Causes of formation of heart failure and difficulties in its diagnosing in patients with type 2 diabetes mellitus

Druk I.V., Safronova S.S., Kanunnikova O.I.
Omsk State Medical University, Omsk, Russia.

AUTHORS

Inna V. Druk*, MD, PhD, Associate Professor, Head of the Department of Internal Medicine and Family Medicine, Omsk State Medical University, Omsk, Russia. ORCID: 0000-0001-8317-7765

Svetlana S. Safronova, Assistant of the Department of Internal Medicine and Family Medicine, Omsk State Medical University, Omsk, Russia. ORCID: 0000-0001-5852-2782

Olesya I. Kanunnikova, MD, PhD, Assistant of the Department of Internal Medicine and Family Medicine, Omsk State Medical University, Omsk, Russia. ORCID: 0009-0003-3721-4379

Diabetes mellitus (DM) is one of the fastest growing diseases worldwide, with prevalence reaching global pandemic proportions in recent decades. The significant increase in diabetes increases morbidity and mortality from cardiovascular complications, with heart failure (HF) being the most prominent one. In patients with DM, the presence of HF leads to a greater severity of clinical symptoms, increased hospitalization rates, poorer quality of life and poorer prognosis. HF with preserved ejection fraction is more common in type 2 DM, and its diagnosis is not an easy task. Special attention is paid to left ventricular diastolic dysfunction, which is an important prognostic factor of HF in the group of type 2 DM patients. This review article is devoted to the problem of interrelation and diagnosis of HF in patients with type 2 diabetes mellitus.

Keywords: Diabetes mellitus, heart failure, diastolic left ventricular dysfunction, diabetic cardiomyopathy, cardiovascular diseases.

Conflict of interests: none declared.

Recieved: 15.09.2024
Accepted: 12.11.2024

For citation: Druk I.V., Safronova S.S., Kanunnikova O.I. Causes of formation of heart failure and difficulties in its diagnosing in patients with type 2 diabetes mellitus. International Journal of Heart and Vascular Diseases. 2024. 12(44):46-54. DOI: 10.24412/2311-1623-2024-44-46-54

* Corresponding author. Tel.: +7 (913) 964-15-55. E-mail: drukinna@yandex.ru

Introduction

According to the International Diabetes Federation, 643 million people will suffer from diabetes mellitus (DM) by 2030 and 783 million by 2045, of whom type 2 DM will account for 90% of cases, while the situation in developing countries is projected to be even more severe [1–3]. In the Russian Federation, as in most countries of the world, there is a trend of not only a continuous increase in the prevalence of diabetes, but also a significant expansion of morbidity — a shift in the debut of type 2 DM in the young age group with a steady increase in life expectancy with diabetes [4].

The commonality of risk factors (RF) for the development of diabetes and atherosclerotic cardiovascular diseases (ACVD), confirmed by studies based on Mendeleev randomization [5], determines the observed increase in the incidence of ACVD, accompanying the increase in the incidence of diabetes. At the same time, an increased risk of ACVD begins to form already at the stage of pre-diabetic hyperglycemia [6].

Over the last decades, a number of population studies (Sweden, Korea, USA, Canada, UK) have shown a dynamic decrease in the incidence of ACVD, cardiovascular and total mortality in DM, which demonstrates the fundamental possibility of influencing the prognosis of patients [7–9]. Undoubtedly, this positive trend is a consequence of many factors: better control of CVD RF due to active lifestyle changes or targeted drug therapy, including the use of drugs with cardioprotective effects, individualization of glycemic targets and wider prescription of sugar-lowering drugs with a low risk of hypoglycemia, multidisciplinary approach to patients with DM [10]. A recent systematic review of 57 articles with a total number of participants of about 4 million patients with DM demonstrated that the overall prevalence of ACVD is 32.2% [6, 11].

Thus, ACVD have been, are and will be the main pathology determining the prognosis of life in patients with diabetes. Reduced mortality due to acute cardiovascular events, increased years of life with diabetes, a steady trend of population aging, changing the spectrum of comorbid pathology in diabetes, contribute to the maintenance of a significant prevalence of the end stage of the cardiovascular continuum — heart failure (HF).

Heart failure in patients with type 2 diabetes mellitus: epidemiology and causes of formation

HF, as an inevitable final outcome of almost all CVD, is a growing epidemic, occupies leading positions in the structure of total mortality and permanent disability of patients, including those of working age. Regardless of HF phenotype among patients, the prevalence of type 2 DM significantly exceeds the population average (Table 1) [12]. According to the Russian EPOCH-CHF study (representative sample of the European part of the Russian Federation), the frequency of DM in the group of patients with HF was 16.6%, which is slightly lower than the corresponding number in most foreign studies [13]

Table 1. **Prevalence of type 2 DM in HF studies**

Study	Prevalence of type 2 DM
EPOCH-CHF [15]	16.6 %
HFrEF [12]	
PARADIGM-HF	35 %
SHIFT	30 %
EchoCRT	41 %
HF-ACTION	32 %
SENIORS	26 %
SOLVD	15 %
MERIT-HF	25 %
CHARM-Added	29 %
DIG-REF	28 %
HFpEF [12]	
I-Preserve	27 %
PEP-CHF	21 %
DIG-PEF	29 %
CHARM-Preserved	28 %
TOPCAT	33 %

Type 2 DM is associated with worse clinical status and increased cardiovascular and total mortality in both patients with HF with reduced (HFrEF) and HF with preserved ejection fraction (HFpEF) compared with HF patients without type 2 DM. HF is an independent predictor of fatal and non-fatal events in patients with type 2 DM [12]. Once HF is diagnosed in patients with type 2 DM over 65 years of age, the risk of mortality increases tenfold, and the 5-year survival rate decreases to 12.5% [14, 15].

By the age of over 40 years, 40-50% of patients with diabetes develop at least one CVD — unstable angina pectoris, myocardial infarction (MI), life-threatening heart rhythm disorders, with chronic heart failure (CHF) developing the fastest [16]. Type 2 DM

patients have a high incidence of silent forms of coronary heart disease (CHD) and myocardial infarction (MI) in combination with dyslipidemia, arterial hypertension (AH), smoking, aggravated family history of CVD, micro- or macroalbuminuria [17]. CHD and MI are associated with irreversible changes in the heart and represent a permanent substrate for the development and progression of HF [18]. Approximately 2/3 of deaths in patients with DM are related to ACVD: of these, 40% are due to CHD, about 10% to stroke, and 15% to other CVD, mainly HF. Among patients with diabetes, an increased risk of death from ACVD is observed in younger individuals with a long history of hyperglycemia and significant renal complications [19].

The leading factors of ACVD are considered to be diabetes and AH, which are regarded as unfavorable mutually aggravating diseases due to the common pathogenesis and causal relationships. AH is found in up to 80% of patients with type 2 DM [20]. The combination of DM and AH has a negative impact on left ventricular (LV) structure, myocardial dysfunction and arterial stiffness. AH and DM have been shown to be independently associated with impaired LV diastolic function (LVDF), with their coexistence leading to the most severe impact on LV diastolic mechanics and associated with higher filling pressures than in patients with either disease alone [21]. AH and DM are the main links of the cardiometabolic process, the outcome of which is ACVD.

Nevertheless, numerous population-based studies suggest a significantly increased risk of HF in patients with type 2 DM, unexplained by traditional risk factors such as obesity, AH, age, CHD, dyslipidemia, and heart valve disease. Even after adjusting for these factors, the relative risk of developing HF in patients with DM is 2-fold higher than the general population, which may be explained by the development of diabetic cardiomyopathy, most commonly associated with LV diastolic dysfunction (LVDD) and the development of HFpEF [3]. One study reported that optimal management of CVD RF in type 2 DM cannot neutralize the excess risk of HF, which remains high compared to patients without type 2 DM. These data suggest that HF preventive interventions are particularly challenging in type 2 DM [14].

In 2013, the American College of Cardiology, the American Heart Association, and the European Society of Cardiology (ESC), in collaboration with the European Association for the Study of Diabetes, defined diabetic cardiomyopathy (DCMP) as a clinical condition of ventricular dysfunction occurring in the absence of coronary atherosclerosis, AH, and heart valve pathology in patients with DM [22]. The term itself emphasizes the special etiology of cardiomyopathy, which distinguishes it from other forms. According to one of the largest foreign population studies, the prevalence of DCMP is 16.9% [23]. According to Russian researchers, the prevalence of DCMP is 18.7% [24].

The following are considered as the main factors of DCMP pathogenesis: direct effect of hyperglycemia, insulin resistance, mild inflammation, endothelial dysfunction, fibrosis, lipotoxicity and steatosis of myocardium, loss of myocardial "metabolic plasticity" [22, 25, 26]. The staged course of DCMP is characterized by progression from early stages with insignificant pathophysiological changes in the myocardium, normal LV myocardial mass to late manifestations with impaired diastolic and systolic function, symptoms/signs of HF [22, 27, 28]. At present, there are no reliable specific histologic signs, biochemical markers or clinical manifestations of early stages of DCMP [22]. The earliest objectively reported functional manifestation of DCMP is LVDD, which includes prolonged and delayed LV filling and relaxation in the absence of concomitant impairment of LV systolic function [29]. It is noteworthy that the existence of isolated LVDD as an indicator of DCMP has been disputed until recently, because patients in the early stages of DM were not subjected to routine careful assessment of diastolic function [30].

Many studies report that DCMP does not have any overt clinical manifestations and is more characterized by known symptoms/signs of HF with progression to late stage. Despite the rapid increase in the number of preclinical and clinical studies of DCMP in recent decades, the course of DCMP is still unclear. However, the feasibility of a multifactorial strategy in DCMP, as in HF, is implied [31]. It should be noted that DCMP is one of the most controversial aspects of cardiovascular manifestations of DM. The very existence of this phenomenon is not recognized by all expert communities in the field of cardiology [32]. Nevertheless, the possibility of DCMP development determines the necessity of HF screening in all patients with diabetes, regardless of the presence of CHD or AH.

Problems of diagnosing heart failure in patients with type 2 diabetes mellitus

It is known that HF is one of the most common initial manifestations of CVD in patients with type 2 DM and can manifest as HFpEF, HF with moderately reduced ejection fraction (HFmrEF) or HFrEF [32]. HFpEF has become the dominant form of HF worldwide in association with population aging and increasing prevalence of obesity, diabetes, and AH [33].

It has been shown that in the general population of patients with HF, the HFpEF phenotype is characterized by a slightly higher frequency of AH, obesity, and diabetes [34]. In particular, more than 40% of patients with HFpEF have type 2 DM, while in patients with type 2 DM, according to some data, HFpEF is more common [29]. In a Korean study, 64%, 14.4%, and 21.6% of patients with type 2 DM have HFpEF, HFmrEF, and HFrEF, respectively [35]. It is likely that the associations of DM and HFpEF objectively exist, but are not sufficiently accurate, primarily due to the difficulties in verifying HFpEF.

Among patients with DM, regular systematic screening at each visit for symptoms or signs of HF is recommended [32]. As in the general population of patients undergoing HF screening, the most problematic group is patients with diabetes and HFpEF. Currently, the following criteria must be met to make the diagnosis of HFpEF according to the recommendations of the European Society of Cardiology for the Diagnosis and Treatment of HF [36].

1. Presence of symptoms and signs of HF.
2. Preserved EF (≥50 %).
3. Elevated levels of natriuretic peptides (NUP).
4. Presence of heart LVDD.

The main problem in diagnosing HFpEF is its asymptomatic course in the early stages, and the similarity of symptoms between HF and other diseases (obesity, chronic obstructive pulmonary disease) further increases the risk of both hypo- and overdiagnosis of HF [29]. HFpEF is characterized by clinical manifestations similar to those of patients suffering from HFrEF [37]. The development of HF clinic in conditions of preserved LV ejection fraction (LVEF) can be explained only by one thing — difficulty of LV diastolic filling and compensatory increase of LV filling pressure [18].

The most widely used markers of myocardial stress for the diagnosis and prognosis of HF in everyday clinical practice are: brain natriuretic peptide (BNP) and N-terminal fragment of brain natriuretic propeptide (NT-proBNP) in blood. NT-proBNP and BNP below 125 pg/ml and 35 pg/ml, respectively, indicate the absence of HF [37]. The difficulty in identifying concentrations with positive diagnostic value is due to various clinical conditions that lead to elevated BNP regardless of the presence of HF (e.g., renal failure, atrial fibrillation (AF), hyperthyroidism, sacubitril/valsartan drug administration, acute coronary syndrome, mitral regurgitation, pulmonary disease, as well as older age, female gender) [38–40].

The most significant limitations of NUP sensitivity are that the established threshold values used for HF diagnosis are not applicable to overweight/obese people, which naturally characterizes the clinical status of patients with type 2 DM [41]. It has been demonstrated that an increase for each unit of body mass index is associated with a 9 pg/mL decrease in NUP [41, 42]. Nevertheless, potentially NUP have valuable prognostic value for both short-term and long-term cardiovascular events in individuals with DM [25]. The SAVOR-TIMI 53 study reported that individuals with diabetes without known CVD but with elevated NT-proBNP levels had a 3-fold higher risk of developing HF than those with known CVD and normal NT-proBNP levels [43]. Similarly, the ADVANCE study showed that NT-proBNP predicts the risk of HF, total mortality and CVD mortality in people with type 2 DM [44].

In view of the accumulated data, the updated European Society of Cardiology guidelines on CVD management in DM (2023) indicate that in patients with DM with one or more symptoms/signs of HF, NUP determination is one of the screening procedures, as in the general population. In general, NUP determination in patients with diabetes is recommended to exclude, but not to diagnose HF [25].

LVDD is defined by impaired relaxation and increased stiffness of heart chambers, which are manifested by increased filling pressure at rest or during exercise [45]. The independent prognostic value of LVDD, which is accompanied by a significant increase in the risk of death from CVD, regardless of LV size and systolic function, has been proved [18]. In the group of patients with type 2 DM, as in the general population, LVDD is an important prognostic factor of HF. About a quarter of asymptomatic patients with DM may have LVDD, and this group is found to have twice the risk of developing HF (37% vs. 17%) after 5

DOI: 10.24412/2311-1623-2024-44-46-54

Table 2. **LVDF assessment parameters in patients with preserved EF (ASE/EACVI, 2016)**

Parameter	Threshold value
E/e' mean	>14
e' septal/lateral	<7 cm/s/<10 cm/s
tricuspid regurgitation velocity	>2,8 m/s
LAVI	>34 ml/m^2

Note. E — LV early diastolic filling velocity, e' — early diastolic velocity of the mitral annulus fibrosus, LAVI — left atrium volume index.

years of follow-up. Echocardiography (EchoCG) is the most widely used imaging modality to assess cardiac function and cardiac morphology due to its non-invasive assessment of LV filling parameters, availability, and relatively low cost [46].

In accordance with the current guidelines of the American Society of Echocardiography and the European Society of Cardiovascular Imaging, LVDF assessment is based on a comprehensive analysis of a number of parameters obtained using two-dimensional and Doppler scanning modes (Table 2). Depending on the number of detected signs, LVDF can be defined as normal (in the presence of one sign), impaired (in the presence of three or more signs), or uncertain (in the presence of two signs) [47].

The limitations of the ASE/EACVI algorithm are related to the fact that it does not allow to assess LVDF in a number of clinical situations (AF, marked mitral regurgitation, marked calcification of the mitral valve, etc.), as well as due to technical and methodological limitations of EchoCG. The low diagnostic accuracy of the ASE/EACVI algorithm has been shown in a number of studies [48–50].

In 2019, the Association of Heart Failure Specialists proposed a new step-by-step algorithm for the diagnosis of HFpEF — HFA-PEFF, which is based on the identification of "major" and "minor" criteria defined according to their sensitivity and specificity [51] (Table 3). According to the ESC recommendations, a set of parameters is also used to confirm diastolic dysfunction (DD), highlighting the greater importance of determining the E/e' ratio as the best non-invasive way to assess LV filling pressure [36].

According to European and Russian guidelines for the diagnosis of HFpEF, diastolic stress test is an essential component of the diagnostic algorithm

Table 3. **Comparative characterization of echocardiographic criteria for the diagnosis of HFpEF in the ESC guidelines for the diagnosis and treatment of acute and chronic HF**

Echocardiographic criteria for HFpEF of the HFA-PEFF algorithm (2019) [52]			HFpEF criteria in the ESC guidelines (2021) [36]
	Functional	Morphological	Normal LVEF
Major	— e´sept. <7 cm/s or e´ lat. <10 cm/s (age <75 years)/ e´ sept. <5 cm/s or e´ lat. <7 cm/s (age ⩾ 75 years) or — E/e´ ⩾15 or — TV velocity >2,8 m/s (PASP>35 mmHg)	— LAVI >34 ml/m^2 (sinus rhythm)/ >40 ml/m^2 (AF); or — LVMMI ⩾149 g/m^2 (males) and ⩾ 122 g/m^2 (females) at RTI >0,42	Objective examination of heart function and structure: Main structural changes: LAVI >34 ml/m^2 and (or) LVMMI for males 115g/m^2, for females 95g/m^2 Main functional changes: ratio of peak early diastolic blood flow at the mitral valve to the mean value of mitral valve annulus velocity in early diastole of the interventricular septum and lateral wall (E/e') >9, mean value of mitral valve annulus velocity in early diastole of the interventricular septum and lateral wall (e')<9 cm/s In uncertain cases, perform stress test or invasive measurement of LV filling pressure
Minor	— E/e´ 9-14; or — GLS <16%;	— LAVI 29-34 ml/m^2 (sinus rhythm) и 34-40 ml/m^2 (AF) or — LVMMI ⩾115 g/m^2 (males) и ⩾ 95 g/m^2 (females) or — RTI >0,42 or — LV wall thickness ⩾12 mm.	
Each major criterion is worth 2 points and minor criteria is worth 1 point. Score ⩾5: HFpEF is considered confirmed Score 0-1: diagnosis of HFpEF is unlikely. Score 2-4: perform diastolic stress test or invasive assessment of hemodynamic parameters of LV filling.			

Notes. e´sept. — velocity of the early diastolic motion of the septal part of the mitral fibrous ring, e´lat. — velocity of early diastolic motion of the lateral part of the mitral fibrous ring, E — velocity of the early diastolic component of transmitral blood flow, RTI — relative thickness index, PASP — pulmonary artery systolic pressure.

for HFpEF [36, 37]. Diastolic stress test can be performed with the help of EchoCG, usually using a loading protocol on a semi-recumbent bicycle ergometer. When evaluating the results, such parameters as E/e' and tricuspid regurgitation velocity have the greatest diagnostic value.

Since the diagnosis of HFpEF based on echocardiographic data and NUP levels has limited sensitivity, algorithms with a scoring system have recently been proposed [33]. In particular, the H2FPEF scale (H2 FPEF score; **H**eavy, **H**ypertensive (H2); atrial **F**ibrillation; **P**ulmonary hypertesion; **E**lder; **F**illing pressure) consists of six variables evaluated dichotomously (if a sign is present, the corresponding score is counted):

— H2 (Body mass index >30 kg/m^2 = 2 points; use of ≥2 antihypertensive medications = 1 point);

— F (AF = 3 points);

— P (systolic pulmonary artery pressure> 35 mmHg = 1 point);

— E (age> 60 years = 1 point);

— F (E/e >9 = 1 point).

The points range from 0 to 9, and with a score of ≥ 6, HFpEF is detected with a probability of ≥90% [33].

The algorithm proposed by the ESC HF Study Association (HFA-PEFF score) consists of the following steps:

(1) Preliminary assessment

(2) EchoCG diagnostic examination (parameters include: e', E/e', left atrial volume index (LAVI), LVMMI, relative LV wall thickness, tricuspid regurgitation velocity, global longitudinal LV deformation and NUP.

(3) Extensive examination with functional testing in case of uncertainty (echocardiographic or invasive techniques).

(4) HF etiology determination.

When calculating HPA-HEFF, 2 points are given for each major criterion met, and 1 point is given for each minor criterion. A score of ≥5 points in step 2 allows the diagnosis of HFpEF, a score of ≤1 makes the diagnosis of HFpEF highly unlikely, and a score of 2–4 points requires proceeding to step 3 [52].

Thus, the accurate non-invasive diagnosis of LVDD remains a challenge, which leads to problems in the diagnosis of HFpEF. The search for examination methods that improve the diagnosis of HF in type 2 DM continues. A promising direction in LVDD diagnosis seems to be the use of three-dimensional EchoCG, as well as the assessment of LV myocardial longitudinal deformation by two-dimensional tracking of "gray scale" spots. The number of works confirming the possibility of LVDF assessment using these methods is constantly growing, but the number of them is still insufficient for them to be recommended for use in routine practice, which may well be explained by the need for special equipment, complex and expensive software. New biomarkers in addition to NUP (troponins, secreted proteins as markers of myocardial fibrosis [secreted Frizzled proteins], metabolites of intestinal microbiota [trimethylamine-N-oxide]) are actively investigated as a component of HFpEF diagnostic panel [25, 35]. Early diagnosis of HF in patients with type 2 DM is all the more important because with a new view on the mechanisms of development of cardioprotective effect of modern means of treatment of type 2 DM and HF (first of all, sodium glucose co-transporter type 2 inhibitors) the prospects of maximum early intervention for better treatment of this very serious complication of type 2 DM open up [52].

Conclusion

HF remains an important clinical problem for physicians managing patients with type 2 DM. Patients with HF and DM have a worse prognosis than patients without DM. AH and CHD are the main causes of HF in type 2 DM. Despite the growing interest in the study of DCMP, including the study of the role of DCMP in the development of HF, to date, there is no clear understanding of this pathological condition. The problem of the relationship between HF and type 2 DM is multifaceted and requires further continued research. The importance of HF screening in diabetes can hardly be overestimated, as the CVD continuum starts with such RF as diabetes, progresses to vasculopathy and myocardial dysfunction, and finally ends with cardiovascular death. HF screening is a must in the management of patients with type 2 DM. Diagnosis of HF in type 2 DM is performed according to generally accepted principles. Accurate non-invasive diagnosis of LVDD remains a challenge, which leads to problems in the diagnosis of HFpEF, one of the leading phenotypes of HF in patients with diabetes. We are actively searching for an optimal algorithm for diagnosing HF in patients with diabetes in the direction of improving echocardiographic criteria and searching for additional biomarkers of structural and functional changes of the heart.

Conflict of interests: none declared.

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