DIABETIC CARDIOMYOPATHY AND DIASTOLIC HEART FAILURE

Diana SASU - assistant professor, Ph. D.,
Svetlana GAVRILIUC – assistant professor,
Valeriu ISTRATI - university professor

Department of Internal Medicine and semiotics, Nicolae Testemitan State University of Medicine and Pharmacy
tel: + 37369290004, s_dianna2002@yahoo.com

Summary.
Diabetic cardiomyopathy (DCM) is a distinct condition with a pathogenesis that is independent from coronary artery disease and can lead to heart failure in diabetic patients. In some patients, diastolic dysfunction may progress to heart failure with reduced ejection fraction and results in systolic heart failure. Since DCM is highly prevalent in the asymptomatic diabetic patients, screening for its presence and the diagnosis of functional myocardial abnormalities (echocardiography and other cardiac imaging techniques) in diabetic populations can have a favorable impact on the progression to chronic heart failure.

Key-words: diabetic cardiomyopathy, heart failure, diabetes mellitus.

Rezumat. Cardiomiopatia diabetică şi insuficienţa cardiacă diastolică.
Cardiomiopatia diabetica este o afecţiune particulară prin mecanisme de instalare independente de aterosleroza coronariana şi în evoluţie conduce la instalarea insuficienţei cardiace. La unii pacienţi disfuncţia diastolică poate progresa spre insuficienţa cardiacă cu fracţia de ejecţie păstrată şi ulterior spre insuficienţa cardiacă sistolică. Deoarece cardiomiopatia diabetică are o prevalenţă înaltă la pacienţii cu diabet zaharat, screening-ul populaţiei şi diagnosticarea anomaliilor miocardice (examen ecocardiografic şi alte teste imagistice) pot duce la prevenirea progresiei insuficienţei cardiace.
Cuvinte-cheie: cardiomiopatia diabetică, insuficienţa cardiacă, diabetul zaharat.

Резюме. Диабетическая кардиомиопатия и диастолическая сердечная недостаточность.
Диабетическая кардиомиопатия это особенная патология, характеризующаяся независимыми механизмами развития коронарного атеросклероза, и в результате эволюции ведет к установлению сердечной недостаточности. У некоторых пациентов диастолическая дисфункция может прогрессировать до сердечной недостаточности с сохраненной фракцией выброса, и в последующем развитие систолической сердечной недостаточности. Поскольку диабетическая кардиомиопатия очень часто встречается у больных с сахарным диабетом, скрининг популяции и диагностика аномалий миокарда (ультразвуковое исследование и другие тесты) могут позволить раннюю диагностику прогрессирования сердечной недостаточности.
Ключевые слова: диабетическая кардиомиопатия, сердечная недостаточность, сахарный диабет

Introduction

The close association between diabetes mellitus and heart failure is well-known and is clearly supported by data from many epidemiological studies [1]. Approximately 40% of patients hospitalized with heart failure (HF) and reduced ejection fraction (EF) have diabetes mellitus (DM) with an important epidemiologic, economic and clinical impact [1, 2].

Diabetic heart disease is a growing and important public health risk. It affects the heart in three ways: cardiac autonomic neuropathy (CAN), coronary artery disease (CAD) due to accelerated atherosclerosis, and diabetic cardiomyopathy (DCM) [3].

In 1881, Leyden first reported that diabetic cardiomyopathy is a typical complication of diabetes mellitus. In 1888, Mayer asserted that diabetes mellitus is a metabolic disorder that can induce heart disease. The term "diabetic cardiomyopathy" was proposed in 1972 by Rubler after postmortem studies in diabetic patients with heart failure, but without hypertension or coronary artery disease and has been confirmed by large epidemiological studies [4].

In 2013, the American College of Cardiology Foundation, the American Heart Association, and the European Society of Cardiology in collaboration with the European Association for the Study of Diabetes defined diabetic cardiomyopathy as a clinical condition of ventricular dysfunction that occurs in the absence of coronary atherosclerosis and hypertension in patients with diabetes mellitus [5]. In its early stages, diabetic cardiomyopathy includes a hidden subclinical period characterized by structural and functional abnormalities, including left ventricular hypertrophy, fibrosis, and cell signaling abnormalities. The pathological changes of cardiac fibrosis, stiffness and associated subclinical diastolic dysfunction progress to heart failure with normal ejection fraction and to heart failure with reduced ejection fraction (HFrEF) [6, 7].

Epidemiology

Clinical trials showed that the prevalence of HF in diabetic patients ranging from 19-26%. The Framingham Heart Study reported that 19% of patients with HF have type 2 diabetes mellitus (T2DM) and that the risk of heart failure increases 2- to 8-fold in the presence of T2DM [8, 9].

The prevalence of diastolic dysfunction in patients with T2DM was up to 30% in some studies. However, there are other studies that reported a prevalence rate as high as 40% to 60% [9].

Epidemiological studies have affirmed that impaired glucose tolerance, increased serum glucose levels and glycated haemoglobin levels are associated not only with incidence of systolic HF but also with the prevalence of diastolic dysfunction [10].

Pathophysiological mechanism

Patients with HF and DM show specific metabolic, neurohormonal and structural heart abnormalities which potentially contribute to worse outcomes compared to those without comorbid DM. The relationship between DM and HF is bidirectional, with each disease independently increasing the risk for the other [11].

The most frequent abnormality in the diabetic heart is impaired diastolic compliance, setting the stage for HF with normal EF. Diastolic dysfunction has been detected in up to 75% of asymptomatic patients with DM [11].

Diabetic cardiomyopathy is manifested by heart failure with preserved ejection fraction (HFpEF) at an early stage. In some patients, diastolic dysfunction

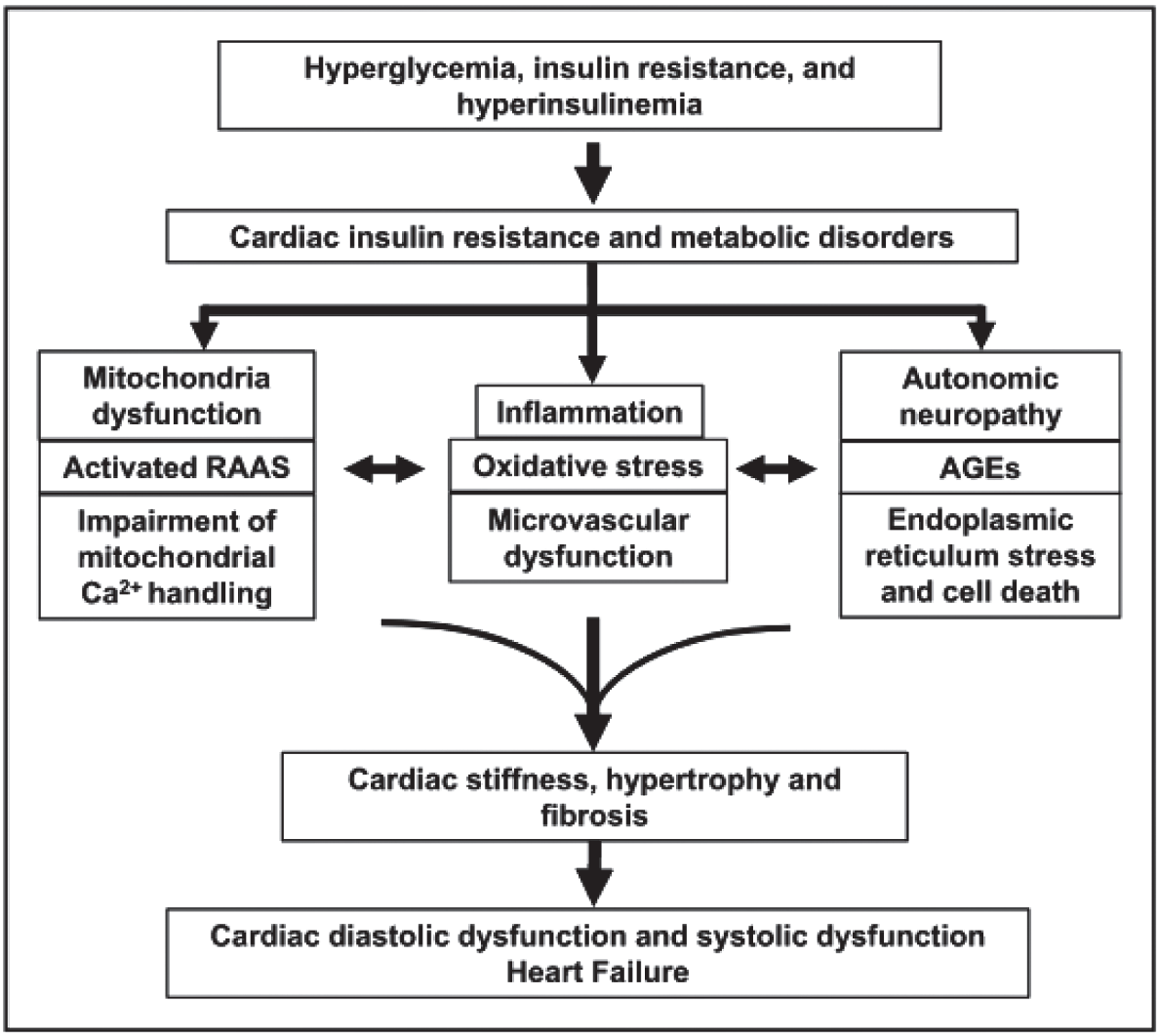

Fig.1. Pathophysiological mechanisms of diabetic cardiomyopathy [13].

may progress to compromised left ventricular function and result in overt HFrEF [11].

Hyperglycemia is one of the main pathogenic factor leading to diabetic cardiomyopathy, initiating a series of adaptive and maladaptive processes (fig.1). Also, hyperglycemia contributes to the activation of free radicals, to consecutive tissue damage in different organs, local renin-angiotensin-aldosteron system activation, endothelial dysfunction and hypertrophy [12, 13].

Hyperglycemia, insulin resistance, and hyperinsulinemia induce cardiac insulin resistance and metabolic disorders that increase mitochondria dysfunction, oxidative stress, advanced glycation end products (AGEs), impairment of mitochondria Ca2+ handling, inflammation, activation of renin–angiotensin–aldosterone system (RAAS), autonomic neuropathy, endoplasmic reticulum stress, cardiomyocyte death, as well as microvascular dysfunction. These pathophysiological abnormalities promote cardiac stiffness, hypertrophy, and fibrosis, resulting in cardiac diastolic dysfunction, systolic dysfunction, and heart failure [13, 14].

Increased glucose metabolism due to hyperglycemia increases oxidative stress via the development of nitrogen species or reactive oxygen species from the mitochondria [15]. Oxidative stress caused by the overproduction of superoxide in the mitochondrial respiratory chain leads to reduced myocardial contractility and eventually induces myocardial fibrosis [16]. Oxidative stress and reactive oxygen species can accelerate cardiomyocyte apoptosis and cellular DNA damage. Oxidative stress-induced DNA damage also activates DNA repair enzymes such as poly ADP ribose polymerase (PARP) [17]. PARP redirects glucose metabolism from its usual glycolytic pathway to an alternative biochemical pathway that results in the development of various mediators and causes hyperglycemia-induced cellular injury. These injuries include increased hexosamine and polyol flux, pro-

tein kinase C activation, and advanced glycation end product (AGE) levels [18].

AGEs are a stable form of cross-linked collagen that accumulate in vessel walls and in myocardial tissue and increase diastolic stiffness of the heart and contribute to endothelial dysfunction [16].

Renin Angiotensin Aldosterone System Activation

Increased activation of the systemic and tissue renin-angiotensin-aldosterone in states of hyperglycemia and insulin resistance plays an important role in the pathogenesis of diabetic cardiomyopathy and HF (Fig 1) [13].

Intracellular angiotensin II levels were 3.4-fold higher in the myocardial cells of diabetic patients compared with non-diabetics. Cytoplasmic angiotensin II promotes cell growth in animal models. Experimental evidence also supports a role for increased mineralocorticoids in systemic and tissue insulin resistance [18]. Both angiotensin II and aldosterone cause increased production of reactive oxygen species and the activation of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, and the increase of cytosolic oxidative stress. Aldosterone also worsens cardiac fibrosis by triggering pro-inflammatory factors through activation of metalloproteinases and the transforming growth factor β [20].

Large randomized controlled trials have shown that inhibition of the aldosterone signaling pathway reduces morbidity and mortality in diabetic patients with both mild and moderately severe heart failure [19].

Cardiac autonomic neuropathy is a common microvascular complication of DM affecting almost 17% of the patients with type 1 diabetes and 22% of those with type 2 diabetes. Diabetic autonomic neuropathy may result in changes of the sympathetic innervation, through disturbed expression of adrenoreceptors and altered catecholamine levels in the myocardium [11].

The increased expression of β 1-adrenoreceptors intensifies apoptosis, fibrosis and hypertrophy, resulting in restricted myocardial function [21].

Cardiac autonomic neuropathy is associated with depressed baroreflex function that leads to impaired regulation in the heart rate control, stroke volume and blood pressure that have been associated with both systolic and diastolic dysfunction [22].

Sympathetic overactivity is a common feature in DM and HF with different causal chains. In non-diabetic HF, sympathetic activation occurs in the later HF stages leading to insulin-resistance, whereas cardiac autonomic neuropathy is a central determinant of the diabetes-induced microvascular complication worsening metabolic and functional alterations in diabetic cardiomyopathy [21].

Evolution of Diabetic Cardiomyopathy to Clinical Heart Failure

Diabetic cardiomyopathy is usually asymptomatic in the early stage of its evolution. The first stage is characterized by increased fibrosis and stiffness, reduction of early diastolic filling and increase in atrial filling and enlargement, and an elevated LV end-diastolic pressure [23].

The second stage of diabetic cardiomyopathy is characterized by LV hypertrophy, cardiac remodeling, advancing cardiac diastolic dysfunction. With the progression of diabetic cardiomyopathy, diastolic dysfunction and reduced cardiac compliance may coexist with systolic dysfunction which leads to reduced ejection fraction, prolonged pre-ejection performance, an enlarged LV chamber and shortened ejection period [19, 23].

The Cardiovascular Health Study found that, in a cohort of 5201 men and women, the ventricular septal and left posterior myocardial wall thicknesses were greater in diabetic patients than in nondiabetic individuals and this was associated with compromised systolic or diastolic function [24].

According to echocardiographic studies, approximately 40-75% of diabetic patients without coronary heart disease present with diastolic dysfunction. Isolated diastolic dysfunction in the presence of normal left ventricular ejection fraction can be found in 30-50% of the patients with clinical symptoms of heart failure [24].

The restriction of cardiac output in HFpEF is due to impaired diastolic ventricular filling, especially under stress. LV dysfunction in diabetic heart can be unmasked during exercise even in asymptomatic subjects [25]. Patients with type 2 DM with normal myocardial function at rest but an abnormal response to exercise stress had significantly reduced longitudinal diastolic functional reserve index compared to those with a normal stress response, highlighting the important role of myocardial diastolic relaxation in maintaining normal myocardial function and exercise capacity. These findings suggest that impaired cardiac performance after exercise could be a potential tool to detect early contractile dysfunction in DM [24].

Subjects with type 2 DM are more susceptible to preclinical diastolic and systolic dysfunction compared to type 1 patients, supporting a role of insulin resistance-mediated alterations in the determination of early cardiac dysfunction. Diastolic dysfunction was associated with the presence of mild complica-

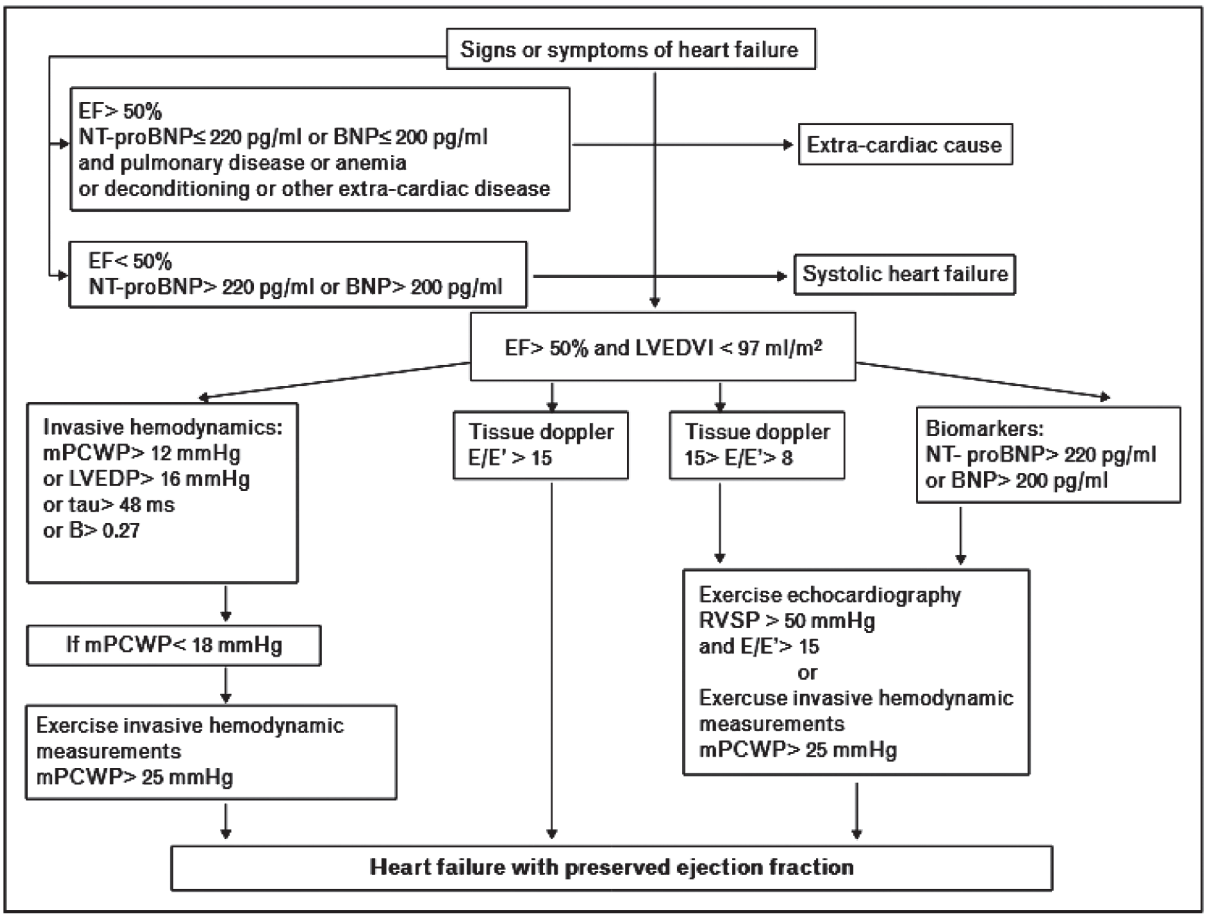

Fig. 2. Algorithm for the diagnosis of diastolic heart failure [29,31].
mPCWP- mean pulmonary capillary wedge pressure; LVEDP- left ventricular end-diastolic pressure, tau- time constant of left ventricular relaxation; B- constant of left ventricular chamber stiffness; E-maximum velocity of early diastolic transmitral flow; E'- early tissue Doppler lengthening velocity

tions, suggesting that the extent of systolic dysfunction may depend more on the magnitude and duration of hyperglycemia [26].

The prognostic significance of elevated blood glucose levels was shown in a study with 454 patients who had been hospitalized for decompensated heart failure. The patients with heart failure with concomitant impaired glucose tolerance or diabetes mellitus died in 50% of cases compared with 36.6% of patients with normal blood glucose levels [27]. In a large cohort study of diabetic patient was shown that glycemic control is an important prognostic factor, in which each 1% increase in glycosylated hemoglobin was associated with 8% increased risk of HF [28].

Diagnosis of diastolic dysfunction

Left ventricular hypertrophy and diastolic dysfunction are early and characteristics but not specific for diabetic cardiomyopathy.

The European Society of Cardiology has suggested criteria for the diagnosis of diastolic dysfunction [29]:

1. Signs or symptoms of heart failure;
2. Preserved left ventricular systolic function and normal left ventricular volume indices;
3. Evidence of diastolic dysfunction.

The combination of two assessments such as Doppler index E/E' by echocardiography and the measurement of the heart failure marker like brain natriuretic peptide (BNP) and N-terminal- pro- brain natriuretic peptide (NT-proBNP in diabetic patients may confirm the diagnosis of diastolic heart failure (Fig.2) [26, 31]:

BNP and pro-BNP levels tend to be lower in patients with diastolic heart failure (DHF) when compared with patients with systolic heart failure and may be within normal limits. BNP showed a sensitivity of 92% and specificity of 72 % for LV systolic dysfunction [30]. Furthermore, plasma brain natriuretic peptide levels have been found significantly higher in HF patients with DM than in non-diabetic patients at the same HF score.

Cardiac catherization is the gold standard to assess abnormal left ventricular relaxation, filling, di-

astolic distensibility and stiffness. An end-diastolic pressure >16mmHg measured in the left ventricle provides an evidence of diastolic dysfunction (Fig.2) [29,31].

Patients with DHF have a high prevalence of structural heart disease such as concentric LV remodeling and concentric hypertrophy. Left ventricular (LV) hypertrophy and mass can be easily identified by echocardiography, and it is recommended as the primary noninvasive test in the diagnosis of DHF. Echocardiograms obtained in patients enrolled in the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) trial before initiation of randomized therapy found that 14% had normal LV geometry, 34% concentric remodeling, 43% concentric hypertrophy, and 9% eccentric hypertrophy [32]. The echocardiographic substudy of the Irbesartan for Heart Failure with Preserved Ejection Fraction (I-PRESERVE) trial found that 46% of the patients enrolled had normal LV geometry [33].

The development of new ultrasound techniques such as echo strain imaging and the use of magnetic resonance imaging has proved to be effective in the measurements of diastolic functional status [32]. The Doppler measurement of trans mitral blood flow during left ventricular filling is widely used. The velocity ratio (E/A) of the passive, early diastolic inflow (E wave) to the active influx as a result of atrial contraction (A wave) is simple to determine. Impaired compliance of the left ventricle results in an increased proportion of active filling by atrial contraction and the E/A ration is reversed (E/A<1) [34]. Color Doppler M-mode is a method for measuring mitral to apical early diastolic flow propagation.

The time delay of apical filling is related to left ventricular relaxation. A velocity of flow propagation (V) >50 cm/s is considered normal, while a velocity <45cm/s reflects diastolic dysfunction. Tissue Doppler techniques allow the measurement of myocardial velocities at the level of the mitral ring. The E/e- ratio correlates well with the end-diastolic filling pressure [34, 35].

Another structural indicator of diastolic dysfunction is the assessment of left atrial size and function. Left atrial (LA) enlargement was present in the majority of patients with DHF; 53% of patients enrolled in the TOPCAT trial and 66% of patients enrolled in the I-PRESERVE trial had some degree of left atrial enlargement [32,33].

References

1. Gottdiener J.S., Arnold A.M., Aurigemma G.P., Polak J.F., Tracy R.P., Kitzman D.W. et al. *Predictors of congestive heart failure in the elderly: the Cardiovascular Health Study.* J Am Coll Cardiol. 2000, 35(6), p. 1628–37.

2. Sarma S., Mentz R.J., Kwasny M.J., Fought A.J., Huffman M., Subacius H. et al. on behalf of the EVEREST investigators. *Association between diabetes mellitus and post-discharge outcomes in patients hospitalized with heart failure: findings from the EVEREST trial*. Eur J Heart Fail. 2013, 15, p. 194-202.

3. Wang Z.V., Hill J.A. *Diabetic cardiomyopathy: catabolism driving metabolism*. Circulation. 2015, 131, p. 771–773.

4. Trachanas K., Sideris S., Aggeli C. et al. *Diabetic cardiomyopathy: from pathophysiology to treatment.* Hellenic J Cardiol. 2014, 55, p. 411–421.

5. Ryden L., Grant P.J., Anker S.D. et al. Authors/Task Force Members; ESC Committee for Practice Guidelines (CPG); Document Reviewers. *ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD: the Task Force on diabetes, pre-diabetes, and cardiovascular diseases of the European Society of Cardiology (ESC) and developed in collaboration with the European Association for the Study of Diabetes (EASD).* Eur Heart J. 2013, 4, p. 3035–3087. doi: 10.1093/eurheartj/eht108

6. Yancy C.W., Jessup M., Bozkurt B. et al. American College of Cardiology Foundation; American Heart Association Task Force on Practice Guidelines. *2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines*. J Am Coll Cardiol. 2013, 62, p. 147–239. doi: 10.1016/j.jacc.2013.05.019.

7. Guanghong Jia, Michael A. Hill, James R. Sowers. *Diabetic Cardiomyopathy*. Circulation Research. 2018, 122, p. 624-638.

8. Maisch B., Alter P., Pankuweit S. *Diabetic cardiomyopathy: fact or fiction*? Herz. 2011, 36, p. 102–115.

9. Witteles R.M., Fowler M.B. *Insulin-resistant cardiomyopathy clinical evidence, mechanisms, and treatment options.* J Am Coll Cardiol. 2008, 51, p. 93–102.

10. Yancy C.W., Jessup M., Bozkurt B. et al. *2013 ACCF/AHA guideline for the management of heart failure: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines.* Circulation. 2013, 128, p. 1810–52.

11. Lindman B.R., Dávila-Román V.G., Mann D.L. et.al. *Cardiovascular Phenotypes in HFpEF Patients with and without Diabetes. JACC.* 2014, 64, p. 541-549.

12. Boyer J.K., Thanigaraj S., Schechtman K.B., Pérez J.E. *Prevalence of ventricular diastolic dysfunction in asymptomatic, normotensive patients with diabetes mellitus.* Am J Cardiol. 2004, 93, p. 870-5.

13. Teupe C., Rosak C. *Diabetic cardiomyopathy and diastolic heart failure, Difficulties with relaxation.* Diabetes Research and Clinical Practice. 2012, 97, p. 185-194.

14. Jia G., De Marco V.G., Sowers J.R. *Insulin resistance and hyperinsulinemia in diabetic cardiomyopathy* . Nat Rev Endocrinol. 2016, 12, p. 144-153.

15. Aragno M., Mastrocola R., Medana C. et al. *Oxidative stress-dependent impairment of cardiac-specific transcription factors in experimental diabetes*. Endocrinology. 2006, 147, p. 5967–5974.

16. Cai L., Li W., Wang G., Guo L., Jiang Y., Kang Y.J. *Hyperglycemia-induced apoptosis in mouse myocardium: mitochondrial cytochrome C-mediated caspase-3 activation pathway.* Diabetes. 2002, 51, p. 1938–1948.

17. Letonja M., Petrovic D. *Is diabetic cardiomyopahy a specific entity*? World J Cardiology. 2014, 6(1), p. 8-13.

18. Guanghong Jia, Michael A. Hill, James R. Sowers. *Diabetic Cardiomyopathy.* Circulation Research. 2018, 122, p. 624-638.

19. Tate M., Deo M., Cao A.H., Hood S.G., Huynh K., Kiriazis H., Du X.J., Julius T.L., Figtree G.A., Dusting G.J., Kaye D.M., Ritchie R.H. *Insulin replacement limits progression of diabetic cardiomyopathy in the low-dose strepto-izotocin-induced diabetic rat*. Dab Vasc Dis Res.

20. Catena C., Colussi G., Brosolo G. et al. *Aldosterone and aldosterone antagonists in cardiac disease: what is known, what is new.* Am J Cardiovasc Dis. 2012, 2, p. 50-57.

21. Falcao-Pires I., Leite-Moreira A.F. *Diabetic cardiomyopathy: understanding the molecular and cellular basis to progress in diagnosis and treatment*. Heart Fail Rev. 2012, 17, p. 325–344.

22. Kumar R., Yong Q.C., Thomas C.M., Baker K.M. *Intracardiac intracellular angiotensin system in diabetes.* Am J Physiol Regul Integr Comp Physiol. 2012, 302, p. 510-517.

23. Lee M., Gardin J.M., Lynch J.C., Smith V.E., Tracy R.P., Savage P.J., Szklo M., Ward B.J. *Diabetes mellitus and echocardiographic left ventricular function in free-living elderly men and women: the Cardiovascular Health Study*. Am Heart J. 1997, 133, p. 36–43.

24. Brooks B.A., Franjic B., Ban C.R., Swaraj K., Yue D.K., Celermajer D.S. et al. *Diastolic dysfunction abnormalities of the microcirculation in type2 diabetes.* Diabetes Obes Metab. 2008, 10(9), p. 739–46.

25. Poulsen M.K., Henriksen J.E., Dahl J., Johansen A., Gerke O., Vach W. et al. *Left ventricular diastolic function in type 2 diabetes mellitus: prevalence and association with myocardial and vascular disease.* Circ Cardiovasc Imaging. 2010, 3(1), p. 24–31.

26. Astorri E., Fiorina P., Contini G.A., Albertini D., Magnati G., Astorri A. et al. *Isolated and preclinical impairment of left ventricular filling in insulin- dependent and non-insulin-dependent diabetic patients.* Clin Cardiol. 1997, 20, p. 536-40.

27. Berry C., Brett M., Stevenson K., McMurray J.J., Norrie *J. Nature and prognostic importance of abnormal glucose tolerance diabetes in acute heart failure.* Heart. 2008, 94(3), p. 296–304.

28. Iribarren C., Karter A.J., Go A.S., Ferrara A., Liu J.Y., Sidney S. et al. *Glycemic control and heart failure among adult patients with diabetes.* Circulation. 2001, 103, p. 2668-73.

29. Paulus W.J., Tschope C., Sanderson J.E., Rusconi C., Flachskampf F.A., Rademakers F.E. et al. *How to diagnose diastolic heart failure: a consensus statement on the diagnosis of heart failure with normal left ventricular ejection fraction by the Heart Failure and Echocardiography Associations of the European Society of Cardiology*. Eur Heart J. 2007, 28(20), p. 2539–50.

30. Bhalla M.A., Chiang A., Epshteyn V.A., Kazanegra R., Bhalla V., Clopton P. et al. *Prognostic role of B-type natriuretic peptide levels in patients with type 2 diabetes mellitus*. J Am Coll Cardiol. 2004, 44, p. 1047-52.

31. Zile M.R., Baicu C.F., Gaasch W.H. *Diastolic heart failure— abnormalities in active relaxation and passive stiffness of the left ventricle.* N Engl J Med. 2004, 350(19), p. 1953–9.

32. Shah A.M., Shah S.J., Anand I.S. *Cardiac structure and function in heart failure with preserved ejection fraction: baseline findings from the echocardiographic study of the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) trial.* Circ Heart Fail. 2014, 7, p. 104–115.

33. Zile M.R., Gottdiener J.S., Hetzel S.J. et al. *Prevalence and significance of alterations in cardiac structure and function in patients with heart failure and a preserved ejection fraction*. Circulation. 2011, 124, p. 2491 – 2501.

34. Mandinov L., Eberli F.R., Seiler C., Hess O.M. *Diastolic heart failure*. Cardiovasc Res. 2000, 45(4), p. 813–25.

35. Santos A.B., Kraigher-Krainer E., Gupta D.K. et al. *Impaired left atrial function in heart failure with preserved ejection fraction.* Eur J Heart Fail. 2014, 16, p. 1096 – 1103.