Pregledni članak / Review article

# Dijabetička kardiomiopatija
# *Diabetic cardiomyopathy*

**Jasna Čerkez Habek*, Jozica Šikić**
Klinička bolnica "Sveti Duh", Zagreb, Hrvatska
*Sveti Duh University Hospital, Zagreb, Croatia*

**SAŽETAK:** Dijabetička kardiomiopatija, koronarna bolest srca (KBS) i autonomna neuropatija su bolesti koje povećavaju morbiditet i mortalitet pacijenta sa šećernom bolesti. Dijabetičku kardiomiopatiju definiraju asimptomatske, progresivne promjene u strukturi, a potom i funkciji miokarda koje dovode do njegovog remodeliranja, a nisu vezane uz KBS, arterijsku hipertenziju ili valvularnu patologiju. Etiologija navedenih promjena je multifaktorska i posljedica je metaboličkog disbalansa koji je vezan prvenstveno uz dugotrajnu hiperglikemiju. Nažalost, dijabetička kardiomiopatija usprkos svog značaja ostaje često neprepoznata komplikacija višegodišnjeg dijabetesa koja značajno povećava smrtnost. Klinička slika može varirati od subkliničke ventrikularne disfunkcije, do razvijene kliničke slike srčanog zatajivanja. Bolesnici s razvijenom dijabetičkom kardiomiopatijom imaju dva do pet puta veći rizik od srčanog zatajivanja. Ehokardiografija je standard u otkivanju kardiomiopatije, u početnoj fazi bolesti nalazi se oštećenje dijastoličke funkcije različitog stupnja, a tek u terminalnoj fazi kardiomiopatije se verificira i smanjenje sistoličke funkcije lijeve klijetke. Rjeđe se dijagnoza postavlja uporabom magnetske rezonance, a u istraživanjima su i novi biomarkeri koji bi olakašli dijagnostiku u asimptiomatskih bolesnika. Liječenje dijabetičke kardiomiopatije podrazumijeva promjene u životnom stilu, bolju regulaciju glikemije, lipidnog profila i arterijske hipertenzije i redovitu fizičku aktivnost, a terapija srčanog zatajivanja se ne razlikuje se od bolesnika bez dijabetesa. Nažalost, strukturalne i morfološke promjene miokarda započinju već u pre-dijabetičkoj fazi, stoga se očekuje da će nova istraživanja indentificirati biomarkere koji mogu detektirati asimptomatske bolesnike uz pronalazak strategije koja bi navedene promjene učinila reverzibilnima.

**KLJUČNE RIJEČI:** dijabetička kardimiopatija, zatajivanje srca, čimbenici rizika, patofiziološki mehanizmi, prevencija.

**SUMMARY:** Diabetic cardiomyopathy, coronary heart disease (CHD) and autonomic neuropathy are the diseases that increase morbidity and mortality in patients with diabetes mellitus. Diabetic cardiomyopathy is characterized by asymptomatic, progressive changes in the structure, and also in the myocardial function that lead to myocardial remodeling, and are not related to CHD, hypertension or valvular pathology. The etiology of these changes is multifactorial and is the consequence of metabolic imbalance that is primarily related to long-term hyperglycemia. Unfortunately, diabetic cardiomyopathy, despite its significance often remains an unrecognized complication of diabetes that patients suffer from for several years that however, greatly increases mortality. The clinical symptoms may vary from subclinical ventricular dysfunction to advanced clinical symptoms of heart failure. Patients with advanced diabetic cardiomyopathy have two to five time higher risk of heart failure. Echocardiography is the standard in detecting cardiomyopathies, in the initial stage of the disease there is an impairment of the diastolic function of a different degree, and the reduction of systolic left ventricular function is verified only in the end-stage of cardiomyopathy. Rarely, the diagnosis is made by using magnetic resonance imaging, and reserchers have found new biomarkers that would facilitate the diagnostics in asymptomatic patients. The treatment of diabetic cardiomyopathy involves changes in lifestyle, better glycemic control, lipid profile and hypertension accompanied by regular physical activity, whereas the therapy of heart failure does not differ from the therapy administered to the patients without diabetes. Unfortunately, the myocardial structural and morphological changes start already in the pre-diabetic stage, therefore, the new trials are expected to identify biomarkers that can detect asymptomatic patients thereby finding a strategy that would make the above changes reversible.

**KEYWORDS:** diabetic cardiomyopathy, heart failure, risk factors, pathophysiological mechanisms, prevention.
**CITATION:** Cardiol Croat. 2013;8(12):456-464.

## Uvod

U svijetu više od 194 milijuna ljudi boluje od šećerne bolesti, a Svjetska zdravstvena organizacija procjenjuje da će u svijetu do 2025. godine broj oboljelih porasti na 350 milijuna, odnosno udvostručit će se broj oboljelih u odnosu na 2000. godinu[1]. Dobro je poznata činjenica da pacijenti s dijabetesom imaju učestalije od opće populacije značajne aterosklerotske promjene na epikardijalnim koronarnim arterijama uz poremećaj mikrocirkulacije uz mogući razvoj autonomne

## Introduction

There are more than 194 million of people worldwide that suffer from diabetes mellitus, and the World Health Organization estimates that by the year 2025 the number of the diseased will increase to 350 million, that is, the number of the diseased will double compared to the year 2000 at an international level[1]. It is well known that patients with diabetes mellitus more commonly have significant atherosclerotic changes in the epicardial coronary arteries compared

disfunkcije, što sve pridonosi njihovom povećanom pobolu i nažalost smrtnosti[2]. Navedena stanja se rijetko javljaju izolirano, već se obično preklapaju i međusobno potenciraju[3]. Ipak, poznato je da dijabetičari i u odsustvu navedne patologije imaju veći rizik za zatajivanje srca.

Još je 1954. godine Lundbeak definirao dijabetičku kardiomiopatiju kao bolest miokarda uzrokovanu dijabetesom, ali neovisno o vaskularnoj patologiji[4], a kasnije se u definiciju dodaje da je bolest neovisna i o valvularnim greškama i arterijskoj hipertenziji[5]. Danas se u literaturi još naziva i neishemijska dijabetička kardiomiopatija. Kroz literaturu se prate članci u kojima se dijabetička kardiomiopatija tretira kao mit[6]. Zahvaljujući brojnim kliničkim i eksperimentalnim studijama koje su dokazale funkcionalne, morfološke i biokemijske promjene u miokardu[7] s posljedičnom disfunkcijom lijeve klijetke, podjednako kod pacijenta s tipom 1 i 2 dijabetesa, teško je postojanje entiteta ignorirati, posebice što se neinvazivnim dijagnostičkim metodama u svakodnevnoj kliničkoj praksi mogu dijagnosticirati pacijenti s dijabetičkom kardiomiopatijom. Pravovremena dijagnostika uz medikamentoznu terapiju potpomognutu promjenama u stilu života, mogu osigurati bolesnicima značajno bolju kvalitetu života i odgodu nastanka simptoma zatajivanja miokarda.

## Epidemiologija

Prevalencija dijabetičke kardiomiopatije nije poznata zbog nedostatka velike studije u različitim populacijama dijabetičara[8]. Međutim, dobro je istražena povezanost dijabetesa i srčanog zatajivanja. Framinghamska studija dokazuje da je rizik od zatajivanja srca veći 2,4 puta u muškaraca i čak 5 puta u žena[9], ali neovisno o postojanju koronarne bolesti srca (KBS) i arterijske hipertenzije. Dodatnim isključenjem iz analize svih bolesnika s od ranije poznatom koronarnom i reumatskom bolesti srca, tada rizik za razvoj zatajivanja srca raste na 3.8 kod muškaraca i 5,5 kod žena s dijabetesom. I brojne druge studije navode slične rezultate[10]. Nove studije potvrđuju hipotezu da osobe s dijebetesom i lošom regulacijom glikemije imaju značajno veći rizik za razvoj kardiomiopatije[11]. Tako je kohortna studija na 31.1997 pacijenta, koji su predominatno imali dijabetes tipa 2, dokazala da za svaki 1% porasta HbA1c raste rizik od zatajivanja srca za 8%[11]. Neke studije ukazuju da i osobe s inzulinskom rezistencijom, bez kriterija za dijagnozu dijabetesa, također imaju povećani rizik od zatajivanja srca[12]. Prevalencija dijastoličke disfunkcije kod dijabetičara varira od 30-60%[13]. Nedavna prospektivna studija kod bolesnika sa šećernom bolesti tipa 1 koja je trajala najmanje 10 godina, daje rezultate o prevalenciji disfunkcije miokarda u 14,5% i srčanog zatajivanja 3,7% nakon sedmogodišnjeg praćenja[14].

Kod dijabetičara tipa 2 se može u 80% bolesnika očekavati pojava dijastoličke disfunkcije, a bolesnici s lošijom regulacijom glikemije i duljim trajanjem bolesti imaju teži stupanj dijastoličke disfunkcije[15]. Osim hiperglikemije, najspominjaniji čimbenici rizika za razvoj zatajivanja srca kod dijabetičara su: starija životna dob[16], trajanje dijabetesa, inzulinska terapija, KBS, periferna arterijska bolest, povišenje kreatinina u serumu i mikroalbuminurija[17]. Poznato je i da nakon revaskularazcije miokarda angioplastikom ili ugradnom premosnica je češća kardijalna dekompenzacija kod dijabetičara. Vrijedi i obrnuta statistika, u OPTIMIZE HF registru 42% hospitaliziranih zbog popuštanja srca su bili dijabetičari[18].

to the general population with the microcirculatory disorder accompanied by a potential development of autonomic dysfunction, where all of this unfortunately contributes to their increased morbidity and mortality[2]. These conditions rarely occur separately, but they usually overlap and are mutually potentiated[3]. Anyway, it is known that diabetic patients are at an increased risk for heart failure (HF) even in the absence of above mentioned pathology.

In 1954 Lundbeak defined diabetic cardiomyopathy as myocardial disease caused by diabetes mellitus, but independent of vascular pathology[4], and later the definition is added by the fact that the disease is also independent of valvular defects and hypertension[5]. Today, it is also referred to as non-ischemic diabetic cardiomyopathy in the literature. Through the literature the articles are followed which treat the diabetic cardiomyopathy as a myth[6]. Owing to numerous clinical and experimental studies that have proven functional, morphological and biochemical changes in the myocardium[7] with consequential left ventricular dysfunction, both in patients with type 1 and type 2 of diabetes, it is difficult to ignore the existence of the entity, especially as the non-invasive diagnostic methods in daily clinical practice are used to diagnose patients with diabetic cardiomyopathy. Timely diagnosis with medical therapy assisted by changes in lifestyle, can provide patients an improved quality of life and delay of the occurrence of myocardial infarction symptoms.

## Epidemiology

The prevalence of diabetic cardiomyopathy is not known due to the lack of a large study in different populations of diabetic patients[8]. However, the link between diabetes and HF has been well studied. The Framingham study proves that the risk of HF is 2.4 times higher in men and even five times in woman[9], but regardless of the presence of coronary heart disease (CHD) and hypertension. If we additionally exclude all patients with previously known coronary and rheumatic heart disease from the analysis, then the risk of developing HF increases to 3.8 in men and 5.5 in women with diabetes mellitus. Numerous other studies report similar results as well[10]. New studies support the hypothesis that persons with diabetes and poor glycemic control are at significantly higher risk for developing cardiomyopathy[11]. Thus, the cohort study involving 31.1997 patients, who predominantly had type 2 diabetes, demonstrated that for every 1% increase in HbA1c the risk of HF increases by 8%[11]. Some studies suggest that people with insulin resistance, with no criteria for diagnosis of diabetes are also at a higher risk for HF[12]. The prevalence of diastolic dysfunction in diabetic patients ranges from 30-60%[13]. A recent prospective study in patients with type 1 diabetes which lasted at least 10 years gives results on the prevalence of myocardial dysfunction in 14.5% and HF in 3.7% after a seven-year follow-up[14].

In type 2 diabetic patients, the occurrence of diastolic dysfunction can be expected in 80% of patients, while the patients with poorer glycemic control and longer duration of the disease tend to have a more severe degree of diastolic dysfunction[15]. In addition to hyperglycemia, the most often mentioned risk factors for the development of HF in diabetic patients are: older age[16], duration of diabetes, insulin therapy, CHD, peripheral arterial disease, elevation of serum creatinine and microalbuminuria[17]. It is known that after myocardial revascularazation by angioplasty or stent implantation, the cardiac decompensation is more common in diabetic patients. The completely different statistics applies, in OPTIMIZE HF registry 42% of hospitalized patients were diabetic patients due to HF[18].

## Patofiziologija

Šećerna bolest dovodi do strukturnih i funkcijskih abnormalnosti u koronarnoj mikrocirkulaciji koje uzrokuju smanjenje protoka krvi kroz tkivo miokarda, iako ne nalazimo značajnih patomorfološki promjena na epikardijalnim arterijama. Kliničke i eksperimentalne studije su dokazale da dijabetes uzrokuje hipertrofiju miokarda, apoptozu i nekrozu miocita, remodelaciju matriksa, povećava intersticijsko tkivo te dovodi do aktivacija simpatikusa i povećava renalnu absorpciju natrija[19].

Patogeneza dijabetičke kardiomiopatije je složena i postoji nekoliko mehanizama pomoću kojih se objašnjava navedeno stanje. Metabolički disbalans kao hiperglikemija[20], hiperlipidemija, hiperinzulinemija, defekt stimulacije glikolize i oksidacije glukoze[21] dovode u stanicama miokarda do strukturalnih i funkcionalnih promjena. Opisane promjene uzrokuju oštećenje i odumiranje miocita povećanim oksidativnim stresom, razvojem neželjene intersticijske fibroze, poremećajima u transportu elektrolita i gubitak homeostaze. Čini se da hiperglikemija inducira maladaptivne mehanizme koji oštete metabolizam miokarda i funkciju miofibrila što rezultira promjenama u citoskeletu i povišenoj neurohumoralnoj aktivnosti. Posljedica navedenih mehanizama je neželjena remodelacija miokarda koja vodi u circulus vitiosus gdje zatajivanje srca povećava inzulinsku rezistenciju i obratno[11]. Ipak, neinvazivnim dijagnostičkim metodama fibroza se izdvaja kao najznačajnija za razvoj dijabetičke kardiomiopatije, jer kod dijabetičara i tipa 1 i 2 nalazi se povećana količina kolagena u miokardu koji dovodi u početku do dijastoličke disfunkcije. Izrazita fibroza miokarda može biti perivaskularna, intersticijska ili kombinirana. Progresijom bolesti dolazi do redukcije broja miocita koji bivaju zamijenjeni vezivnim tkivom[22,23].

Povišena razina slobodnih masnih kiselina[24] se također smatra jednim od glavnih čimbenika koji doprinosi razvoju dijabetičke kardiomiopatije povećanjem periferne inzulinske rezistencije i time pokreće apoptozu miocita[25]. Povećana koncentracija cirkulirajućih slobodnih masnih kiselina, kao i onih intercelularnih, dovodi do nakupljanja potencijalno toksičnih metabolita prilikom njihove razgradnje i do smanjenja oksidacije glukoze što se smatra jednim od važnijih uzroka razvoja dijabetičke kardiomiopatije. Težini kliničke slike doprinosi i razvoj autonomne disfunkcije uz sniženje varijabilnosti srčanog ritma i tahikardije[26] te razvoj endotelne disfunkcije uz smanjenje protoka kroz koronarne arterije. Nadalje, intersticijsko gomilanje glikoproteina, spori ulazak kalcija u sarkoplazmatski retikulum[27], slabo oslobađanje dušikovog oksida iz endotela koronarnih arterija[28] često se opisuju kao mogući uzroci razvoja dijabetičke kardiomiopatije.

Kod pacijenta s DM tip 2 postoji jasna poveznica između regulacije glikemije i razine faktora rasta IGF-I (engl. Insulin-like growth factor). Lošija regulacija glikemije dovodi do sniženja koncentracije IGF-I u plazmi. Eksperimentalnim modelima je dokazano da IGF-I smanjuje apoptozu miocita i poboljšava funkciju miokarda višestrukim učincima[29]. Zbog lučenja IGF, interleukina, citokina i ostalih pro-inflamatornih agenasa, dolazi do ekspresije mikro RNA (MiRNA), posebice mi R-155 i mi R-223, koji imaju anti-inflamatornu i kardioprotektivnu funkciju[30]. MiRNA su male molekule, do 22 nukleotida, koje moduliraju gensku ekspesiju i čine se upravo ključno i obećavajuće mjesto mogućeg liječenja kardiovaskularne i šećerne bolesti[31]. S obzirom da je njihova razina promijenjena kod bolesnika s dijabetičkim srcem, smatra-

## Pathophysiology

Diabetes mellitus leads to structural and functional abnormalities in the coronary microcirculation causing a reduction of blood flow through the myocardial tissue, although we find no significant pathomorphological changes in the epicardial arteries. Clinical and experimental studies have shown that diabetes causes myocardial hyperthrophy, apoptosis and necrosis of myocytes, matrix remodeling, increases interstitial tissue and leads to the activation of sympathicus and increases renal sodium absorption[19].

The pathogenesis of diabetic cardiomyopathy is complex and there are several mechanisms which explain the above mentioned situation. Metabolic imbalance as hyperglycemia[20], hyperlipidemia, hyperinsulinemia, defect of stimulation of glycolysis and glucose oxidation[21] lead to structural and functional changes in myocardial cells. The described changes cause damage and decay of myocytes by increased oxidative stress, development of undesired interstitial fibrosis, disorders in the transport of electrolytes and loss of homeostasis. It seems that hyperglycemia induces maladaptive mechanisms that damage myocardial metabolism and function of myofibrils resulting in changes in the cytoskeleton and elevated neurohumoral activity. The consequence of these mechanisms is the undesirable myocardial remodeling that leads to the vicious circle where HF increases insulin resistance and vice versa[11]. However, using non-invasive diagnostic methods show that the fibrosis is the most responsible for the development of diabetic cardiomyopathy, because in diabetics type 1 and type 2 the amount of collagen in the myocardium is increased, which leads to the diastolic dysfunction at the beginning. Severe fibrosis of the myocardium can be perivascular, interstitial or combined. Disease progression leads to reduction of the number of myocytes, which are replaced by connective tissue[22,23].

The elevated level of free fatty acids[24] is also considered one of the major factors that contribute to the development of the diabetic cardiomyopathy by increasing peripheral insulin resistance thereby inducing apoptosis of myocytes[25]. The increased concentration of circulating free fatty acids, as well as intercellular ones, leads to the accumulation of potentially toxic metabolites during their degradation and to the reduction of the oxidation of glucose which is considered to be one of the most important causes of the development of diabetic cardiomyopathy. The severity of the clinical manifestations is contributed by the development of autonomic dysfunction with a reduction in heart rate variability and tachycardia[26] and development of endothelial dysfunction with a reduction of blood flow through the coronary arteries. Furthermore, interstitial accumulation of glycoproteins, a slow entry of calcium into sarcoplasmatic reticulum[27], a poor release of nitric oxide from the endothelium of coronary arteries[28] are often described as the potential causes of the development of diabetic cardiomyopathy.

In patients with type 2 DM there is a clear link between glycemic control and the insulin-like growth factor (IGF-I). Poorer glycemic control leads to lower concentrations of IGF-I concentrations in plasma. Experimental models have proved that IGF-I reduces myocyte apoptosis and improves myocardial function with multiple effects[29]. Secretion of IGF, interleukin, cytokines and other pro-inflammatory agents cause the expression of micro RNA (MiRNA), especially mi R-155 and mi R-223, which have anti-inflammatory and cardioprotective function[30]. MiRNA are small molecules, up to 22 nucleotides, which modulate gene expression and seem to be the key and promising site for potential treatment of cardiovascular and diabetic disease[31]. Since their level has been altered in patients with diabetic heart, they are considered to be a

ju se dobrim biomarkerom za kardiovaskularnu bolest, a različita ekspresija specifičnih MiRNA u cirkulaciji se može koristiti za dijagnostiku različitih stupnjava dijabetičke kardiomiopatije.

Navedeno objašnjava kako liječenjem metaboličkih poremećaja poboljšavamo i funkciju miocita, nažalost opisane funkcijske promjene lijeve klijetke se javljaju i kod pacijenata s dobro reguliranom glikemijom[32].

## Dijagnostika dijabetičke kardiomiopatije

Prepoznavanje dijabetičke kardiomiopatije u ranoj fazi bolesti i dalje ostaje izazov. Ehokardiografija je za sada najčešće korištena metoda. U najrajnijoj fazi bolesti primjećuje se povećanje gustoće miokarda ili abnormalnosti u funkciji subendokarda upotrebom strain i strain rate funkcije. Tkivnim Dopplerom se mogu uočiti najranije abnormalnosti u dijastoličkom protoku, a kako bolest progredira bilježi se patološki zapis pulsnim dopplerom transvalvularnog mitralnog protoka i protoka u plućnim venama, što je najčešća tehnika za dokazivanje dijastoličke disfunkcije. Progresijom stupnja kardiomiopatije dolazi do iscrpljenja inotropne rezerve u fizičkom naporu, a u uznapredovaloj fazi hipotetske "kardiomiopatske kaskade" nalaze se regionalni, a kasnije i globalni ispadi kontraktilnosti i u mirovanju[33]. Kod bolesnika s reduciranom sistoličkim funkcijom nalazimo ekscentričnu, za razliku od bolesnika s dijastoličkom disfunkcijom koji imaju koncentričnu hipertrofiju miokarda[34].

U dijastoličkom zatajivanju srca lijeva klijetka poprima osobitosti neelastične šupljine, tako da dio volumena krvi u protodijastoli utječe brzinom koju određuje gradijent tlaka između volumnog opterećenja i brzine kojom se klijetka relaksira. U mezo- i teledijastoliji dolazi do punjenja lijeve klijetke uz znatan porast tlaka u lijevom atriju i u plućnim venama, što može dovesti do kongestije pluća i čak do edema pluća[35]. Povećanje tlaka u lijevoj pretklijetki je kompenzacijski mehanizam jer omogućuje učinkovitije punjenje lijeve klijetke. S progresijom bolesti može se očekivati pojava sistoličke disfunkcije, a poznato je da svi pacijenti kod kojih je verificiran različiti stupanj sistoličke disfunkcije imaju već sigurno oštećenu i dijastoličku funkciju lijeve klijetke[36]. Čini se da ne postoji bolest koja bi samo dovela do sistoličkog kongestivnog zatajivanja miokarda, a uz očuvanu dijastoličku funkciju.

Dijagnoza dijabetičke kardiomiopatije već u pretkliničkoj fazi bolesti može se dokazati i magnetskom rezonacom koja je visoko selektivni alat za otkrivanje hipertofije lijevog ventrikula, promjene njegove geometrije ili poremećaja u kontraktilnosti, a daje informaciju o stupnju kardiomiopatije i mogućoj aritmiji. Također je dobra metoda za dijagnosticiranje dijastoličke disfunkcije kao i steatoze miokarda[37]. Ako se tijekom snimanja magentskom rezonancom koriste i različiti radionuklidi i pozitronska emisijska tomografija (PET) mogu se otkriti i metoboličke abnormalnosti, što omogućuje dijagnozu dijabetičke kardiomiopatije u najranijoj fazi bolesti.

Postoje i serološki biomarkeri koji olakšavaju dijagnostiku i procjenu težine kardiomiopatije, to su dobro poznati: HbA1c, NT-proBNP i troponin. Vrijednost NT-proBNP-a iznad 90 pg/mL u dijabetičkih bolesnika s visokom pozitivnom prediktivnom vrijednošću od 96% detektira dijastoličku disfunkciju lijeve klijetke dokazanu ehokardiografijom. Kardijalni troponini (I, T, N) se otpuštaju u cirkulaciju kod oštećenja miokarda bilo zbog ishemije ili upale, a uloga povišenih troponina kod dijabetičke kardiomiopatije još nije posve jasna. Povišena koncentracija matriks metaloproteinaze (MMP), posegood biomarker for cardiovascular disease, and the different expression of specific MiRNA in the circulation can be used for diagnostics of various degrees of diabetic cardiomyopathy.

The above explains that the treatment of metabolic disorders leads to the improvement of the function of myocytes. Unfortunately, the described functional changes to the left ventricle occur even in patients with good glycemic control[32].

## Diagnostics of diabetic cardiomyopathy

Identifying diabetic cardiomyopathy at an early stage of the disease remains a challenge. Echocardiography is currently the most widely used method. In the earliest stage of the disease we can notice an increase in the myocardial density or abnormalities in the subendocardial function by using the strain and strain rate function. Tissue Doppler imaging may show the earliest abnormalities in diastolic flow, and as the disease progresses, it can be record an abnormal record by pulse-Doppler ultrasound of transvalvular mitral flow and pulmonary venous flow, which is the most common technique for proving diastolic dysfunction. The progression of the cardiomyopathy stage leads to exhaustion of inotropic reserve in physical strain, and at an advanced stage of the hypothetical "cardiomyopathic cascade" there are regional and later global contractile deficits even at rest[33]. In patients with reduced systolic function we have recorded an eccentric myocardial hypertrophy, unlike the patients with diastolic dysfunction who have concentric myocardial hypertrophy.[34]

In diastolic HF, the left ventricle takes on characteristics of inelastic cavity, so that a part of the blood volumen in protodiastole affects the speed determined by the pressure gradient between the volume load and the velocity at which the ventricle relaxes. Filling of the left ventricle occurs in the meso-and tele-diastole with a significant increase in pressure in the left atrium and pulmonary veins, which can lead to congestion of the lungs and even to pulmonary edema[35]. Increasing the pressure in the left atrium is a compensatory mechanism because it allows more efficient filling of the left ventricle. As the disease progresses, we can expect the occurrence of systolic dysfunction, and it is known that all patients known to have a different degree of systolic dysfunction certainly have an impaired diastolic function of the left ventricle as well[36]. It seems that there is no disease that would only lead to systolic congestive myocardial failure with a preserved diastolic function.

The diagnosis of diabetic cardiomyopathy already at preclinical stage of the disease can be proved by magnetic resonance imaging, which is a highly selective tool for the detection of left ventricular hypotrophy, a change in its geometry or disorder in contractility, and provides the information about the degree of cardiomyopathy and potential arrhythmia. It is also a good method for diagnosing diastolic dysfunction as well as myocardial steatosis[37]. If different radionuclides and positron emission tomography (PET) are used during the magnetic resonance imaging, we can also detect metabolic abnormalities, which enables the diagnosis of diabetic cardiomyopathy in the earliest stage of the disease.

There are serological biomarkers that facilitate the diagnosis and assessment of severity of cardiomyopathy, these are the following which are well known: HbA1c, NT-proBNP and troponin. The value of NT-proBNP above 90 pg/mL in diabetic patients with a highly positive predictive value of 96% detects the diastolic dysfunction of the left ventricle proven by echocardiography. Cardiac troponins (I, T, N) are

bice tipa 9 (MMP9) i snižena koncentracija tkivnog inhibitora metaloproteinaza (TIMP) su dobri indikatori fibroze miokarda[38]. Metaloproteze sudjeluju u razgradnji ekstracelularnog matriksa i dovode so promjeni u ekspresiji nekoliko mikro RNA (Mi RNA) što za posljedicu ima kontraktilnu disfunkciju miokarda. Kao prediktor dijabetičke kardiomiopatije se može koristiti i povišena koncentracija enzima beta-N acetilglukozamina (0-GlcNAc)[39]. Točno kliničko značanje navedenih novih biomolekula u dijagnosti dijabetičke kardiomiopatije bit će poznato nakon rezultata istraživanja koja su u tijeku.

Koronarografija je često potrebna u terminaloj fazi dijabetičke kardiomiopatije.

## Klinička slika dijabetičke kardiomiopatije

Otežana relaksacija i smanjena rastegljivost miokarda dovode do značajnog povećanja tlaka punjenja već pri malom povećanju volumena punjenja, što se u testu opterećenjem prezentira kao rano nastala zaduha i sistolički porast arterijskog tlaka. Uznapredovala dijastolička disfunkcija dovodi vremenom do plućne kongestije koja se klinički očituje intolerancijom napora, progresivnom i paroksizmalnom noćnom dispnejom, ortopnejom, kašljem i kroničnim umorom u kasnijoj fazi bolesti. Dijastoličko zatajivanje iznosi oko 50% svih srčanih zatajivanja. U fizikalnom statusu čuju se krepitacije na plućima sve do plućnog edema, vide se otečene potkoljenice, povećana jetra, nabrekle vene vrata i ostali znakovi globalnog srčanog zatajivanja.

Diferencijalna dijagnoza dispneje posebno je teška kod starijih i pretilih pacijenata, naročito ako se kliničkim pregledom ne nalazi znakova kongestije. Tada je potrebno ehokardiografski isključiti početno dijastoličko zatajivanje srca. Bolesnici s razvijenom kardijalnom dekompenzacijom imaju lošiju prognozu bez obzira na njihovu istisnu frakciju, odnosno o tipu zatajivanja. Godišnja smrtnost kod dijastoličkog zatajivanja srca iznosi oko 8%, a ako se radi o sistoličkom-dijastoličkom zatajivanju tada godišnja smrtnost iznosi 19%[40].

## Liječenje dijabetičke kardiomiopatije

Liječenje dijabetičke kardiomiopatije uključuje promjene životnog stila, bolju kontrolu glikemije i lipodograma, liječenje koegzistirajuće hipertenzije, kao i liječenje srčanog zatajivanja.

Liječenje srčanog zatajivanja kod bolesnika s dijabetičkom kardiomiopatijom se ne razlikuje od liječenja ne-dijabetičkog popuštanja miokarda, a definirano je Smjernicama Europskog kradiološkog društva za liječenje akutnog i kroničnog srčanog zatajivanja iz 2012. godine[41]. Naglašeno je da za sada nema liječenja koje bi sa sigurnošću moglo smanjiti mortalitet i morbiditet bolesnika s dijastoličkim zatajivanjem srca. Diuretici se koriste za kontrolu natrija i retencije vode i kako bi se olakšali simptomi zaduhe i edema. Koriste se diuretici Henijeve petlje (furosemid, torasemid, bumetanid) i tiazidski diuretici (hidroklortiazid i indapamid), a kod nekih bolesnika i diuretici kojim štede kalij (spironolakton, eplerenon, amilorid i triamteren). Prepoznata je važnost adekvatnog liječenja hipertenzije, ishemije miokarda, kao i adekvatne regulacije ventrikularnog odgovora kod bolesnika s fibrilacijom atrija. Obeshrabrujući su rezultati tri velike studije na kandesartanu[42] (CHARM), perindoprilu[43] (PEP-CHF) i irbesatanu[44] (I-Preserve) koje nisu dokazale smanjenje smrtnosti u hospitaliziranih bolesnika s dijastoličkim zatajivanjem srca.

released into the circulation in case of myocardial damage either due to ischemia or inflammation, and the role of elevated troponin levels in diabetic cardiomyopathy is not yet entirely clear. An increased concentration of matrix metalloproteinase (MMP), especially type 9 (MMP9), and a decreased concentration of tissue inhibitor of metalloproteinases (TIMPs) are good indicators of myocardial fibrosis[38]. Metaloproteases participate in the degradation of extracellular matrix and lead to a change in the expression of a number of micro RNA (Mi RNA) which results in myocardial contractile dysfunction. An elevated concentration of the enzymes beta-N-acetylglucosamine (0-GlcNAc) can also be used as a predictor of diabetic cardiomyopathy.[39] A proper clinical meaning of the mentioned new biomolecules in diagnostics of diabetic cardiomyopathy will be known after the publication of the findings of the trials that are in progress.

Coronary angiography is often required in end-stage of diabetic cardiomyopathy.

## Clinical manifestations of diabetic cardiomyopathy

Impaired relaxation and reduced myocardial extensibility lead to a significant increase in filling pressure even at the time of a small increase in filling volume, which in the stress test is presented as an early dyspnoa and an increase in systolic blood pressure. Advanced diastolic dysfunction eventually leads to pulmonary congestion, which is clinically manifested as intolerance of exertion, progressive and paroxysmal nocturnal dyspnea, orthopnea, cough and chronic fatigue in the later stages of the disease. Diastolic HF is about 50% of all HFs. In the physical status we can hear lung crepitations including the pulmonary edema, and we can see the swollen legs, enlarged liver, swollen neck veins and other signs of global HF.

Differential diagnosis of dyspnea is particularly difficult in elderly and obese patients, especially if the clinical examination finds no signs of congestion. In such a case it is necessary to use the echocardiography to exclude the initial diastolic HF. The patients with developed HF have a worse prognosis, regardless of their ejection fraction or a type of the failure. Annual mortality in diastolic HF is about 8%, and if a systolic-diastolic failure is concerned, the annual mortality rate is 19%[40].

## The treatment of diabetic cardiomyopathy

The treatment of diabetic cardiomyopathy includes lifestyle changes, better glycemic and lipodogram control, the treatment of coexisting hypertension, as well as the treatment of HF.

The treatment of HF in patients with diabetic cardiomyopathy is no different from the treatment of non-diabetic HF, and is defined in the European Society of Cardiology Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012[41]. It has been emphasized that there is no treatment that could safely reduce mortality and morbidity in patients with diastolic HF. Diuretics are used to control sodium and water retention, and to mitigate the symptoms of dyspnea and edema. Henle's loop diuretics (furosemide, torsemide, bumetanide) and thiazide diuretics (hydrochlorothiazide and indapamide) are used while potassium-sparing diuretics such as (spironolactone, eplerenone, amiloride and triamterene) are used in some patients. The importance of adequate treatment of hypertension, myocardial ischemia, as well as adequate control of ventricular response in patients with atrial fibrillation has been identified. The findings of three large studies on candesartan[42] (CHARM), perindo-

Liječenje srčanog zatajivanja uz oštećenu sistoličku funkciju lijeve klijetke provodi se s ciljem olakašavanja simptoma, poboljšanja kvalitete života i povećanja funkcijskog kapaciteta. Za to su nužni lijekovi iz tri velike neuro-humoralne skupine: inhibitori angiotenzin konvertirajućeg enzima (ACE inhibitori), blokatori angiotenzinskih receptora (ARB) i antagonsti receptora mineralokortikoida. Diuretska terapija smanjuje simptome i znakove kongestije. SOLVD i SAVE studije dokazale su da je dobrobit liječenja ACE inhibitorima jednaka kod bolesnika s i bez dijabetesa[45].

Liječenje beta-blokatorima značajno povećava preživljenje bolesnika sa srčanim popuštanjem, neovisno imaju li dijabetes ili nemaju, bez razlike u redukciji rizika. Tri su ključne studije dokazale doprinos bisoprolola[46] (CIBIS II), metaprolola[47] (MERIT-HF) i karvediolola[48] (COPERNICUS) u smanjenju smrtnosti. U svakoj studiji bilježi se smanjenje mortaliteta oko 34% i smanjenje hospitalizacija od 28-36% zbog zatajivanja srca tijekom godine dana. Više od 90% bolesnika u navedenim studijama uz beta-blokator su bili na terapiji ACE inhibitorom ili ARB.

Brojni vazoaktivni lijekovi su istraživani kod pacijenta s dijabetičkom kardiomiopatijom i u animalnim modelima. Najviše studija ima s lijekovima koji blokiraju renin-angiotenzin-aldosteronski sustav. Kao mogući mehanizam razvoja kardiomipatije smatrala se i produkcija angiotenzina II u miokardu. Studije vezane uz aliskiren (inhibitor renina), benazeprilat i valsartan dokazale su njihovu protektivnu ulogu na razvoj kardiomiopatije na životinjskim modelima[49] i bolesnicima[50].

Lijekovi koji se trebaju izbjegavati i kod sistoličko i dijastoličkog zatajivanja srca su: blokatori kalcijevih kanala zbog njihovog negativnog inotropnog učinka osim amlodipina i felodipina, nesteroidni antireumatici i COX 2 inhibitori zbog retencije soli i vode i pogoršavanja funkcije bubrega te je potrebno izbjegavati kombinaciju ACE inhibitora i ARB te lijekove iz skupine tiazolidindiona[41].

Od lijekova iz skupine tiazolidindiona, kod nas na tržištu je prisutan pioglitazon, koji kao najznačajniju nuspojavu ima porast tjelesne mase zbog zadržavanja tekućine u tijelu retencijom resorpcije natrija u bubrezima. Kontraindiciran je kod pacijenta u NYHA III. i IV. funkcijskim razredom, a može doći u obzir kod pažljivo odabranih bolesnika s NYHA I. i II. stupnju uz pažljivo praćenje zbog moguće retencije tekućine[51]. U animalnim modelima ima protupalno djelovanje i može usporiti razvoj fibroze i time prevenirati dijabetičku kardiomiopatiju[52].

Metformin je najpropisivani oralni hipoglikemik u svijetu. Povećava perifernu osjetljivost na inzulin, poboljšava kontrolu glikemije i u animalnim modelima može prevenirati razvoj dijabetičke kardiomiopatije, za što još nema dokaza u osoba s razvijenom kardiomiopatijom[53].

Abnormalnosti u lipidom profilu puno više štete bolesnicima s dijabetesom nego u nedijabetičkoj populaciji zbog njihove sklonosti ubrzanoj aterosklerozi. Terapija statinima značajno smanjuje mortalitet dijabetičkih bolesnika od kardiovaskularnih događaja. Terapija atrovastatinom, neovisno o visini LDL kolestrola, smanjuje intramiokardijalnu upalu, fibrozu i poboljšava funkciju lijeve klijetke na animalnim modelima[54]. Na isti način je dokazana i sposobnost fluvastatina koji smanjuje intersticijsku fibrozu miokarda i njegovu disfunkciju. Iako nema kliničke studije koja bi dokazala učinkovitost statina u prevenciji dijabetičke kardiomiopatije, poželjni efekti liječenja dislipidemije imaju važnu ulogu u primarnoj prevenciji bolesti.

pril[43] (PEP-CHF) and irbesatan[44] (I-Preserve) that have not proved the reduction in mortality of hospitalized patients with diastolic HF are discouraging.

The treatment of HF with the impaired left ventricular systolic function is conducted with the aim to reduce the symptoms, improve quality of life and increase functional capacity. This requires drugs from the three major neuro-humoral groups: angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARB), and mineralocorticoid receptor agonists. Diuretic therapy reduces symptoms and signs of congestion. SOLVD and SAVE studies have demonstrated that the benefit of the treatment by ACE inhibitors is equal in patients with and without diabetes[45].

The treatment with beta-blockers significantly increases the survival of patients with HF, regardless of whether they have diabetes or not with no difference in reduction in risk. Three key studies have proved the benefit of bisoprolol[46] (CIBIS II), metaprolol[47] (MERIT-HF) and carvediolol[48] (COPERNICUS) in reduction of mortality. Each study reports on a reduction in mortality by around 34% and a reduction in hospitalizations from 28-36% for HF during the year. More than 90% of patients in these studies with beta-blocker were treated with the ACE inhibitor or ARB.

A number of vasoactive drugs were investigated in patients with diabetic cardiomyopathy and in animal models. Most studies have been designed on drugs that block the renin-angiotensin-aldosterone system. The production of angiotensin II in the myocardium was considered to be a potential mechanism of developing cardiomyopathy. Studies related to aliskiren (renin inhibitor), benazepril and valsartan have proved their protective role in the development of cardiomyopathy in animal models[49] and patients[50].

Drugs to be avoided in case of systolic and diastolic HF are: calcium channel blockers due to their negative inotropic effect other than amlodipine and felodipine, non-steroidal antirheumatic drugs and COX 2 inhibitors for salt and water retention and impairment of renal function, the combination of ACE inhibitor and ARB, and thiazolidinediones should be avoided[41].

Out of the drugs from the group of thiazolidinediones, pioglitazone is present in our market, with a significant side-effect such as a weight gain as a result of fluid retention in the body caused by renal sodium retention and reabsorption. It is contraindicated in patients with NYHA functional class III and IV, and can be considered in carefully selected patients with NYHA class I and II with careful monitoring for potential fluid retention[51]. In animal models it has anti-inflammatory effect and may slow down the development of fibrosis and thus prevent diabetic cardiomyopathy[52].

Metformin is the most prescribed oral hyperglycemic agent in the world. It increases peripheral insulin sensitivity, improves glycemic control and it can prevent the development of diabetic cardiomyopathy in animal models, for which there is still no evidence in persons with advanced cardiomyopathy[53].

Abnormalities in lipid profile do much more harm to the patients with diabetes than to the non-diabetic population, due to their tendency for accelerated atherosclerosis. Statin therapy significantly reduces mortality of diabetic patients from cardiovascular events. Atorvastatin therapy, regardless of the amount of LDL cholesterol, reduces intramyocardial inflammation, fibrosis and improves left ventricular function in animal models[54]. In the same way, the potency of fluvastatin that reduces interstitial myocardial fibrosis and its dysfunc-

Uloga antioksidansa se intenzivno ispituje na životnjskim modelima. Istražuje se mogući učinak riboflavina, luteolina i resferatrola na prevenciju dijabetičke kardiomipatije. Za sada je dokazan povoljan antioksidatvni učinak trimetazidina zbog njegovog djelovanja na dobivanje energije u miokardu iz oksidacije glukoze, a ne slobodnih masnih kiselina. Lijek ima obećajavući učinak kod ishemijske i dilatativne kardiomiopatije i čini se, usporava razvoj dijabetičke kardiomiopatije[55].

Šećerna bolest je relativna kontraindikacija za transplantaciju srca, iako se pokazalo da pažlivo odabrani dijabetičari nemaju statistički značajno lošije preživljenje godinu dana nakon transplantacije i nakon pet godina[56]. U tijeku su studije s matičnim stanicama u cilju regeneracije beta stanica pankreasa i miokarda kako bi se poboljšao metabolizam glukoze i oporavila funkcija miokarda[30].

## Prevencija dijabetičke kardiomiopatije

Stroga kontrole glikemije smatrana je kao najvažni čimbenik prevencije razvoja kardiomiopatije, no velike studije (UKPDS 33. ACCOD, ADVANCE, VADT) nisu to i potvrdile[57]. Stroga kontrola glikemije prevenira razvoj prvenstveno mikroangiopatije, nije još jasna njena uloga na prevenciju makroangiopatije. Kako u patogenezi dijabetičke kardiomiopatije imaju značajnu ulogu upravo poremećaju na razini mikrocirkulacije, za očekivati je da će bolja regulacije glikemije rezultirati povoljnim učinkom na njenu prevenciju. Preventivni mehanizmi ovise o stupnju razvoja kardiomiopatije. U najranijoj fazi promjena stila života i pravilna prehrana siromašna masnoćama i ugljikohidratima uz svakodvnu fizičku aktivnost dokazano usporavaju razvoj kardiomiopatije. To podrazumijeva i optimalizaciju tjelesne težine i svakodnevnu fizičku aktivnost. Fizička aktivnost je povezana sa značajnim smanjenjem svih uzroka smrtnosti i koronarne bolesti kod dijabetičkih bolesnika, a smanjuje i incidenciju dijabetičke kardiomiopatije dokazano na animalnim modelima i u studijama na dijabetičarima[58].

Kod srednje teške kardiomiopatije uz pravilnu prehranu i fizičku aktivnost, terapija metforminom za tip 2, odnosno inzulinom za tip 1 bolesti i pioglitazoni poboljšavaju dijastoličku funkciju. U ovoj fazi za regulaciju arterijskog tlaka, optimalan su izbor beta-blokatori.

U kasnom stupnju dijabetičke kardiomiopatije sve mjere prevencije koje su navedene kod srednje teškog stupnja su i ovdje nužne, ali uz angiografiju u cilju otkrivanja makroangiopatije.

## Zaključak

Dijabetička kardimiopatija je često neprepoznata komplikacija šećerne bolesti, a posljedica je morfoloških i strukturalnih promjena u miokardu koje nastaju zbog brojnih metaboličkih rekacija koje prate dugotrajnu, nereguliranu hiperglikemiju. Zbog remodelacije miokarda u početnoj fazi bolesti vidi se hipertofija miokarda uz razvoj dijastoličke, potom i sistoličke disfunkcije, što značajno povećava srčano zatajivanje i smrtnost dijabetičkih bolesnika. Ehokardiografija je najčešće korištena metoda za procjenu funkcije miokarda, nužna je i u asimptomatskih dijabetičkih bolesnika, a posebice u onih koji se žale na zaduhu i intoleranciju napora. Istraživanja idu u smjeru otkrivanja novih specifičnih biomarkera, za sada najviše obećava MiRNA, koji mogu otkriti bolest već u samom začetku promjena i pomoću kojih se može stupnjevati težina dijabetičke kardiomiopatije i provoditi cition has been proved. Although there are no clinical studies that would prove the efficacy of statins in the prevention of diabetic cardiomyopathy, the desirable effects of treatment of dyslipidemia play an important role in the primary prevention of the disease.

The role of antioxidants is intensively being tested on animal models. A potential effect of riboflavin, luteolin and resveratrol in the prevention of diabetic cardiomyopathy is being investigated. A beneficial antioxidat effect of triemthazidine for its effect on production of energy in the myocardium from glucose oxidation, not from free fatty acid has been proven so far. The drug has a promising effect on ischemic and dilated cardiomyopathy and seems to be slowing down the development of diabetic cardiomyopathy[55].

Diabetes mellitus is a relative contraindication for heart transplantation, although it was shown that carefully selected diabetic patients have significantly worse survival one year after the transplantation and after five years' period[56]. The studies with stem cells aimed at regenerating pancreatic beta cells and myocardial cells in order to improve glucose metabolism and recover the myocardial function are underway.[30]

## Prevention of diabetic cardiomyopathy

Strict glycemic control is considered to be the most important factor in preventing the development of cardiomyopathy, but larger studies (UKPDS 33, ACCOD, ADVANCE, VADT) have not verified it[57]. Strict glycemic control primarily prevents the development of microangiopathy, its role in the prevention of macroangiopathy is not clear yet. Since in the pathogenesis, diabetic cardiomyopathies have an important role in the disorder at the level of microcirculation, it is expected that a better glycemic control will result in a beneficial effect on its prevention. Preventive mechanisms depend on the degree of development of cardiomyopathy. In the earliest stage of lifestyle changes, even a proper diet low in fat and carbohydrates with a daily physical activity is proved to delay the development of cardiomyopathy. This includes the optimization of body weight and a daily physical activity. Physical activity is associated with a significant reduction in all-cause mortality and coronary heart disease in diabetic patients and it also reduces the incidence of diabetic cardiomyopathy demonstrated on animal models and studies on diabetics[58].

In the moderate cardiomyopathy with proper nutrition and physical activity, the metformin therapy for type 2 or insulin for type 1 disease and pioglitazone improve the diastolic function. At this stage, the beta blockers are the optimal choice for the blood pressure control.

In the late stage of diabetic cardiomyopathy, all the preventive measures mentioned for moderate degree of severity are required here, but along with angiography aimed at detecting macroangiopathy.

## Conclusion

Diabetic cardimyopathy is often an unrecognized complication of diabetes, and is a consequence of morphological and structural changes in the myocardium that occur as a result of a number of metabolic reactions accompanying long-term, not controlled hyperglycemia. Due to myocardial remodeling in the initial stage, we can see the myocardial hypertrophy with a development of diastolic and then systolic dysfunction, which significantly increases HF and mortality

ljana terapija. U radu su prikazani postupci koji mogu usporiti razvoj kardiomiopatije, ali potrebne su nove spoznaje i o prevenciji i učinkovitoj terapiji.

Received: 17th Nov 2013; Updated: 3rd Dec 2013

*Address for correspondence: Klinička bolnica "Sveti Duh", Sveti Duh 64, HR-10000 Zagreb, Croatia.

Phone: +385-1-3712-111

E-mail: jasna.habek@gmail.com

of diabetic patients. Echocardiography is the most commonly used method for assessing myocardial function. It is necessary in asymptomatic diabetic patients, especially in those who complain of dyspnoea and intolerance of stress. The goal of the trials is to discover new specific biomarkers, where MiRNA is the most promising one, which can detect the disease as soon as the changes start to occur and which are used for scoring the severity of diabetic cardiomyopathy and conducting the target therapy. This paper presents the procedures that can slow down the development of cardiomyopathy, but we also need some new insights about the prevention and efficient therapy.

## Literature

1. Mathaei S, Stumvoll M. Pathophysiology and pharmacological treatment of insulin resistence. Endocrine Reviews. 2000;216:585-618.

2. Grundy SM, Benjamin IJ, Burke GL, et al. Diabetes and cardiovascular disease: a statement for healthcare professionals from the American Heart Association. Circulation. 1999;100:1134-46.

3. Piacano E. Diabetic cardiomyopaty, the imporatance of being earliest. J Am Coll Cardiol. 2003;42: 454-57.

4. Lundbeak K. Diabetische Angiopathie und Neuropathie. Handbuch der Innere medicin. 1997;2:175-87.

5. Starmann B, Strok I, Tschoepe D. Diabetic cardiomyopathy- a type of coronary artery disease? Internist. 2008;132:31.

6. Gery F. Diabetic cardiomyopthy: fact or fiction? Heart. 2001;85:247-248.

7. Devereux RB, Roman MJ, Paranicas M, et al. Impact of diabetes on cardiac structure and function. The strong heart study. Circulation. 2000;101:2271-6.

8. Pappachan JM, Varughese GI, Sruraman R, Arunagirinathan G. Diabetic cardiomyoptahy: Pathophysiology, diagnostic, evaluation and mangement. World Journal of Diabetes. 2013;15:177-89.

9. Kannel Wb, Hjortland M, Casteli Wp. Role of diabetes in congestiv hear failure: the Framingham study. Am J Cardiol. 1974;34:29.

10. de Simone G, Devereux RB, Chinali M, et al. Diabetes and incident heart failure in hypertensive and normotensive participants of the Strong Heart Study. J Hypertens. 2010;28:353-60.

11. Iribarren C, Karter AJ, Go AS, et al. Glycemic control and heart failure among adult patients with diabetes. Circulation. 2001;103:2668-73.

12. Ingelsson E, Sundstr^m J, Arnl^v J. Insulin resistance and risk of congestive heart failure. JAMA. 2005;294:334-41.

13. Di Bonito P, Cuomo S, Moio N, et al. Diastolic dysfunction in patients with non-insulin-dependent diabetes mellitus of short duration. Diabet Med. 1996;13:321-4.

14. Konduracka E, Cieslik G, Galicka-Latala D, et. Myocardial dysfunction and chronic heart failure in patients with long-lasting type 1 diabetes: a 7-year prospective cohort study. Acta Diabetol. 2013;50:597-606.

15. Čerkez Habek J. Dijastolička funkcija lijeve klijetke u bolesnika sa šećernom bolešću tipa 2. Povezanost s frekvencijom srca i njenom varijabilnosti (disertacija). Osijek: Medicinski fakultet; 2009.

16. Bertoni AG, Hundley WG, Massing MW, et al. Heart failure prevalence, incidence, and mortality in the elderly with diabetes. Diabetes Care. 2004;27:699-703.

17. Carr AA, Kowey PR, Devereux RB. Hospitalization for new heart failure among subjects with diabetes mellitus in the RENAL and LIFE studies. Am J Cardiol. 2005;96:1530.

18. Fonarow GF, Abraham WT, Albert NM, et al. Factors identified as precipitating hospital admissions for heart failure and clinical outcomes: findings from OPTIMIZE-HF. Arch Intern Med. 2008;168:847-54.

19. Rutter MK, Paraise H, Benjamin EJ. Impact glucose intolerance and insulin resistance on cardiac structure et function: sex-related differences in the Framingham Heart study. Circulation. 2003;107: 448.

20. Chatham JC, Seymour AM. Cardiac carbohydrate metabolilism in Zucker diabetic fatty rats. Cardiovasc Res. 2002;55:104-12.

21. Mokuda O, Sakamoto Y, Ikeda T, Mashiba H. Effects of anoxia of low free fatty acid on myocardial energy metabolism in stretozocin- diabetic rats. Ann Nutr Metab. 1990;34:259-65.

22. Regan TJ, Lyons MM, Ahmed SS, et al. Evidence of cardiomyopathy in familial diabetes mellitus. J Clin Invest. 1977;60:884-99.

23. Nunoda S, Genda A, Sugihara N, Nakayana A, Mizuno, Tekada R. Quantitative approach to the histopathology of the biopsied right ventricular myocardium in patients with diabetes mellitus. Heart Vessels. 1985;26:43-47.

24. Boudina S, Abel ED. Diabetic cardiomyopathy revisited. Circulation. 2007;115:3213-23.

25. Rodrigues B, Cam MC, Mcneill Jh. Metabolic disturbances in diabetic cardiomyopathy. Mol Cell Biochem. 1998;180:53-7.

26. Vinik AI, Maser RE, Mitchell BD. Diabetic autonomic neuropathy. Diabetes Care. 2003;26:1553-8.

27. Malhootra A, Sanghi V. Regulation of contractile proteins in diabetic heart. Cardiovac Res. 1999;34:34-40.

28. Nitenberg A, Valensi P, Sachs R, Dali M, Aptecer E, Attali JR. Imapairment of coronary vascular reserve and ACh- induced coronary vasodilatation in diabetic patients with angiographically normal coronary arteries and normal left ventricular systolic function. Diabetes. 1993;42:1017-25.

29. Anversa P, Leri A, Beltrami CA, Guerra S, Kajstura J. Myocite death and growth in the failing heart. Lab Invest. 1998; 78:767-86.

30. Chavali V, Tyagi SC, Mishra PK. Predictors and prevention of diabetic cardiomyopathy. Diabetes Metab Syndr Obes. 2013;6:151-60.

31. Tyagi AC, Sen U, Mishara PK. Synergy of micro RNA and stemm cell: a novel theraputic approach fot diabetes mellitus and cardiovascular diseases. Curr Diabetes Rev. 2011;7:367-76.

32. Scognamiglio R, Avorago A, casara D, Crepaldi C, Volta s. Myocardial dysfunction and adrenergic cardiac innervation in patients with insulin- depended diabetes mellitus. J Am Coll Cardiol. 1998;31: 404-12.

33. Dimitrow PP. Transthoracic Doppler echocardiography - noninvasive diagnostic window for coronary reserve flow assessment. Cardiovasc Ultrasound. 2003;1:4-12.

34. Katz AM, Zile MR. Mew molecular mechanisms in diastolic heart failure. Circulation. 2006;113:1922-5.

35. Božić I, Polić S, Rakić D, Carević V. Doplerehokardiografska procjena dijastoličke funkcije lijeve klijetke. Liječ Vjesn. 2006;128:153-61.

36. Brautsaert DL, Sys SU. Diastolic disfunction of a heart failure. J Card Fail. 1997;3:225-42.

37. Rijzewijk LJ, van der Meer RW, Smit JW, et al. Myocardial steatosis is an independent predictor of diastolic dysfunction in type 2 diabetes mellitus. J Am Coll Cardiol. 2008;52:1793-9.

38. D'Souza A, Howarth FC, Yanni J, et al. Left ventricle structural remodelling in the prediabetic Goto-Kakizaki rat. Exp Physiol. 2011;96:875-88.

39. Zachara NE. The roles of O-linked beta-N-acetylglucosamine in cardiovascular physiology and disease. Am J Physiol Heart Circ Physiol. 2012;302:H1905-H1918.

40. Mandinov L, Eberli F, Seiler C, Hess OM. Diastolic heart failure. Cardiovasc Res. 2000;45:813-25.

41. The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012. Europ Heart J 2008;33:1787-847.

42. Yusuf S, Pfeffer MA, Swedberg K, et al. Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved Trial. Lancet. 2003;362:777-81.

43. Cleland GF, Tendera M, Adamus J, Freemantle L. The perindopril in elderly people with chronic heart failure (PEP-CHF) study. Euro Heart J. 2006;27:2338-45.

44. Massie BM, Carson PE, McMurray JJ, et al. Irbesartan in patients with heart failure and preserved ejection fraction. N Engl J Med. 2008;359:2456-67.

45. Shindler DM, Kostis JB, Yusuf S. Diabetes mellitus, a predictor of morbidy and mortality in the StudiesLeft Ventricul dysfunction (SOLVD). Am J Cardiol. 1966;77:1017.

46. The Cardiac Insuf?ciency Bisoprolol Study II (CIBIS-II): a randomised trial. Lancet. 1999;353:9-13.

47. Hjalmarson A, Goldstein S, Fagerberg B, et al. Effects of controlled-release metoprolol on total mortality, hospitalizations, and well-being in patients with heart failure: the Metoprolol CR/XL Randomized Intervention Trial in congestive heart failure (MERIT-HF). MERIT-HF Study Group. JAMA. 2000;283:1295-1302.

48. Packer M, Fowler MB, Roecker EB, et al. Effect of carvedilol on the morbidity of patients with severe chronic heart failure: results of the carvedilol prospective randomized cumulative survival (COPERNICUS) study. Circulation. 2002;106:2194-9.

49. Thomas CM, Yong QC, Seqqat R, et al. Direct renin inhibition prevents cardiac dysfunction in a diabetic mouse model: comparison with an angiotensin receptor antagonist and angiotensin-converting enzyme inhibitor. Clin Sci. 2013;124:529-41.

50. Symeonides P, Koulouris S, Vratsista E, et al. Both ramipril and telmisartan reverse indices of early diabetic cardiomyopathy: a comparative study. Eur J Echocardiogr. 2007;8:480-6.

51. Magaš S. Cardiovascular effects of oral medications in the treatment of type 2 diabetes. Cardiol Croat. 2013;8:345-51.

52. Caglayan E, Stauber B, Collins AR, et al. Differential roles of cardiomyocyte and macrophage peroxisome proliferator-activated receptor gamma in cardiac fibrosis. Diabetes. 2008;57:2470-9.

53. Xie Z, Lau K, Eby B, et al. Improvement of cardiac functions by chronic metformin treatment is associated with enhanced cardiac autophagy in diabetic OVE26 mice. Diabetes. 2011;60:177-8.

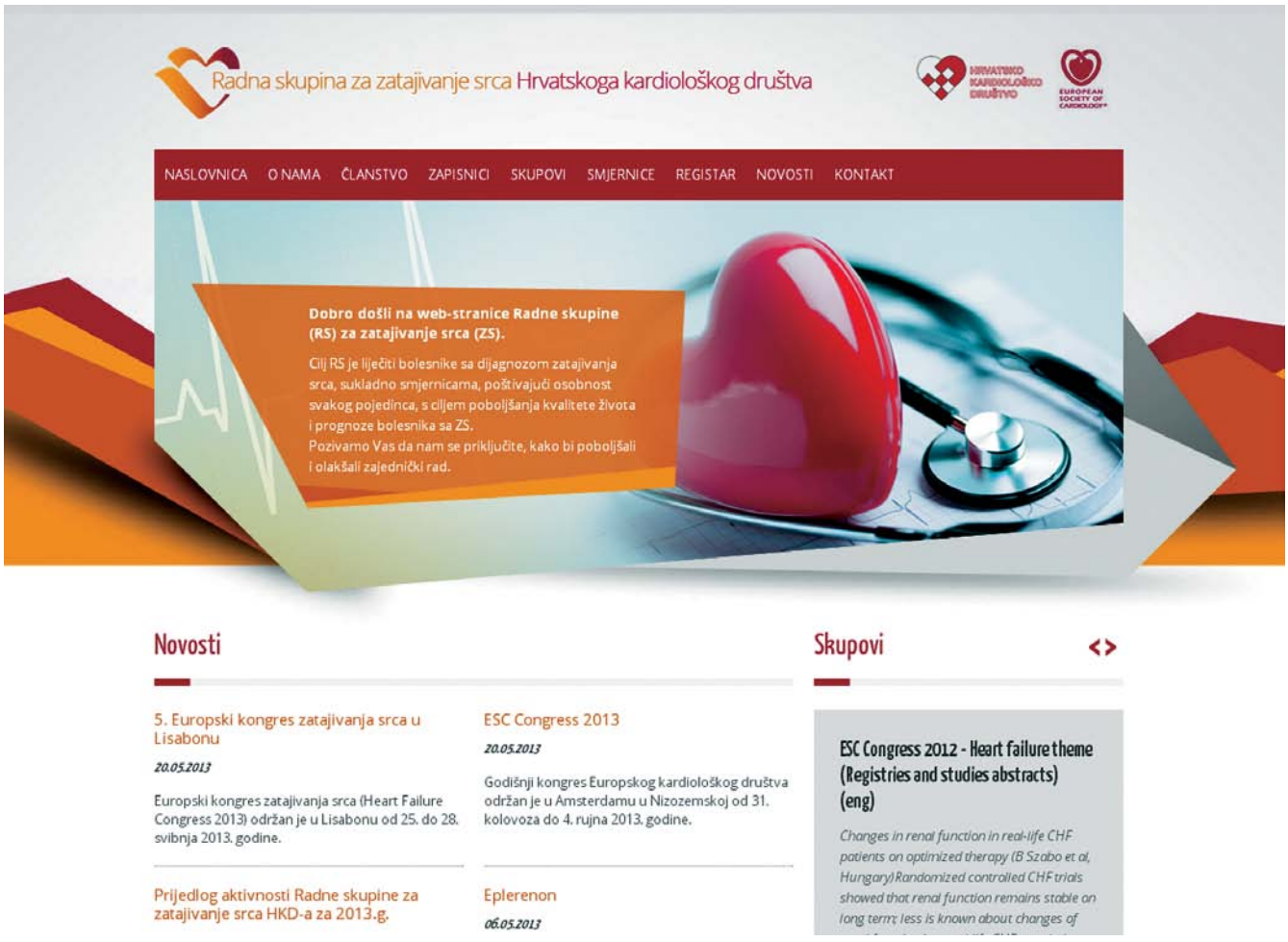
54. Van Linthout S, Riad A, Dhayat N, et al. Anti-inflammatory effects of atorvastatin improve left ventricular function in experimental diabetic cardiomyopathy. Diabetologia. 2007;50:1977-86.

55. Li YJ, Wang PH, Chen C, Zou MH, Wang DW. Improvement of mechanical heart function by trimetazidine in db/db mice. Acta Pharmacol Sin. 2010;31:560-9.

56. Marelli D, Laks H, Patel B. Heart transplantation in patients with diabetes mellitus in the current era, J Heart Lung Transplanation. 2003;22:1091.

57. Miki T, Yuda S, Kouzu H, Miura T. Diabetic cardiomyopathy: pathophysiology and clinical features. Heart Fail Rev. 2013;18:149-66.

58. Hordern MD, Coombes JS, Cooney LM, Jeffriess L, Prins JB, Marwick TH. Effects of exercise intervention on myocardial function in type 2 diabetes. Heart. 2009;95:1343-9.




http://crohf.kardio.hr