropathy multiplex) involves one or several nerves/nerve roots and thus presents with isolated symptoms.

Polyradiculopathy refers to disease caused by damage to nerve roots, particularly in the cervical, thoracic, and lumbar spine. Onset is usually rapid with pain a prominent early component, followed by proximal weakness. Presentation is often unilateral but eventually bilateral involvement is common. Symptoms often resolve over time. Immunotherapy has been proposed as treatment of diabetic polyradiculopathy[7]:

- Cervical polyradiculopathy typically starts acutely with pain, weakness, and loss of sensation in the upper extremities.[8]
- Thoracic polyradiculopathy presents with abdominal pain and weight loss.[9] Findings on exam include abdominal wall paresis and/or paresthesias. Diagnosis can be challenging as many disorders can lead to abdominal pain
- Lumbar polyradiculopathy is characterized by pain and proximal limb weakness as well as weight loss.[10]

Focal mononeuropathy is a disease of an individual peripheral nerve. In the focal mononeuropathies direct mechanical trauma (ie, entrapment) can be a contributing factor above and beyond those listed above. The chance for recovery is best with milder cases. Median nerve neuropathy (carpal tunnel syndrome) is the most common focal mononeuropathy in diabetes but also occurs frequently in the general population.[1]

Musculoskeletal		
Complication	*Location*	*Manifestation*
Frozen shoulder	Shoulder	Pain, stiffness, reduced mobility
Cheiroarthropathy	Hands	Waxy skin, stiff joints
Dupuytren's contracture	Finger	Flexion contracture
Trigger finger	Finger	Locked in flexion
Carpal tunnel syndrome	Hand	Pain and paresthesias
Charcot foot	Foot	Inflammation, collapse of foot arch
Diffuse idiopathic skeletal hyperostosis	Spine	Stiffness, reduced range of motion
Muscle infarction	Thigh	Pain and swelling
Nerve		
Complication	*Location*	*Manifestation*
Symmetric polyneuropathy	Distal extremities "glove and stocking"	Decreased sensation, burning pain
Radiculopathy	Cervical, thoracic, and/or lumbar spine	Pain+weakness of affected region and weight loss
Mononeuropathy	Isolated nerve involvement	Decreased sensation/function of affected nerve
Cardiovascular autonomic neuropathy	Cardiovascular system	Tachycardia, orthostatic hypotension, exercise intolerance, silent ischemia
Gastrointestinal autonomic neuropathy	GI tract	Reflux, gastroparesis, diarrhea
Genitourinary autonomic neuropathy	GU system	Overflow incontinence, dyspareunia, erectile dysfunction
Peripheral autonomic neuropathy	Feet	Edema and dry skin with increased sweating in the proximal limb
Treatment-induced neuropathy	Distal extremities (+/- autonomic neuropathy; +/- retinopathy/nephropathy)	Burning pain
Skin		
Complication	*Location*	*Manifestation*
Diabetic dermopathy	Shins	Small, well-demarcated, hyperpigmented, and depressed lesions
Necrobiosis lipoidica	Anterior shin	Yellowish, atrophic plaques with purplish borders
Granuloma annulare	Dorsum of hands and feet	Grouped papules that expand in an annular shape
Acanthosis nigricans	Folds of the neck	Hyperpigmented, hyperkeratoic areas
Diabetic bullae	Feet	Spontaneous blisters

Table I *Summary of musculoskeletal, neuropathic and skin complications in diabetes.*

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The pathophysiology centers around entrapment of the median nerve, although in diabetes there may be intrinsic damage to the nerve itself. Symptoms include tingling, pain, and paresthesias of the thumb, index, and middle fingers which can be elicited in the clinic by employing Tinel's test (percussion of the median nerve) and Phalen's test (dorsiflexion of the wrists). Other sites involved in diabetic focal mononeuropathy include the ulnar, peroneal, and cranial nerves. Mononeuropathy multiplex is similar to focal mononeuropathy but involves multiple individual nerves.

Autonomic neuropathy is common and likely underdiagnosed in diabetes patients.[11] Incidence increases with duration of disease and worsening glycemic control. Treatment is focused on reducing blood glucose levels. Autonomic neuropathy can affect the cardiovascular system, gastrointestinal tract, genitourinary system, and peripheral tissue:

- Cardiovascular autonomic neuropathy usually presents with resting tachycardia. This can be associated with decreased heart rate variability. Progression of cardiovascular autonomic neuropathy can lead to a fixed heart rate, exercise intolerance, orthostatic hypotension, and silent ischemia[12]
- Gastrointestinal autonomic neuropathy causes both upper GI symptoms (ie, reflux and gastroparesis) and lower GI symptoms (diarrhea).[13,14] Symptoms of gastroparesis include nausea, early satiety, vomiting, and abdominal pain. Diagnosis can be made by measuring gastric emptying. Patients with diabetes can also develop dumping syndrome, or rapid gastric emptying. Diarrhea related to autonomic neuropathy is watery, may alternate with bouts of constipation, and can be associated with fecal incontinence
- Genitourinary autonomic neuropathy can cause overflow incontinence of the bladder, dyspareunia in women, and erectile dysfunction as well as retrograde ejaculation in men
- Peripheral autonomic neuropathy leads to impaired autonomic control of sweat glands and blood flow distally. Patients notice dry, itchy, and swollen feet with increased sweat production more proximally.[5] The changes in skin and blood flow likely contribute to the development of diabetic foot ulcers.

Treatment-induced neuropathy is a rare category of diabetic neuropathy which occurs in patients with poor glycemic control who experience a rapid improvement in blood sugar levels.[15] Type 1 diabetes and prolonged hyperglycemia are risk factors for this complication. Studies suggest that a greater than 3% decline in HbA_{1c} over a period of 3 months or less greatly increases the risk of developing treatment-induced neuropathy. Although the syndrome was previously known as "insulin neuritis," any treatment modality that acutely lowers blood glucose can trigger the disease. Patients note rapid onset of "burning" neuropathic pain in the distal extremities. This can be accompanied by autonomic neuropathy. The severity of involvement increases with the magnitude of blood-sugar lowering. Treatment-induced neuropathy is managed by slowing the decline in A_{1c} levels. Interestingly, patients who have treatment-induced neuropathy are also at risk for acutely developing worsening retinopathy and nephropathy, suggesting a common underlying microvascular cause for all three conditions.

Skin complications

Most clinicians are familiar with the cellulitis which can appear in a poorly perfused insensate foot of a patient with diabetes. However, there are many other skin lesions which can be found in patients with diabetes.[16] These skin lesions are sometimes the first indication of the presence of systemic disease. Diabetes-related skin findings are more common in patients with poor glycemic control. The pathogenesis is poorly understood but direct glucose toxicity, fibrosis, and altered immune function are all thought to play a part:

- Diabetic dermopathy is common in patients with diabetes.[17] The characteristic findings are small, well-demarcated, hyperpigmented, and depressed lesions, usually on the shins
- Necrobiosis lipoidica is a relatively rare granulomatous disease of the skin associated with diabetes.[18] It manifests as yellowish plaques affecting the anterior shin. The plaques have purplish borders with central atrophic-appearing skin
- Granuloma annulare occurs in diabetes as well as other medical conditions. It appears as grouped papules that expand in an annular shape, typically in the dorsum of the hands and feet
- Acanthosis nigricans occurs as hyperpigmented, hyperkeratotic areas, typically in the folds of the skin which is associated with insulin resistance/diabetes. It is often an early visible manifestation of insulin resistance

- Diabetic bullae are recurrent spontaneous blisters that appear mostly in the feet of patients with diabetes.[19]

Conclusion

Clinicians devote a lot of energy to monitoring and managing the cardiovascular, renal, and eye complications of diabetes. It is important to consider that the disease affects other organ systems. In this review we have summarized some of the major musculoskeletal, neuropathic, and skin complications linked to diabetes. The pathogenesis of these complications involves not only metabolic dysregulation and inflammation but also fibrosis, hypercoagulability, and ischemia. Unfortunately, there are generally few treatment options for these complications, and even simple relief of symptoms can be challenging. Perhaps in future better prevention and/or control of diabetes will reduce the frequency and severity of these complications. ■

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Personalized approach for patients with heart failure and diabetes: responding to current unmet needs

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Presentation of the case

A 67-year-old female hispanic patient presented with effort angina, dyspnea, and fatigue despite pharmacologic therapy.

Clinical history and treatments

- Diabetes mellitus (DM -14 y), obesity (30 y)
- Anterior myocardial infarction with nonobstructive coronary arteries (MINOCA) in 2017 *(Figure 1)*
- Heart failure (HF) since 2018 without HF hospitalizations in the last 12 months
- Current medications: sacubitril/valsartan 200 mg bid, bisoprolol 5 mg od, ivabradine 7.5 mg bid, spironolactone 25 mg od, furosemide 20 mg od, aspirin 100 mg od, atorvastatin 20 mg od, metformin 500 mg bid, empaglifozin 10 mg od

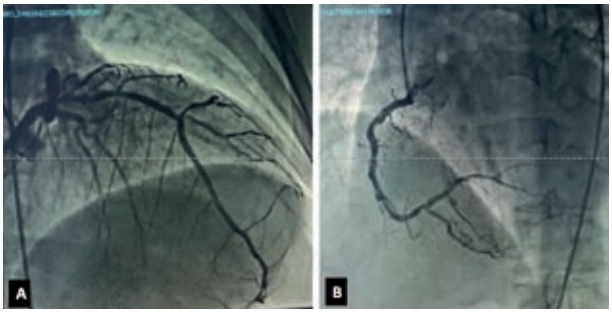

Figure 1 *Coronary angiogram. Coronary angiogram showed no obstructive coronary arteries. A: Right coronary artery, B: Left coronary artery*

Clinical status and symptoms (in consult)

Functional Class II-III NYHA & CSS, heart rate (HR) 60 bpm, blood pressure (BP) 115/80 mm Hg, O_2 saturation 90%, Clear lung fields, holosystolic apical murmur I/IV suggestive of mitral regurgitation (MR), no S3, no hepatomegaly, mild peripheral edema.

Resting electrocardiogram: sinus rhythm, HR 60 bpm, QRS 110 msec, QS in V1-4, cQT 400 msec.

Echocardiogram: Left ventricular (LV) dilation, anteroapical hypokinesis, mild MR, left ventricular ejection fraction (LVEF) 38%, Pulmonary arterial pressure 40 mm Hg, tricuspid annular plane systolic excursion 19 mm.

Laboratory: fasting glucose 89 mg/dL, glycated hemoglobin 7.0%, serum creatinine 1.1 mg/dL, N-terminal-pro- B-type natriuretic peptide (NT-proBNP) 450 pg/mL, serum Na 134 mEq/L, serum potassium 4.5 mEq/L, hemoglobin 13 g/dL, serum ferritin 300 µg/L.

Kansas City Cardiomyopathy Questionnaire (KCCQ): Clinical summary score: 64 pts, total symptom score 65 pts, overall summary score 60 pts.

6-minute walking test (6MWT) distance: 280 meters.

MAGGIC heart failure risk score: 20, risk of dying within 1 year 10.2%, risk of dying within 3 years 24.7%.

At this point we have a patient with ischemic heart disease (IHD), diabetes mellitus (DM), and HF with

reduced ejection fraction (HFrEF) who has received apparent optimized treatment with guideline recommendations including novel therapies like angiotensin receptor–neprilysin inhibitors (ARNIs) and SGLT2 inhibitors. Despite these, the patient persists with moderately severe physical limitation and poor quality of life.

According to the current guidelines and recommendations,[1] the patient is not a candidate for cardiac resynchronization therapy because she has narrow QRS, additional HR control is not necessary because she was already at the HR target of <70 bpm with the treatment with β-blockers and ivabradine, and an implantable cardioverter defibrillator implantation as an alternative for primary prevention of sudden cardiac death is not recommended because the LVEF is over 35%. Other causes for her clinical deterioration such as anemia and/or iron deficiency and renal failure were not present, so iron supplements are not indicated.

The LVEF, the absence of recurrent HF hospitalizations, and the MAGGIC Score reveal a patient with low risk of mortality at 1 year, and for this reason she is not a candidate for a left ventricle assist device.

For all of the above, the guidelines[1] recommend the use of hydralazine–isosorbide dinitrate or digoxin for symptomatic control, but the nitrates and hydralazine have shown maximum efficacy in populations different from our patient. On the other hand, the use of digoxin could be controversial, specifically in patients with polypharmacy and without evidence of atrial fibrillation. Additionally, recent evidence suggests that digoxin could be harmful in many patients with HF.

At this point, we decided to start trimetazidine because of its antianginal effects and some evidence of benefits in HF patients. The patient started the drug with 35 mg bid.

The follow-up at 1, 3, and 6 months showed a significant improvement in symptoms, with angina attacks reduced from 4 per week to 1 per month, and the NYHA Functional Class improved from III to I-II. At 3 months after the start of trimetazidine treatment, the patient increased the distance walked in the 6-min walking test from 290 to 360 meters, and the overall summary score in the KCCQ improved from 60 to 70 points.

After 6 months of follow-up the NYHA Functional Class was I-II, the transthoracic echocardiogram reported LVEF 40%, NT-proBNP 300 pg/mL. The patient had no rehospitalizations during this period.

Discussion

Ischemic heart disease (IHD), HF, and DM are clinical conditions that frequently coexist, and this represents a challenge for the clinicians. The prevalence of diabetes in patients with HF is 20% in outpatients, and could be 40% in HF hospitalized patients. DM increases the risk of major cardiovascular events in HF such as hospitalizations and mortality.[2] The triad of IHD, HF, and DM means the worst-case scenario for this population.

The guidelines of clinical practice are a powerful tool in terms of controlling symptoms and reducing the risk of major adverse events like hospitalizations; even more, the implementation of the guidelines recommendations improve the life prognosis in the majority of HF patients.

Unfortunately, despite these good results, many patients with HF, and/or IHD, and/or DM persist with symptoms that affect their quality of life and constitute a real burden of disease, with negative impact in the evolution of the disease. In those cases it is necessary to reanalyze the case in terms of detecting potential factors that contribute to the persistence of symptoms, and tailor a personalized treatment according to the individual clinical scenarios.

In this particular case, the coexistence of three clinical conditions (HF, IHD with no obstructed coronary arteries, and DM) require an approach that takes account of the diverse pathophysiological pathways that are observed in patients with these conditions.

Recently, the metabolic origins of HF are under profound analysis, especially in ischemic patients. Some of the common pathways are: (i) endothelial dysfunction; (ii) increase in neurohormonal activation (sympathetic nervous system and renin-angiotensin-aldosterone system); (iii) changes in intracellular Ca^{2+} homeostasis; (iv) diastolic dysfunction; (v) altered energy production by cardiac mitochondria.[2]

Many therapeutic targets have been studied, and by now the mandatory use of renin-angiotensin-aldosterone system inhibitors such as angiotensin-converting enzyme inhibitors (ACEIs)/angiotensin receptor blockers (ARBs), β-blockers, and mineralocorticoid antagonists are recommended by the majority of the clinical guidelines. Recently, HR control with drugs such as ivabradine as an adjunctive treatment in selected patients show an additional benefit in terms of reducing the risk of HF hospitalizations and mortality. Moreover,

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the inclusion of ARNIs in patients with persistent symptoms despite the use of ACEIs/ARBs is a good strategy for the optimization of the treatment.[3] With regard to the control of diabetes in HF patients, the use of SGLT2 inhibitors (empaglifozin, canaglifozin, and dapaglifozin) added to metformin have been showing promising results and their use in nondiabetic HF patients is being researched in terms of incorporating another option for the optimized treatment for HF. However, currently, routine use is not recommended.[4]

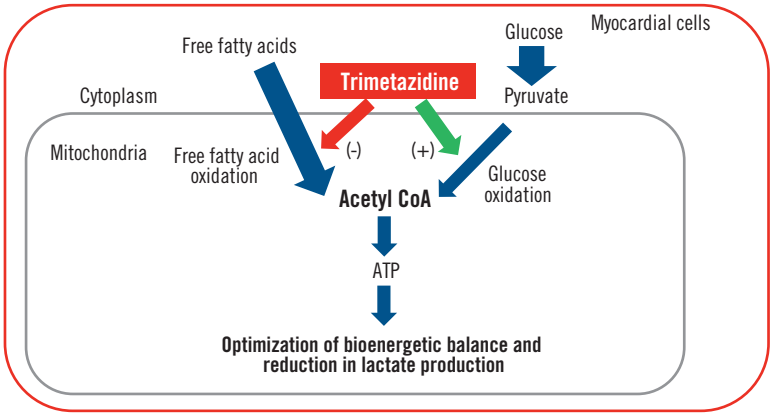

Figure 2 *Trimetazidine – mechanism of action.*

With regard to the metabolic approach for the treatment of IHD and HF, pharmacologic agents such as trimetazidine have been studied because it is clear that in HF and is ischemic heart disease, there is an increase in the uptake of free fatty acids (FFAs) and glucose into cardiac myocytes. The increase in FFA oxidation and decrease in glucose oxidation leads to the accumulation of metabolic intermediates like lactate and promotes cellular maladaptative signaling and cardiomyocyte dysfunction.[5]

Trimetazidine is a metabolic regulating agent that blocks FFA oxidation in the cardiac myocyte mitochondria *(Figure 2).* This blockade allows an increase

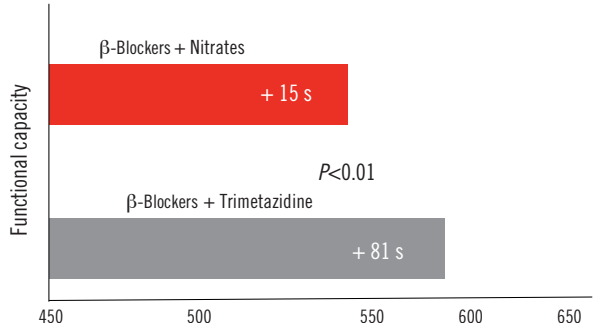

Figure 3 *Effects of combination β-blockers plus trimetazidine on functional capacity in patients with chronic ischemic heart disease. Modified from ref 8: Michaelides AP, Spiropoulos K, Dimopoulos K, Athanasiades D, Toutouzas P. Antianginal efficacy of the combination of trimetazidine-propranolol compared with isosorbide dinitrate-propranolol in patients with stable angina.* Clin Drug Invest. *1997;13:8-14.*

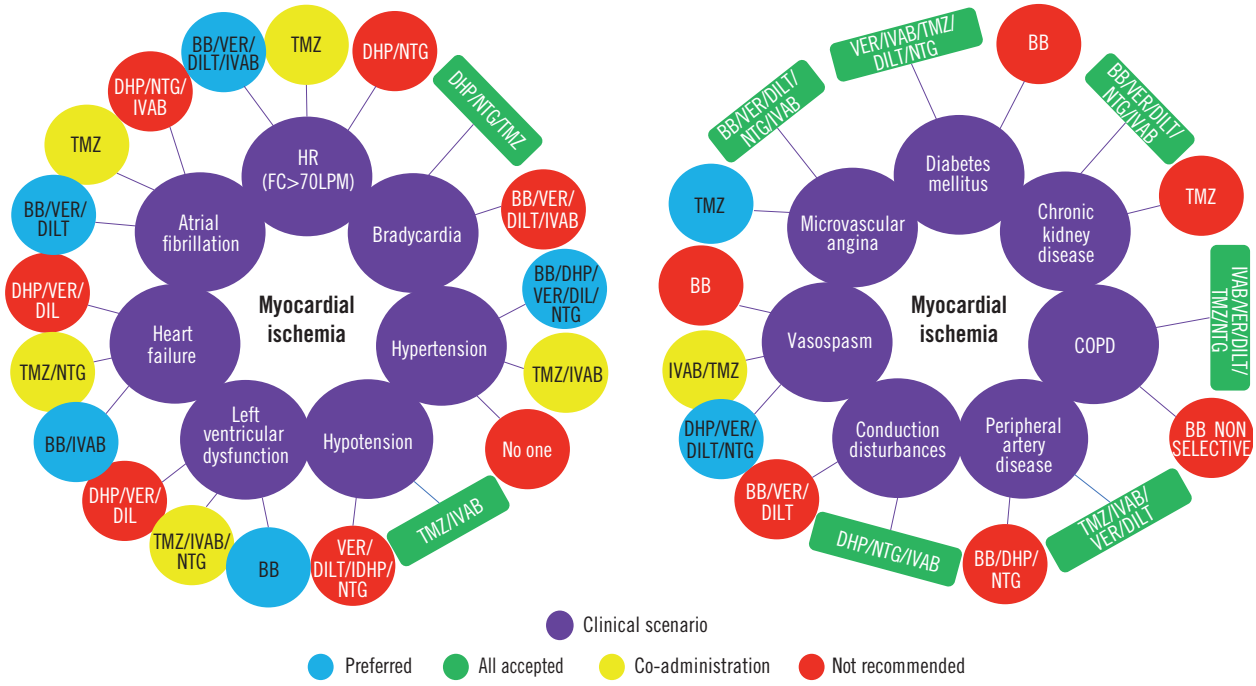

Figure 4 *Individualized treatment for ischemic heart disease.*
Adapted from ref 9: Ferrari R, Camici P, Crea F, et al. A 'Diamond' approach to personalized treatment of angina. Nat Rev Cardiol. *2018;15:120-132.*
Abreviatures: BB, β-blockers, DHP, Dihydropyridines, DILT, Diltiazem, IVAB, Ivabradine, NTG, Nitrates, TMZ Trimetazidine, VER, Verapamil, COPD, Chronic obstructive pulmonary disease

in glucose oxidation, and consequently lactate production is diminished and cell homeostasis could be restored partially. The final result of this metabolic switch is an effective ATP production by the cardiac cells with minimal ATP consumption and better utilization of bioenergetic substrates.[6,7]

In ischemic patients with and without coronary obstructive lesions, the use of trimetazidine has been shown to bring about a significant reduction in angina episodes and increase the functional capacity of patients *(Figure 3).*[8] These results are particularly important in patients with microvascular angina, IHD, and diabetes, with persistent angina after myocardial revascularization procedures (coronary artery bypass graft and/or percutaneous coronary intervention).[7] For this reason the European consensus for the personalized therapeutic approach for the treatment of ischemic heart disease proposes the use of trimetazidine in these specific conditions *(Figure 4).*[9]

In HF, the addition of trimetazidine to standard therapy has been reported to provide slight improvement in LVEF, a significant improvement in NYHA Functional Class, and a reduction of cardiac biomarkers, specifically natriuretic peptides *(Figure 5).*

In our case, the optimization of the treatment with the addition of trimetazidine demonstrated an important improvement in the clinical course of the patient and confirmed the indication of this drug in selected populations in terms to cover some unmet needs and gaps in the treatment of HF, IHD, and diabetes. For this reason, it could be important to have more studies designed specifically to reinforce this data, and possibly add this option in expert consensus, recommendations, and guidelines. ■

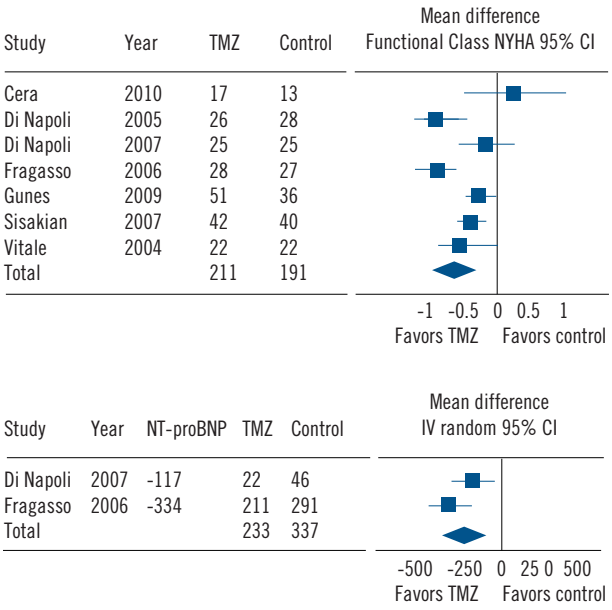

Figure 5 *Efficacy of trimetazidine (TMZ) in heart failure.*
Modified from ref 10: Zhang L, Lu Y, Jiang H, Zhang L, Sun A, Zou Y, Ge J. Additional use of trimetazidine in patients with heart failure: a meta analysis. J Am Coll Cardiol. *2012;59:913-922.*

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Energy metabolism in patients with diabetes and heart failure

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Abstract: The heart has a very high energy demand, which is mostly met by mitochondrial oxidative phosphorylation and, to a lesser extent, by glycolysis. In heart failure, there are substantial alterations in myocardial energy metabolism that lead to an "energy-deficient" state. This includes a marked reduction in overall mitochondrial oxidative phosphorylation and an uncoupling between high glycolysis rates and low glucose oxidation, which together contributes to the energy deficit and deteriorates contractile dysfunction. Cardiac ketone oxidation is also increased in heart failure, although it has yet to be determined whether this is an adaptive or maladaptive alteration. Diabetes is a major risk factor for heart failure development. It induces alterations in myocardial energy metabolism and is often associated with ventricular dysfunction. Similar to heart failure, a major change in myocardial energy metabolism in diabetic patients is a reduction in glucose oxidation, which negatively influences cardiac function. In both heart failure and diabetes, a growing body of evidence suggests that targeting myocardial energy metabolism by optimizing cardiac energy substrate preference could be a potential therapeutic approach to improve patient outcomes. ■ *Heart Metab*. 2019;80:32-36

Keywords: diabetes; fatty acid oxidation; glucose oxidation; heart failure

Introduction

Heart failure is a major cause of death and disability, and represents a huge economic and social burden worldwide.[1] Despite recent improvement in the clinical outcomes of heart failure patients due to new therapies, the mortality and morbidity rates are still high, which emphasizes the need for a new treatment to prevent and/or treat heart failure. Significant metabolic remodeling occurs in heart failure, which includes a marked reduction in mitochondrial oxidative metabolism. These perturbations in cardiac energy metabolism in the failing heart can precede the occurrence of cardiac dysfunction and can influence the progress, as well as the severity, of heart failure.[2,3]

Diabetes is a major metabolic disorder that is associated with either insulin insufficiency (as in type 1 diabetes, T1D) or insulin resistance (as in type 2 diabetes, T2D). Diabetes is a major risk factor for heart failure development, and has been shown to negatively influence contractile function and energy metabolism of the heart. These metabolic changes include the development of cardiac insulin resistance in diabetics, which negatively influences insulin-stimulated cardiac glucose oxidation. High levels of circulating fatty acid in diabetics can further aggravate cardiac insulin resistance, and result in the heart being excessively reliant on fatty acid oxidation as a source of fuel.

The aims of this refresher article are to highlight what the major changes are in myocardial energy

metabolism in heart failure and diabetes, as well as to highlight the similarity between these pathologies. Some controversial issues with regard to energy metabolism on the failing heart and the heart of diabetics will also be discussed.

Energy metabolism in the normal heart

The heart represents less than 1% of the whole body mass, but consumes over 5% of the body's oxygen supply.[4] With essentially no energy reserves, the heart relies on the continuous metabolism of different circulating energy substrates by its highly efficient and complex metabolic machinery to produce its energy (in the form of adenosine triphosphate, ATP). The majority of cardiac ATP production (~95%) occurs in the mitochondria through oxidative phosphorylation, with cytosolic glycolytic ATP production only contributing about 5% of the heart's ATP supply.[1,4] Cardiac energy substrates include fatty acids, carbohydrates (lactate and glucose), ketones, and amino acids.[1,4] The normal healthy heart is metabolically flexible, and can switch its preference between these different energy substrates based on contractility demand, hormonal status, and carbon substrate availability.[1,4] Fatty acids are usually the biggest contributor to cardiac ATP production (40% to 60%), followed by carbohydrates (20% to 30%) and ketone (10% to 20%).[1,4]

Cardiac energy metabolism in the failing heart

One of the main characteristics of the failing heart is that it is generally considered as an "energy-starved" heart *(Figure 1).*[5] This is mainly due to a compromised mitochondrial function, which leads to a considerable reduction in tricarboxylic acid (TCA) cycle activity, mitochondrial oxidative phosphorylation, and cardiac ATP production.[5,6] Mitochondrial dysfunction in the failing heart can be due to reactive oxygen species damage, increased mitophagy and mitochondrial fission, and impaired mitochondrial dynamics/recycling and/or biogenesis.[1,7-9] Another important characteristic of the failing heart is the development of cardiac insulin resistance.[1,4,10-12] Together, these changes impair the metabolic flexibility of the heart and its ability to adapt to different workloads.[1,4] Decreased mitochondrial ATP production results in an upregulation in glycolysis-derived cardiac ATP production in the failing heart in an attempt to compensate for the reduction in oxidative metabolism.[13] However, glycolysis produces a limited amount of ATP (two ATP molecules per molecule of glucose passing through glycolysis) compared with mitochondrial oxidative metabolism (for instance, 31 ATP molecules per molecule of glucose oxidized and 105 ATP molecules per molecule of palmitate oxidized). Accordingly, high glycolytic rates in the failing heart do not compensate for the overall reduction in cardiac ATP production and the heart remains "an engine out of fuel." [5] In addition, the high rates of glycolysis become uncoupled from glucose oxidation, which is impaired in heart failure due in part to a decrease in insulin-stimulation of glucose oxidation.[1,10,11] The increased reliance on glycolysis-derived ATP production leads to the production of lactate and H^+ as metabolic by-products arising from glycolysis uncoupled to glucose oxidation. This compromises cardiac efficiency as ATP is redirecting ATP away from supporting contractile function and towards restoring ionic homeostasis.[14] This decrease in cardiac efficiency[1,4,12,15-17] compounds the energy deficiency problem in the failing heart.

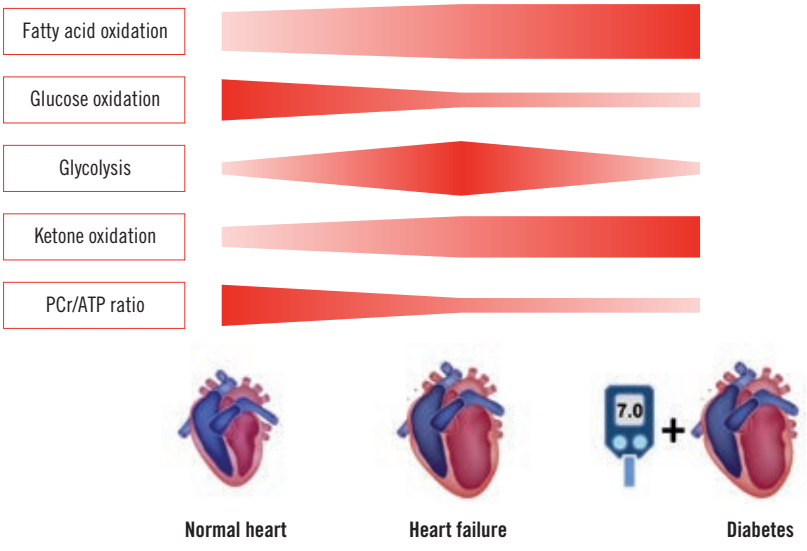

Figure 1 *Perturbations in cardiac energy metabolism in heart failure and diabetes. There is an increase in glycolysis rates in the failing heart which is uncoupled from depressed glucose oxidation rates. In the diabetic heart, there are high rates of fatty acid oxidation which are driven by insulin resistance-induced high levels of circulating fatty acid.*

While cardiac preference for mitochondria oxidative metabolism is still a controversial topic, it is generally accepted that the cardiac preference for fatty acid, glucose, and ketone varies according to the etiology, stage, and severity of heart failure.[1,4] Data from human and animal studies suggest that insulin-stimulated mitochondrial glucose oxidation is decreased, and that this decrease in glucose oxidation is uncoupled from high cytosolic glycolytic rates in the failing heart *(Figure 1).*[10,11,18] In fact, decreased cardiac glucose oxidation rates is a feature of early metabolic remodeling in heart failure and precedes cardiac dysfunction.[2,3,19] Of note, some studies suggested that glucose oxidation is increased in heart failure, but this could be driven by increased glucose uptake and subsequent high glycolytic rates in the failing heart.[20,21]

There is less consensus on the contribution of fatty acid to oxidative metabolism in the failing heart. In 1956, Richard Bing[22] was the first to insert a catheter into the coronary artery in heart failure patients to directly measure the contribution of each cardiac energy substrate to overall energy production. This seminal study showed that fatty acid oxidation is, in fact, increased in heart failure patients compared with healthy volunteers.[22] Using different approaches such as arteriovenous blood sampling and positron-emission tomography (PET), a number of subsequent studies in failing human hearts supported these findings and showed that indeed myocardial fatty acid uptake and oxidation are also increased in heart failure patients.[23-25] It is also worth mentioning that there has been an assumption that fatty acid oxidation is impaired in heart failure due to a decreased expression of fatty acid oxidative enzymes,[5,26] although this is not supported by the majority of experimental and clinical studies where fatty acid uptake and oxidation are directly examined. Measuring myocardial fatty acid oxidation in different murine models of heart failure has not been conclusive, where it has been shown that fatty acid oxidation rates are increased,[10] unchanged,[2,3,12,19] or decreased.[13,21] However, it is not clear whether this reduction in myocardial fatty acid oxidation is secondary to the reduction in cardiac work (which is a major determinant of fatty acid oxidation rates in the heart) in the failing heart.[1,4]

Ketone bodies are another important cardiac energy substrate, the circulating levels of which increase during metabolic stress and starvation.[27,28] Cardiac ketone metabolism has attracted a tremendous interest since it is shown to be increased in the failing heart (*Figure 1).*[12,29,30] In heart failure patients, an increase in circulating ketone levels along with the upregulation of cardiac ketone oxidative enzymes, namely β-hydroxybutyrate dehydrogenase 1 (BDH1), BDH2, and succinyl-coenzyme A (CoA):3-ketoacid CoA transferase (SCOT), have been reported.[30] These increases in ketone oxidation enzymes have also been seen in a mouse model of pressure-overload induced compensated and decompensated heart failure.[12,29] Recently, by directing measuring cardiac ketone oxidation rates, we showed that ketone oxidation rates are increased in the ex vivo isolated failing mouse heart,[12] although this increase in cardiac ketone oxidation is not accompanied by improved cardiac function. Nevertheless, Horton et al[31] demonstrated that augmented level of circulating ß-hydroxybutyrate alleviates cardiac dysfunction and hypertrophy in a canine model of pacing-induced heart failure. Taken together, this may suggest the role that ketone as a signaling molecule could play in mediating its cardioprotection in the setting of heart failure. However, this hypothesis has yet to be directly addressed.

Cardiac energy metabolism in patients with type 1 diabetes

In type 1 diabetes (T1D), there is an insulin deficiency that results in attenuation in the metabolic effects of insulin in the heart. One of the main metabolic effects of insulin in the heart is its stimulatory effect on glucose uptake and subsequent stimulation of glycolysis and glucose oxidation.[4] Through stimulating glucose oxidation, insulin indirectly inhibits cardiac fatty acid oxidation through what is known as the "Randle Cycle."[32] Moreover, insulin indirectly limits cardiac fatty acid oxidation via inhibiting adipose tissue lipolysis and circulating fatty acid levels. In addition to these indirect effects, insulin directly inhibits cardiac fatty acid oxidation via triggering the activity of acetyl CoA carboxylase which increases the level of malonyl CoA, a potent endogenous inhibitor of carnitine palmitoyltransferase-1 (CPT-1), a key regulator of mitochondrial fatty acid uptake.[33] All these metabolic effects of insulin are significantly impaired in T1D patients. In support of that, examining cardiac metabolic profile in patients with T1D, using positron emission tomography (PET) imaging technique, showed high rates of cardiac fatty acid oxidation along with a reduction in

cardiac glucose utilization *(Figure 1).*[34] Similar results have been recapitulated in different animal models of T1D. For instance, cardiac ATP production is almost completely reliant on fatty acid oxidation in ex vivo isolated streptozocin-induced T1D rat hearts.[35] In line with this, high rates of fatty acid oxidation are also observed in the Akita mouse, which is a T1D model due to the mutation in insulin 2 gene, isolated working heart perfusion, while glucose oxidation remains unchanged.[36]

Cardiac energy metabolism in patients with type 2 diabetes and obesity

Despite having different etiology, metabolic perturbations in cardiac energy metabolism which occur in type 2 diabetes (T2D) and obesity are similar to those that occur in heart failure and T1D. Importantly, the occurrence of cardiac insulin resistance (ie, impaired insulin signaling) in obesity and T2D patients leads to the reduction of cardiac glucose oxidation rates along with excessive reliance on fatty acid as a source of cardiac energy *(Figure 1).*[10,37,38] In obese women, Peterson et al[39] reported that high rates of cardiac fatty acid oxidation are positively correlated with glucose intolerance. In addition, high rates of cardiac fatty acid oxidation are negatively correlated with cardiac efficiency in obese subjects.[39] Moreover, it has also been shown that increased cardiac fatty acid oxidation and decreased glucose oxidation in the heart is associated with the development of ventricular dysfunction in patients with T2D.[40,41] These alterations in cardiac metabolism in obese/T2D cause a significant drop in overall cardiac ATP production, as is evident by a reduction in cardiac phosphocreatine/:adenosine triphosphate (PCr:ATP) ratio.[41-43] This suggests that the diabetic heart is energy deficient, similar to what is seen with the failing heart. Of importance, is that weight loss improves myocardial function and energetics in obese/T2DM patients [44] and in obese mice with heart failure.[10] Improvement in cardiac function and energy metabolism following weight loss is associated with improved cardiac insulin-stimulated glucose oxidation and its contribution to overall cardiac ATP production.[10] Emerging evidence suggests that myocardial uptake of both β-hydroxybutyrate and acetoacetate are increased in T2D patients.[45] This may suggest an increase in cardiac ketone oxidation, although it is yet to be directly examined.

Conclusion

A growing body of evidence suggests that the failing heart loses its metabolic flexibility to adapt to different work demands and nutritional/hormonal alterations. This is mainly due to impaired mitochondrial oxidative phosphorylation and cardiac insulin resistance in heart failure. The failing heart becomes highly glycolytic in an attempt to compensate for the energy deficit. While there is still some confusion about what happens to fatty acid oxidation in heart failure, there is a marked reduction in glucose oxidation, due to insulin resistance, which is uncoupled from high rates of glycolysis in the failing heart. Emerging evidence suggesting that ketone metabolism may be upregulated in the failing heart and that augmented levels of circulating ketone elicit cardioprotection in experimental models of heart failure. Myocardial energy metabolism is also altered in T1D and obese/T2D patients. Perturbations in cardiac energy metabolism are positively correlated with glucose intolerance and negatively correlated with cardiac efficiency. This is mainly due to a marked reduction in glucose oxidation and excessive reliance on fatty acid oxidation as a main source of energy in the diabetic heart. Therefore, optimizing cardiac energy metabolism potentially through improving cardiac glucose oxidation rates could be a unifying target to limit left ventricular dysplasia and improve cardiac efficiency and energetics in patients with diabetes and heart failure. ■

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Mechanisms underlying heart failure in type 2 diabetes mellitus

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Abstract: The prevalence of heart failure is markedly increased in individuals with diabetes mellitus. Numerous observational studies suggest that this increased risk for heart failure can be attributed to exacerbated vascular complications and the presence of increased risk factors in diabetic subjects. In addition, experimental studies revealed the presence of a number of distinct molecular alterations in the myocardium that occur independently of vascular disease and hypertension. Many of these molecular alterations are similarly observed in failing hearts of nondiabetic patients and have thus been proposed to contribute to the increased risk for heart failure in diabetes. The interest in understanding the underlying mechanisms of impaired cardiovascular outcomes in diabetic individuals has much increased since the demonstration of cardioprotective effects of SGLT-2 inhibitors and GLP-1 receptor agonists in recent clinical trials. The current review therefore summarizes the distinct mechanisms that have been proposed to increase the risk for heart failure in diabetes mellitus. ■ *Heart Metab*. 2019;80:37-39

Keywords: diabetes; heart failure; mechanism

Introduction

The incidence of type 2 diabetes mellitus (DM) has rapidly increased in recent decades, and will soon affect more than 500 million individuals worldwide. In these individuals, the prevalence of heart failure with preserved (HFpEF) and reduced (HFrEF) ejection fraction is markedly increased, accompanied by an increased risk for hospitalization and mortality.[1-3] While the rate of heart failure hospitalization increases steeply in the 7th decade in nondiabetic subjects, this increase occurs 10 to 15 years earlier in diabetic individuals.[2] Underlying mechanisms for increased HF in DM include a more robust manifestation of cardiac and extracardiac macro- and microvascular complications, and also molecular and structural changes of the myocardium itself.

Macrovascular and microvascular complications

Coronary artery disease (CAD) and myocardial infarction are the most common reasons for heart failure in Western countries, and far more prevalent in patients with DM than without DM. The risk of a diabetic individual without known CAD suffering myocardial infarction is equally high as in nondiabetic individuals with established CAD, thus highlighting the noxious influence of DM on pathogenesis and also acute complications of atherosclerosis in diabetic subjects.[4] In intravascular ultrasound trials, type 2 diabetic individuals had a smaller vascular lumen as well as increased plaque progression rate with greater plaque burden, although atherosclerosis-independent mechanisms may also contribute to increased risk for MI.[5] Furthermore, the clinical outcome in patients with DM seems to be impaired, as suggested by clinical trials in

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different settings of CAD.[6] Complications in diabetes are mainly driven by the systemic metabolic alterations that include hyperglycemia, dyslipidemia, insulin resistance, and hyperinsulinemia. Glucose-induced protein modifications such as advanced glycation end products (AGE) and O-linked N-acetylglucosamine (O-GlcNAc) modifications, increased oxidative stress, the induction of chronic inflammation, and endothelial dysfunction not only lead to the progression of atherosclerosis and pronounced vascular calcification, but also to many of the other accompanying cardiovascular risk factors like arterial hypertension or chronic kidney disease (CKD).[6] Other mechanisms like chronic activation of the renin-angiotensin-aldosterone system (RAAS) or the sympathetic nervous system are further driving the progression of micro- and macrovascular complications.[7] Of note, some evidence exists to show that blood pressure goals are also more difficult to achieve in diabetic individuals and that these patients have worse cardiovascular outcome, regardless of the blood pressure values that were achieved.[8] CKD independently increases the risk of developing CAD, and guideline-directed therapy is less frequently achieved in patients with HF and CKD.[9]

Molecular alterations in the diabetic myocardium

Structural and molecular alterations in the diabetic heart can also occur in the absence of CAD and hypertension, thereby contributing to a clinical phenotype frequently characterized by cardiac hypertrophy, impaired relaxation, and defects in systolic strain, also referred to as diabetic cardiomyopathy (DCM).[10-12] Increased fibrosis occurs as a consequence of increased hyperglycemia-induced modification of structural proteins and crosslinking of collagen molecules, as well as increased profibrotic signaling and impaired extracellular matrix degradation. DCM is also characterized by a proinflammatory state with increased expression of cell adhesion molecules, infiltration with leukocytes, and expression of proinflammatory cytokines. Alterations of myocardial energetics like increased fatty acid oxidation, impaired insulin-stimulated glucose uptake, mitochondrial dysfunction, and mitochondrial uncoupling contribute to myocardial energy depletion and impaired metabolic flexibility. Alterations in cytosolic and mitochondrial Ca^{2+} handling, in particular impaired release and uptake of Ca^{2+} by the sarcoplasmic reticulum, may impair excitation contraction coupling and contractility. Diabetes also induces increased reactive oxygen species (ROS) production both within mitochondria but also in the cytosol by NADPH oxidases, thereby causing damage to lipids, proteins, and DNA. Oxidative stress, but also fibrosis and hypertrophy, are to some extent mediated by local and systemic activation of RAAS. More recently discovered dysregulated mechanisms proposed to contribute to DCM include removal of damaged cellular components (autophagy, mitophagy), or transcriptional (FoxO signaling, alternative splicing, micro-RNAs, epigenetics) and post-translational regulation (O-GlcNAcylation, protein deacetylation) of proteins, among others.[13] Given that many of these molecular mechanisms are altered in a similar fashion in systolic heart failure, a possible contribution to, or at least predisposition for, increased heart failure risk seems likely.

Conclusions

Sufficient evidence exists to assume that the increased HF risk is related both to vascular complications but also to diabetes-induced molecular changes in the myocardium. The exciting recent finding that treatment with the SGLT-2 inhibitor dapagliflozin improved the composite end point of worsening HF or cardiovascular death both in diabetic and nondiabetic individuals with preexisting HF underscores a contribution of myocardium-specific mechanisms to HF in diabetic subjects that are independent of HbA_{1c} lowering and that may overlap between diabetic and nondiabetic failing hearts.[14] Elucidating these as yet incompletely defined mechanisms of SGLT-2 inhibitors in further studies, combined with a better understanding of underlying mechanisms of HF, particularly including the role of myocardial energetics, should increase our understanding of increased HF risk in diabetic individuals and promote the development of new therapeutic avenues to improve outcomes in patients with DM. ■

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Advanced glycation end products (AGEs)

AGEs are lipids and proteins that have become glycated due to increased exposure to carbohydrates (eg, hyperglycemia due to type 2 diabetes). AGEs are thought to play a key role in mediating various pathologies associated with chronic diseases, including promoting vasoconstriction, increasing arterial stiffness, and increasing oxidative stress, all of which can contribute to cardiac dysfunction.

B-type natriuretic peptide (BNP)

BNP is a 32-amino-acid vasoactive peptide secreted by the atria and ventricles in response to ventricular volume expansion and/or to increased wall stress (cardiomyocyte stretch) due to pressure overload. BNP elicits its biological actions—eg, natriuresis, vasodilation, diuresis, inhibition of the renin-angiotensin-aldosterone system, enhanced myocardial relaxation, inhibition of fibrosis and hypertrophy, promotion of cell survival, and inhibition of inflammation—by activating specific natriuretic peptide receptors (NPR-A)/guanylate cyclase (GC-A) that utilize cyclic guanosine monophosphate (cGMP) as an intracellular second messenger. Circulating BNP levels have been demonstrated to be a marker for prognosis and risk stratification in the setting of heart failure.

Cardiac resynchronization therapy

Cardiac resynchronization therapy is a treatment strategy for heart failure that involves the insertion of electrodes into the left and right ventricles of the heart (occasionally an electrode may be inserted into the right atria as well), which acts to coordinate ventricular function via pacemaker.

Cardioprotection

Cardioprotection represents the strategies and treatments for protecting the heart against the various pathologies that affect the myocardium (eg, ischemia/reperfusion injury, heart failure, cardiomyopathy, etc).

Fatty acid oxidation

Fatty acid oxidation is the series of biochemical reactions occurring in the mitochondria that results in the catabolism of a fatty acyl CoA (activated fatty acid) for subsequent energy (ATP) production. Each round of fatty acid oxidation shortens the fatty acyl CoA by 2 carbons (as acetyl CoA) and produces reducing equivalents, which donate their electrons to the electron transport chain, producing the proton motive force that drives ATP production.

Glucagon-like peptide-1 (GLP-1)

GLP-1 is an incretin hormone synthesized and secreted from intestinal L cells. GLP-1 is derived from proglucagon via the action of prohormone convertase 1. Biologically active GLP-1 is generated from GLP-1(1-37) as either GLP-1(7-37) or GLP-1(7-36) amide, which represents the majority of biologically active GLP-1 in human plasma. GLP-1 exerts a variety of effects relevant to the regulation of glucose homeostasis, including enhancing glucose-stimulated insulin secretion, while inhibiting glucagon secretion. In addition, GLP-1 has been demonstrated to promote β-cell proliferation, inhibit β-cell apoptosis, decrease the rate of gastric emptying, and decrease food intake.

Glycolysis

Glycolysis is the series of biochemical reactions occurring in the cytosolic compartment that converts a glucose molecule into two molecules of pyruvate. In the presence of oxygen (ie, the aerobic setting), pyruvate is transported into the mitochondria, and undergoes oxidative decarboxylation yielding acetyl-CoA. In the absence of oxygen (ie, the anaerobic setting), pyruvate is reduced to lactate by the enzyme lactate dehydrogenase, which generates NAD+ required to maintain flux through glycolysis.

Glucose oxidation

Glucose oxidation (ie, pyruvate oxidation) occurs in the mitochondrial matrix, where pyruvate undergoes oxidative decarboxylation via the pyruvate dehydrogenase complex, yielding acetyl coenzyme A (CoA) for the tricarboxylic acid cycle, and reduced nicotinamide adenine dinucleotide (NADH) for the electron transport chain.

Heart failure with preserved ejection fraction (HFpEF)

HFpEF is usually defined as heart failure with an ejection fraction higher than 50% and is characterized by diastolic dysfunction rather than systolic dysfunction. It is primarily accompanied by concentric remodeling and defects in left ventricular compliance. Approximately 50% of all heart failure cases are classified as HFpEF.

Heart failure with reduced ejection fraction (HFrEF)

HFrEF is usually defined as heart failure with an ejection fraction lower than 40% and is characterized by systolic dysfunction. It is primarily accompanied by eccentric remodeling and a decreased left ventricular wall thickness. Approximately 50% of all heart failure cases are classified as HFrEF.

O-linked N-acetylglucosamine (O-GlcNAc)

O-GlcNAc is a reversible post-translational modification, mediated by the enzyme O-linked β-N-acetylglucosamine transferase, consisting of the addition of a single N-acetylglucosamine molecule to serine or threonine residues in proteins. The enzyme O-GlcNAcase removes the modification. Glycosylation with O-GlcNAc modulates cellular signaling, and influences protein expression, degradation, and trafficking.

Phosphocreatine/adenosine triphosphate (PCr/ATP)

ATP is the molecular unit of currency in intracellular energy transfer. PCr is a high-energy phosphate compound that functions to buffer intracellular ATP concentrations. When increases in energy demand deplete ATP, intracellular PCr is utilized to phosphorylate ADP, yielding ATP and creatine, a reversible reaction catalyzed by the enzyme creatine kinase (ie, ADP + H+ + PCr ↔ ATP + Cr). This reaction replenishes intracellular ATP at a rate that is greater than that of ATP generation from catabolic pathways of intermediary substrate metabolism.

Renin-angiotensin-aldosterone system (RAAS)

RAAS is the physiological hormone system responsible for the regulation of blood pressure and fluid balance. Renin, a proteolytic enzyme (originating in the kidneys) stimulates the production of angiotensin I from circulating angiotensinogen. Angiotensin I is subsequently converted to vasoactive angiotensin II, which induces blood vessel constriction and increases blood pressure. Angiotensin II also stimulates the production of aldosterone, which acts on the kidneys to increase sodium and water reabsorption into the blood, also contributing to an increase in blood pressure.

Sodium glucose transporter-2 (SGLT-2)

Sodium glucose transporters belong to the SLC5 human gene family, which contains 12 members, and the activity of which mediates apical sodium and glucose transport across the plasma membrane. SGLT-2 is highly expressed in proximal tubular cells of the kidney and is critical in the reabsorption of filtered glucose. SGLT-2 inhibitors (ie, gliflozin-type drugs) increase the urinary excretion of glucose, and are utilized therapeutically to improve glycemic control.

Coming up next

Myocardial Ischemia: From Disease to Syndrome

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