Diabetična kardiomiopatija – pogosto neprepoznan vzrok srčnega popuščanja pri bolnikih s sladkorno boleznijo

Diabetic cardiomyopathy—an under-recognized cause of heart failure in diabetic patients

Avtor / Author

Ustanova / Institute

David Šuran[1,3], Vojko Kanič[1,3], Andreja Sinkovič[2,3]

[1]Univerzitetni klinični center Maribor, Klinika za interno medicino, Oddelek za kardiologijo in angiologijo, Maribor, Slovenija; [2]Univerzitetni klinični center Maribor, Klinika za interno medicino, Oddelek za intenzivno interno medicino, Maribor, Slovenija; [3]Univerza v Mariboru, Medicinska fakulteta, Katedra za interno medicino, Maribor, Slovenija;

[1]University Medical Centre Maribor, Division of Internal Medicine, Department of Cardiology and Angiology, Maribor, Slovenia; [2]University Medical Centre Maribor, Division of Internal Medicine, Department of Internal Intensive Medicine, Maribor, Slovenia; [3]University of Maribor, Faculty of Medicine, Department of Internal Medicine, Maribor, Slovenia;

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Naslov za dopisovanje / Correspondence
Asist. dr. David Šuran, dr. med., Univerzitetni klinični center Maribor, Oddelek za kardiologijo in angiologijo, Ljubljanska 5, 2000 Maribor, Slovenija
Telefon +386 23212341
Fax: +386 23212845
E–pošta: david.suran@ukc-mb.si

Izvleček

Srčno-žilne bolezni so vodilni vzrok zbolevnosti in umrljivost sladkornih bolnikov. Razširjenost srčnega popuščanja je 3-5 krat večja pri sladkornih bolnikih v primerjavi s splošno populacijo. Diabetična kardiomiopatija je opredeljena kot funkcijska ali strukturna okvara srčne mišice pri sladkornem bolniku, neodvisna od prizadetosti venčnih arterij, bolezni srčnih zaklopk in arterijske hipertenzije. Hiperglikemija, odpornost tkiv na inzulin in hiperinzulinemija povzročajo moteno presnovo srčne mišice in nenormalno delovanje mitohondrijev ter vplivajo na celična rast. Spremembe so bolj izražene pri sladkorni bolezni tipa 2 v primerjavi s sladkorno boleznijo tipa 1. Bolezen ima dva fenotipa. Pogostejši je restriktivni fenotip s koncentričnim preoblikovanjem levega prekata, diastolično disfunkcijo in ohranjenim iztisnim deležem. Dilatativni fenotip z ekscentričnim preoblikovanjem

Abstract

Cardiovascular disorders are the major cause of morbidity and mortality in patients with diabetes mellitus. The prevalence of heart failure is 3–5 times higher in diabetic patients compared with the general population. Diabetic cardiomyopathy is defined as a diabetes-specific disorder characterized by the presence of functional or morphologic changes in the diabetic myocardium, unrelated to coronary artery disease, valvular dysfunction, and arterial hypertension. Hyperglycemia, insulin resistance, and hyperinsulinemia are the major abnormalities affecting cardiac metabolism, mitochondrial function, and cellular growth. Cardiac changes are more pronounced in type 2 diabetes mellitus compared with type 1 diabetes mellitus. The restrictive phenotype is a common presentation with left ventricular remodeling and diastolic dysfunction, while the left ventricular ejection fraction

levega prekata in znižanim iztisnim deležem je redek in je lahko posledica napredovanja bolezni. Čeprav specifičnega zdravjenja diabetične kardiomiopatije še ne poznamo, so rezultati zdravljenja z antidiabetičnimi zdravili nove generacije - zaviralci natrij-glukoznega prenašalnega proteina-2 obetavni.

is preserved. The dilated phenotype with eccentric remodeling and reduced left ventricular ejection fraction is uncommon and might be a hallmark of advanced disease. Although no specific treatment has been recommended, new-generation anti-diabetic drugs (sodium-glucose co-transporter-2 inhibitors) have yielded promising results and extensive research is underway.

INTRODUCTION

Atherosclerotic cardiovascular disease is the leading cause of morbidity and mortality in diabetic patients (1, 2). However, diabetes mellitus (DM) exerts also a direct deleterious effect on the myocardium. In 1974, the Framingham study demonstrated a 2-5 fold risk of developing heart failure in diabetic patients compared with age-matched non-diabetics (3). The Reykjavik study reported an 11.8% prevalence of heart failure among patients with DM compared with 3% among those without DM (4). Diabetes-induced functional or structural myocardial changes, unrelated to arterial hypertension, ischemic, or valvular heart disease, are associated with diabetic cardiomyopathy (3). The term was first described in 1972 by Rubler et al. (5), who demonstrated histologic changes with diffuse myocardial interstitial fibrosis in the autopsy specimens of young patients with DM without obstructive coronary artery disease. Diabetic cardiomyopathy, as well as new anti-diabetic drugs with promising cardioprotective actions, are currently a major focus of research (6). Most of the studies involving diabetic cardiomyopathy included patients with type 2 DM (T2DM).

Although the existence of diabetic cardiomyopathy in patients with type 1 DM (T1DM) has been controversial for years, more convincing evidence has recently emerged, and abnormal findings were more frequent in those with concomitant albuminuria (7-9). Similarly, our study of middle-aged asymptomatic T1DM patients (mean age, 44.3 ± 5.4 years) without other co-morbidities revealed an early onset of cardiac structural and functional changes compared with the age- and gender-matched healthy individuals (10-12).

Mechanisms of myocardial damage in DM

Many potential mechanisms underlying diabetic cardiomyopathy have been proposed. Hyperglycemia enhances non-enzymatic glycation of proteins and promotes deposition of advanced glycation end products in the myocardial interstitium, thereby enhancing cross-linking of collagen fibers, interstitial fibrosis, left ventricular (LV) hypertrophy, and myocardial stiffness (13). Decreased insulin signaling inhibits myocardial glucose utilization and promotes myocardial steatosis due to increased fatty acid uptake and accumulation (14, 15). Mitochondrial dysfunction is a hallmark of diabetic cardiomyopathy with a shift toward less energy efficient fatty acid oxidation, while greater energy-yielding glucose oxidation is reduced. As the supply of fatty acids exceeds mitochondrial oxidative capacity, non-oxidative lipid metabolism ensues with the production of lipotoxic intermediates, such as ceramides and diacylglycerols, which promote oxidative stress, reactive oxidative species formation, and inflammation (16). Furthermore, impaired calcium handling alters excitation-contraction coupling, prolongs action potentials, and the diastolic relation time (17). Insulin resistance and hyperinsulinemia in T2DM also activates the renin-angiotensine-aldosterone system and the sympathetic nervous system, thereby further increasing myocardial hypertrophy and contributing to cardiac remodeling. Endothelial and microvascular dysfunction are also typical findings in diabetic hearts (15).

Clinical presentation

Most patients are initially asymptomatic and may eventually develop symptoms of heart failure (18). Two phenotypes of diabetic cardiomyopathy presenting with

heart failure symptoms have been observed [the common restrictive phenotype with concentric LV remodeling and preserved LV ejection fraction and a rare dilated phenotype with eccentric remodeling and reduced LV ejection fraction] (19, 20).

Diagnosis

The diagnosis of diabetic cardiomyopathy is based on the presence of clinical signs of heart failure or signs of cardiac dysfunction on cardiac imaging after exclusion of ischemic, hypertensive, and valvular heart disease. The gold standard imaging modality is transthoracic echocadiography, while cardiac magnetic resonance has been used mainly for research purposes (21). In our study, tissue Doppler echocardiography yielded a higher diagnostic performance compared with the conventional Doppler to detect early diastolic LV impairment and similar findings were shown by Gul et al. (10, 22). Speckle tracking echocardiography has been used to detect early LV systolic abnormalities due to high sensitivity (9, 23). However, there are no diabetes-specific structural or functional changes detected by cardiac imaging and the diagnosis of diabetic cardiomyopathy is based on the exclusion of other diseases with a similar clinical presentation (21).

Left ventricular remodeling and hypertrophy

Concentric LV remodeling and hypertrophy are the predominant structural abnormalities in patients with T2DM (24). In contrast, increased LV mass is an inconsistent finding in patients with T1DM and is more prevalent in patients with concomitant diabetic nephropathy (8, 24). In our cohort of T1DM patients, we found increased LV wall thickness compared with healthy controls, but the mean values were still in the normal range (10). Although the mean LV mass was normal, the borderline value of the mean relative LV wall thickness indicated a trend of concentric LV remodeling (25).

Both types of DM share common features, such as hypeglycemia. In T2DM patients, however, the increase in LV mass is potentiated by insulin resistance and hyperinsulinemia that stimulate cardiac steatosis and neurohumoral activation (26). Furthermore, obese patients with T2DM have higher interleukin and leptin levels, accelerating the growth of myocardial cells (27).

Left ventricular diastolic dysfunction

Diastolic dysfunction is the earliest and most characteristic feature of diabetic cardiomyopathy. Mild LV diastolic alterations have been demonstrated using tissue Doppler, even in asymptomatic children and adolescents with DM despite good glycemic control (28). The prevalence of LV diastolic dysfunction in well-controlled normotensive T2DM patients ranges from 45% to 75%, and is highest in studies evaluating diastolic function with tissue Doppler echocardiography (29). LV diastolic dysfunction is more frequent and more advanced in older patients with a longer duration of DM, poor glycemic control, central obesity, and concomitant diabetic microvascular complications (19).

Evidence of LV diastolic impairment is less abundant in patients with T1DM. While small-sample studies have reached inconclusive results, the 2014 Thousand and 1 Study demonstrated some degree of diastolic dysfunction in up to 30.7% of middle-aged patients with T1DM, which was comparable with the general population almost 13 years older in the study conducted by Redfield et al. [8, 30]. In the Thousand and 1 Study, 14.4% of T1DM patients were classified with long-standing LV diastolic dysfunction based on tissue Doppler evidence of increased LV filling pressure and left atrial enlargement (8). In agreement with the previous results, we demonstrated a small, but significant increase, in the left atrial volume index and changes in diastolic LV tissue Doppler parameters in asymptomatic T1DM patients compared with age-matched healthy controls (10, 11). Left atrial volume indexed to the body surface area and the ratio E/e` showed the highest diagnostic accuracy to detect early diastolic LV changes in our patients (11).

Left ventricular systolic dysfunction

Most imaging studies found normal LV ejection fraction in both types of DM. Although unlikely, the dilated phenotype with reduced LV ejection fraction might be a sign of advanced disease or evolve independently due to autoantibodies in patients with T1DM (20). In a large observational study, however, the prevalence of a reduced LV ejection fraction (< 45%) in patients with T1DM was only 2%, which was similar to the non-diabetic population (8).

Because the LV ejection fraction is highly dependent on loading conditions, the reduced LV ejection

fraction has low sensitivity to detect early changes in LV systolic function. More recent studies have focused on tissue Doppler imaging or speckle tracking-based tissue deformation analysis of the LV (strain and strain rate) and confirmed LV systolic impairment in both types of DM (9, 31). Because the reduction of LV global longitudinal strain is the most commonly reported abnormality in diabetic patients, it has been hypothesized that metabolic damage is most pronounced in the longitudinal subendocardial fibers, which are responsible for LV longitudinal shortening during systole (32). In addition to speckle tracking echocardiography, our results suggested that assessment of myocardial acceleration during isovolumetric contraction is a useful and relatively novel tissue Doppler-derived parameter to detect early myocardial alterations in patients with DM (10, 11).

The diabetic heart appears to be vulnerable and more susceptible to further noxious stimuli, such as ischemia. Diabetic patients with an acute myocardial infarction on average have larger ischemic areas compared with non-diabetic patients (33). Furthermore, the contractile reserve of the uninfarcted LV myocardium in diabetic patients is lower compared with non-diabetic patients and the incidence of heart failure following myocardial infarction is higher (34).

Right ventricular dysfunction

Although right ventricular (RV) dysfunction has important prognostic implications, few studies have focused on the RV in diabetic patients (35). Small-volume imaging studies using tissue Doppler, speckle tracking echocardiography, or cardiac magnetic resonance reported right ventricular remodeling with impaired RV systolic and diastolic function (9). We found significantly increased right atrial size and tissue Doppler indices of RV diastolic dysfunction in patients with T1DM compared with healthy controls. In contrast, RV systolic impairment was subtle and suggested by the reduced myocardial acceleration during isovolumetric contraction as compared with the control group. There was no difference between the two groups with respect to conventional parameters, such as the tricuspid annular plane systolic excursion (TAPSE) and the peak systolic tricuspid annular velocity (S), and the RV myocardial performance index (10, 11).

Impact of glycemic control and anti-diabetic medications on cardiac function

In the large Diabetes Control and Complications Trial/ Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) trial, intensive versus conventional insulin treatment of patients with T1DM resulted in decreased microvascular complications, reduced fatal and non-fatal cardiovascular events, and all-cause mortality (36, 37). While strong evidence supports a favorable effect of improved glycemic control on cardiovascular outcomes in patients with T1DM, the direct impact of glycemic control on the myocardium is less clear. In the observational Swedish study conducted by Lind et al. (38), patients with T1DM and very poor glycemic control (HbA1c > 10.5%) had a four-fold higher incidence of heart failure compared with patients achieving optimal gylcemic control (HbA1c < 6.5%) over a median observation time of nine years. In an analysis of the mean HbA1c as a continuous variable, each 1% incremental increase in HbA1c in patients with T1DM was associated with a 30% increased risk of developing heart failure (38). By contrast, in a subpopulation of the DCCT/EDIC trial, only mild regression of the LV mass and left atrial volume was demonstrated in the intensively- versus conventionally-treated patients with T1DM over a duration of years (39). Based on our correlation analysis, long-term (five-year) glycemic control was only weakly associated with the Doppler index of the LV filling pressure (E/e`), while no correlation with cardiac chamber size was confirmed. Furthermore, we found no association between cardiac chamber size and function with the five-year trend of glycated hemoglobin. This finding might be due to the good long-term glycemic control and the use of continuous subcutaneous insulin infusion in nearly one-half of our patients. In our study, body mass index was the only parameter consistently associated with early subclinical structural and functional changes in patients with T1DM (25).

Intensive glycemic control in patients with T2DM significantly reduced microvascular complications, while the role of intensive glycemic control in reducing cardiovascular events has been controversial for years (40). Only limited data support cardiovascular benefits in the intensively treated patients with T2DM using sulfonylureas and insulin (41). In contrast, metformin was shown to be beneficial in reducing cardiovascular

events and reducing all-cause mortality in obese patients with T2DM (41).

In clinical trials, older oral anti-diabetic medications did not reduce the incidence of heart failure (40). In contrast, the new generation drugs (sodium-glucose co-transporter-2 inhibitors [SGLT2]) have been shown to have a direct cardioprotective effect beyond hypoglycemic actions with a reduction of heart failure hospitalizations, while some of the new-generation drugs even reduced cardiovascular and all-cause mortality in the diabetic population (6, 42). SGLT2 inhibitors (empagliflozin, dapagliflozin, canagliflozin) enhance glucosuria and thereby reduce body weight, blood pressure, promote a shift of fuel utilization from carbohydrates-to-lipids and ketones, and potentially exert direct favorable effects on cardiac calcium homeostasis via inhibition of the sodium-hydrogen exchanger on the membrane of cardiac cells (43). The precise cardioprotective mechanisms of SGLT-2 inhibitors, however, have not been fully elucidated and further studies are underway. Glucagon-like peptide-1 (GLP-1) agonists (liraglutide, dulaglutide, semaglutide) are also new-generation drugs demonstrating a favorable effect on cardiovascular outcomes in high-risk patients (44, 45). In patients with T2DM, liraglutide reduced the primary composite endpoint comprising cardiovascular mortality, and non-fatal myocardial infarction and stroke, but did not reduce the risk for heart failure (44). Although SGLT-2 inhibitors and GLP-1 agonists are currently the preferred treatment options for patients with T2DM and established cardiovascular disease, no specific therapy for the treatment of diabetic cardiomyopathy has been established (46).

CONCLUSION

Diabetic cardiomyopathy is an increasingly recognized entity in patients with DM. Asymptomatic cardiac dysfunction and heart failure with preserved ejection fraction due to the concentric LV remodeling and increased myocardial stiffness are the most common clinical presentations. Cardiac changes are usually more pronounced in patients with T2DM, but the adverse impact of T1DM on cardiac structure and function has been demonstrated by many recent studies, and it was confirmed by our results. While older anti-diabetic medications did not reduce heart failure and cardiovascular death, newer anti-diabetic drugs, like SGLT-2 inhibitors and GLP-1 agonists, have promising cardioprotective effects.

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