GOJAZNOST, INFLAMACIJA I HFpEF – DELOVI ISTOG *CIRCULUS VITIOSUS*-A

PREGLEDNI RAD

REVIEW ARTICLE

OBESITY, INFLAMMATION AND HFpEF – PARTS OF THE SAME CIRCULUS VITIOSUS

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SAŽETAK

Uvod/Cilj: Srčana insuficijencija sa očuvanom ejekcionom frakcijom (HFpEF) čini više od polovine slučajeva hronične srčane insuficijencije, a gojaznost je jedan od njenih najčešćih komorbiditeta, koji danas dobija epidemijske razmere i svakodnevno utiče na pogoršanje HFpEF-a. Oksidativni stres i sistemska inflamacija čiji je glavni izvor visceralno masno tkivo dovode do endotelne disfunkcije, mikrovaskularnih oštećenja, remodelovanja miokarda i njegove rigidnosti zbog razvoja fibroze, ključnih patofizioloških mehanizama HFpEF-a. Ovaj revijalni rad ima za cilj sumiranje i prikazivanje savremenih podataka o epidemiološkoj povezanosti gojaznosti i HFpEF-a, patofizioloških mehanizama koji ih povezuju, kliničkih i eksperimentalnih dokaza koji potvrđuju da su zajedno sa inflamacijom neraskidivi delovi istog *circulus vitiosus*-a.

Metode: Rad je fokusiran na pregledu relevantne literature i kliničkih istraživanja pretraženih u bazama PubMed, NCBI, ResearchGate, sa fokusom na patofiziološke mehanizme i rezultate kliničkih ispitivanja. Poseban akcenat stavljen je na istraživanje savremenih farmakoterapijskih mera usmerenih na regulaciju telesne težine (SGLT2 inhibitori, GLP-1 receptor agonisti) i kontrole komorbiditeta, sa ciljem smanjenja mortaliteta i morbiditeta ove ne tako male populacije pacijenata.

Rezultati: Razumevanje interakcija glavnih patofizioloških mehanizama kod gojaznosti i HFpEF-a može doprineti razvoju terapijskih strategija kao što su agonisti GLP-1/GIP receptora ili anticitokinska terapija, sa ciljem da se smanji sistemska inflamacija i rizik od pogoršanja HFpEF uz poboljšanje funkcionalnog kapaciteta i kvaliteta života.

Zaključak: Gojaznost je glavni komorbiditet kod pacijenata sa HFpEF u kojem inflamacija ima centralnu ulogu u patogenezi. Ciljane antiinflamatorne i metaboličke terapije pokazuju potencijal u smanjenju mortaliteta i morbiditeta, otvarajući nove mogućnosti za individualizovan pristup lečenju ove bolesti.

Ključne reči: visceralna adipoznost, dijastolna disfunkcija, endotelna disfunkcija, miokardna fibroza, SGLT2 inhibitori, GLP-1/GIP agonisti

ABSTRACT

Introduction/Objective: Heart failure with preserved ejection fraction (HFpEF) accounts for more than half of chronic heart failure cases, and obesity is among its most common comorbidities, which has reached epidemic proportions and is associated with the progressive deterioration of HFpEF. Oxidative stress and systemic inflammation, largely driven by visceral adipose tissue, promote endothelial dysfunction, coronary microvascular injury, myocardial remodeling and stiffness through fibrosis, the key pathophysiological mechanisms in HFpEF. This review paper aims to summarize current evidence on the epidemiological association between obesity and HFpEF, as well as the pathophysiological mechanisms linking these conditions. It also presents clinical and experimental findings demonstrating that obesity, HFpEF, and inflammation constitute interconnected components of one and the same circulus vitiosus.

Methods: This review draws upon relevant literature and clinical research retrieved from the PubMed, NCBI, and ResearchGate databases, focusing primarily on the underlying pathophysiological mechanisms and evidence derived from clinical trials. Particular emphasis was placed on modern weight-management pharmacotherapies (SGLT2 inhibitors, GLP-1 receptor agonists) and management of major comorbidities (DM, AHT, OSA, and NAFLD), with the aim of reducing the considerable burden of morbidity and mortality in this growing patient population.

Results: Better understanding of the interacting mechanisms in obesity and HFpEF supports development of therapeutic strategies such as dual GLP-1/GIP agonists and anti-cytokine approaches aimed at reducing systemic inflammation and the risk of HFpEF worsening, with potential improvements in functional capacity and quality of life.

Conclusion: Obesity is a major comorbidity in HFpEF, with inflammation playing a central role in pathogenesis. Targeted anti-inflammatory and metabolic therapies show potential to reduce morbidity and mortality and enable a more individualized treatment approach.

Keywords: visceral adiposity, diastolic dysfunction, endothelial dysfunction, myocardial fibrosis, SGLT2 inhibitors, GLP-1/GIP agonists

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UVOD

Može se reći da danas živimo u epidemiji gojaznosti. U studiji koja je objavljena u časopisu Lancet prema podacima SZO 2022. godine na svetu je bilo više od milijardu gojaznih ljudi. Od 1990. godine ova brojka se udvostručila medju odraslim ljudima, a 4 puta više je porasla medju decom i adolescentima. Danas svaka 8. osoba živi sa ovom bolešću [1].

Ovaj svetski trend porasta gojaznosti ogleda se i u kardiologiji. Prekomerna telesna težina (BMI ≥ 25 kg/m^2) i gojaznost (BMI ≥ 30 kg/m^2) dominiraju kod pacijenata sa srčanom insuficijencijom i očuvanom ejekcionom frakcijom (HFpEF). Zapravo, visceralna gojaznost, insulinska rezistencija i arterijska hipertenzija, kao i OSA (opstruktivna apneja u snu) vodeći su kardiometabolički faktori rizika za razvoj HFpEF-a [2,3].

U jednom velikom američkom kardiološkom registru Veradigom (ranije poznat PINNACLE) od 264.571 pacijenata sa HFpEF-om gojaznost (BMI ≥ 30 kg/m^2) je bila prisutna kod 55,7% bolesnika, metabolički sindrom zabeležen je kod 52,5%, čak 42,5% imalo je oba poremećaja, dok 34,3% nisu imali ni jedno ni drugo [4].

Gojaznost se danas smatra ključnom u patofiziologiji nastanka HFpEF. Povećanje telesne mase, a pre svega visceralnog masnog tkiva koje se ponaša kao endokrini organ, dovodi do sistemske inflamacije, oksidativnog stresa, posledično do endotelne disfunkcije, mikrovaskularnih koronarnih oštećenja, remodelovanja miokarda i njegove rigidnosti jer se smanjuje elastičnost zbog razvoja fibroze [5].

Jedna velika meta-analiza koja se koristila bazama podataka Medline, Embase i Global Health od njihovog osnivanja do početka 2023. godine uključila je 35 studija sa ukupno million ispitanika od čega je 35.000 bilo sa znakovima srčane insuficijencije. Analiza je pokazala da je svako povećanje obima struka za 10 cm praćeno 28% većim relativnim rizikom za nastanak srčanog popuštanja, pri čemu je taj efekat izraženiji za HFpEF nego za HF sa sniženom EF [6].

Istraživanja su pokazala da ehokardiografski merena veća količina masnog tkiva oko srca korelira sa većom dijastolnom disfunkcijom, sa većim odnosom pritiska punjenja leve komore i plućnim kapilarnim pritiskom (PCWP) pri fizičkom opterećenju [7].

Dalje, analize endomiokardnih biopsija kod bolesnika sa HFpEF-om pokazale su izraženiju kolagenu fibrozu kod gojaznih u poređenju sa osobama normalne telesne težine [8].

Zbog svega navedenog, nove terapijske strategije usmerene na redukciju telesne mase predmet su kliničkih istraživanja današnjice sa ciljem da se smanji sistemska inflamacija i rizik od pogoršanja HFpEF uz poboljšanje funkcionalnog kapaciteta i kvaliteta života.

INTRODUCTION

It can be said that we are currently living through an obesity epidemic. According to the WHO data reported in a study published in the Lancet, more than one billion people worldwide were obese in 2022. Since 1990, this figure has doubled among adults and increased fourfold among children and adolescents. Today one in every eight people lives with this disease [1].

This global trend of rising obesity is also reflected in cardiology Overweight (BMI ≥ 25 kg/m^2) and obesity (BMI ≥ 30 kg/m^2) are highly prevalent among patients with heart failure and preserved ejection fraction (HFpEF). In fact, visceral obesity, insulin resistance, arterial hypertension, and obstructive sleep apnea (OSA) are among the leading cardiometabolic risk factors for the development of HFpEF [2,3].

In the large U.S. cardiology registry Veradigm (formerly known as PINNACLE), which included 264,571 patients with HFpEF, obesity (BMI ≥ 30 kg/m^2) was present in 55.7% of patients, metabolic syndrome in 52.5%, and both conditions in 42.5%, while 34.3% had neither disorder [4].

Obesity is now considered a key factor in the pathophysiology of HFpEF. An increase in body mass, particularly in visceral adipose tissue, which functions as an endocrine organ, leads to systemic inflammation and oxidative stress, resulting in endothelial dysfunction, coronary microvascular injury, myocardial remodeling, and increased myocardial stiffness due to reduced elasticity associated with the development of fibrosis [5].

A large meta-analysis based on data from the Medline, Embase, and Global Health databases, covering the period from their inception to early 2023, included 35 studies with a total of one million participants, of whom 35,000 had signs of heart failure. The analysis showed that each 10 cm increase in waist circumference was associated with a 28% higher relative risk of developing heart failure, with the association being stronger for HFpEF than for heart failure with reduced ejection fraction (HFrEF) [6].

Studies have shown that a greater amount of adipose tissue surrounding the heart, as measured by echocardiography, is associated with more severe diastolic dysfunction, as well as higher left ventricular filling pressures and pulmonary capillary wedge pressure (PCWP) during exercise [7].

Furthermore, analyses of endomyocardial biopsy specimens from patients with HFpEF have shown more pronounced collagen fibrosis in obese individuals than in those with normal body weight [8].

In light of these findings, new therapeutic strategies aimed at reducing body weight are currently the focus of clinical research, with the goal of decreasing systemic

Cilj ovog revijalnog rada je da objedini i kritički analizira i prikaže dokaze kliničkih i eksperimentalnih studija objavljenih u poslednjih 10 godina (2015–2025.) koji povezuju gojaznost, inflamaciju i HFpEF u okviru istog patofiziološkog kruga, kao i da prikažu njihovu epidemiološku povezanost i najnovije farmakološke i nefarmakološke pristupe za prekidanje tog circulus vitiosusa.

EPIDEMIOLOGIJA HFPEF I GOJAZNOSTI

Srčana insuficijencija je složen klinički sindrom koji prema procenama danas pogađa 1% do 3% svetske populacije, a može se reći da HFpEF čini 50% svih dijagnoza hronične srčane slabosti [9].

U zemljama srednje i istočne Evrope prevalenca HF procenjuje se između 1,6% i 4,7%, uz incidencu od 3,1 do 6,0 novih slučajeva na 1000 stanovnika godišnje. Iako za Srbiju ne postoji sveobuhvatan nacionalni registar HF, podaci ukazuju na značajno opterećenje ovom bolešću. Prema Heart Failure Atlas izveštaju Evropskog udruženja za srčanu slabost 2019. godine Srbija je imala oko 1571 hospitalizaciju zbog HF na milion stanovnika godišnje. Smatra se da je ovaj broj, za koji se u praksi može očekivati da je veći, takav zbog nedovoljno ranog prepoznavanja i dijagnostikovanja HFpEF-a, kao i zbog ograničenja u prikupljanju podataka što je jedan od glavnih problema u regionu. Istovremeno, faktori rizika koji pogoduju nastanku HFpEF-a rasprostranjeni su veoma u našoj populaciji. Srbija se ubraja među vodeće zemlje sa vrlo visokom prevalencom gojaznosti i generalno sa metaboličkim poremećajima. Rezultati zdravlja stanovništva Srbije iz 2019. godine na osnovu BMI pokazali su da je tada 40,5% ljudi bilo normalno uhranjeno, a više od polovine (57,1%) je bilo prekomerno uhranjeno (36,3%) ili gojazno (20,8%) [10,11].

HFpEF najčešće pogađa stariju populaciju, s prosečnom starošću obolelih oko 70–75 godina i preovladava u ženskoj populaciji.

U Framingham studiji verovatnoća da se razvije HFpEF kod žena bila je 2,8 puta veća nego kod muškaraca kada su prisutni isti faktori rizika. Studija je pokazala da je i prevalenca HFpEF-a veća kod žena i raste sa godinama (8%–10% kod žena i 4%–6% kod muškaraca za osobe starije od 80 godina), pa se HFpEF često naziva „srčanom slabošću starijih žena". Sve ovo je posledica činjenice da su žene sklonije metaboličkom sindromu, gojaznosti, šećernoj bolesti, hipertenziji, koronarnoj bolesti u srednjem i starijem životnom dobu, što se delimično može objasniti i hormonskim promenama u menopauzi. Takođe, žene imaju manje dimenzije LK, deblji zid miokarda a samim tim i veću sklonost koncentričnoj hipertrofiji i dijastolnoj disfunkciji. Žene su prijavljivale

inflammation and the risk of HFpEF progression while improving functional capacity and quality of life.

The aim of this review is to consolidate, critically analyze, and present evidence from clinical and experimental studies published over the past decade (2015–2025) that link obesity, inflammation, and HFpEF within a common pathophysiological framework. In addition, it seeks to highlight their epidemiological association and review the latest pharmacological and non-pharmacological approaches aimed at disrupting this circulus vitiosus.

EPIDEMIOLOGY OF HFPEF AND OBESITY

Heart failure is a complex clinical syndrome that currently affects an estimated 1% to 3% of the global population, with HFpEF accounting for approximately 50% of all cases of chronic heart failure [9].

In Central and Eastern European countries, the prevalence of heart failure is estimated to range from 1.6% to 4.7%, with an incidence of 3.1 to 6.0 new cases per 1,000 inhabitants annually. Although Serbia lacks a comprehensive national HF registry, available data indicate that the disease represents a substantial healthcare burden. According to the 2019 Heart Failure Atlas report of the European Association for Heart Failure, Serbia recorded approximately 1,571 hospitalizations for heart failure per million inhabitants annually. The actual number is likely to be higher, reflecting challenges in the early recognition and diagnosis of HFpEF, as well as limitations in data collection, which remain among the major healthcare issues in the region. At the same time, risk factors that contribute to the development of HFpEF are highly prevalent in the Serbian population. Serbia ranks among the countries with a particularly high prevalence of obesity and metabolic disorders. According to the 2019 National Health Survey, based on BMI classification, only 40.5% of the population had a normal body weight, while more than half (57.1%) were either overweight (36.3%) or obese (20.8%) [10,11].

HFpEF predominantly affects older adults, with the average age of patients ranging from 70 to 75 years, and it is more common among women.

In the Framingham Study, women were 2.8 times more likely than men to develop HFpEF when exposed to the same risk factors. The study also demonstrated that the prevalence of HFpEF is higher in women and increases with age, reaching 8%–10% in women and 4%–6% in men among individuals older than 80 years. Consequently, HFpEF is often referred to as the "heart failure of older women." These differences are largely attributable to the higher prevalence of metabolic syndrome, obesity, diabetes, hypertension, and coronary artery disease among women in middle and older age, partly as a result

niži kvalitet života u poredjenju sa muškarcima, ali je njihovo ukupno preživljavanje bilo bolje [12].

HFpEF prate česte hospitalizacije, hitni prijemi, dugotrajno ambulantno lečenje, generalno smanjen kvalitet života i skraćen životni vek. Godišnja stopa mortaliteta pacijenata sa HFpEF je približno 8% godišnje, a raste na 10–12% kod starijih od 70 godina. Nakon prve hospitalizacije jednogodišnja stopa moraliteta je do 25%, a petogodišnja od 24% do 54%. Oko 30% pacijenata sa HFpEF umire od nekardijalnih uzroka usled brojnih komorbiditeta (šećerna bolest, gojaznost, HOBP). Ekonomski posmatrano, sve ovo predstavlja rastući izazov za zdravstvene sisteme [13,14].

Uvođenje novih terapija daje nadu u poboljšanje prognoze ovih bolesnika, ali ipak uspeh u kontroli „epidemije" HFpEF zavisi i od populacionih mera – prevencije i lečenja metaboličkog sindroma, gojaznosti, arterijske hipertenzije i šećerne bolesti.

PATOFIZIOLOŠKE PROMENE

Visceralno masno tkivo koje je najzastupljenije kod gojaznih pacijenata ponaša se poput endokrinog organa, luči proinflamatorne citokine kao što su interleukin-6, interleukin-1, faktor nekroze tumora-α, što sve dovodi do sistemske inflamacije. Oksidativni stres dovodi do stvaranja velikog broja slobodnih radikala koji dovode do strukturnih i funkcionalnih promena na mitohondrijama što uzrokuje smanjenje oksidativne fosforilacije, smanjenu produkciju ATP-a u miokardu, poremećaj homeostaze kalcijuma a posledično se smanjuje kontraktilnost kardiomiocita. Oni teže obezbeđuju energiju za relaksaciju i kontrakciju, doprinoseći dijastolnoj disfunkciji u HFpEF. Istovremeno, smanjuje se nivo azot monoksida, povećava se vaskularna rezistencija, što narušava endotelnu funkciju i dovodi do nastajanja aterosklerotskih promena. Sve ovo uzrokuje pogoršanu perfuziju miokarda i razvija se lokalna ishemija koja stimuliše oslobadjanje novih kiseoničnih slobodnih radikala [15,16].

Krajnji rezultat je remodelovanje miokarda tokom koga dolazi do taloženja ekstracelularnog matriksa bogatog kolagenom uz razvoj fibroze. Kao posledica fibroze povećava se rigidnost zida leve komore, ograničena je relaksacija miokarda, a povećan pritisak punjenja što dodatno remeti perfuziju miokarda. Vremenom srčani mišić sve više trpi epizode ishemije i to sve na kraju dovodi do progresije HFpEF [17].

Gojaznost dovodi do poremećaja neurohumoralne ravnoteže. Simpatički nervni sistem i renin-angiotenzin sistem (RASS) pojačano rade. Pojačana aktivnost simpatikusa dovodi do ubrzane srčane frekvence (pozitivan hronotropni efekat), pojačane kontraktilnosti

of hormonal changes associated with menopause. In addition, women tend to have smaller LV dimensions and thicker myocardial walls, which predispose them to concentric hypertrophy and diastolic dysfunction. Although women with HFpEF generally report a lower quality of life than men, their overall survival is better [12].

HFpEF is associated with frequent hospitalizations, emergency admissions, long-term outpatient management, reduced quality of life, and shortened life expectancy. The annual mortality rate among patients with HFpEF is approximately 8%, increasing to 10–12% in individuals older than 70 years. Following the first hospitalization, the one-year mortality rate may reach 25%, while the five-year mortality rate ranges from 24% to 54%. Approximately 30% of patients with HFpEF die from non-cardiac causes, largely due to the presence of multiple comorbidities, such as diabetes, obesity, and COPD. From an economic perspective, these factors constitute an increasing burden on healthcare systems [13,14].

The introduction of new therapies offers hope for improving the prognosis of these patients; however, success in controlling the HFpEF "epidemic" also depends on population-level measures, including the prevention and treatment of metabolic syndrome, obesity, arterial hypertension, and diabetes.

PATOPHYSIOLOGICAL CHANGES

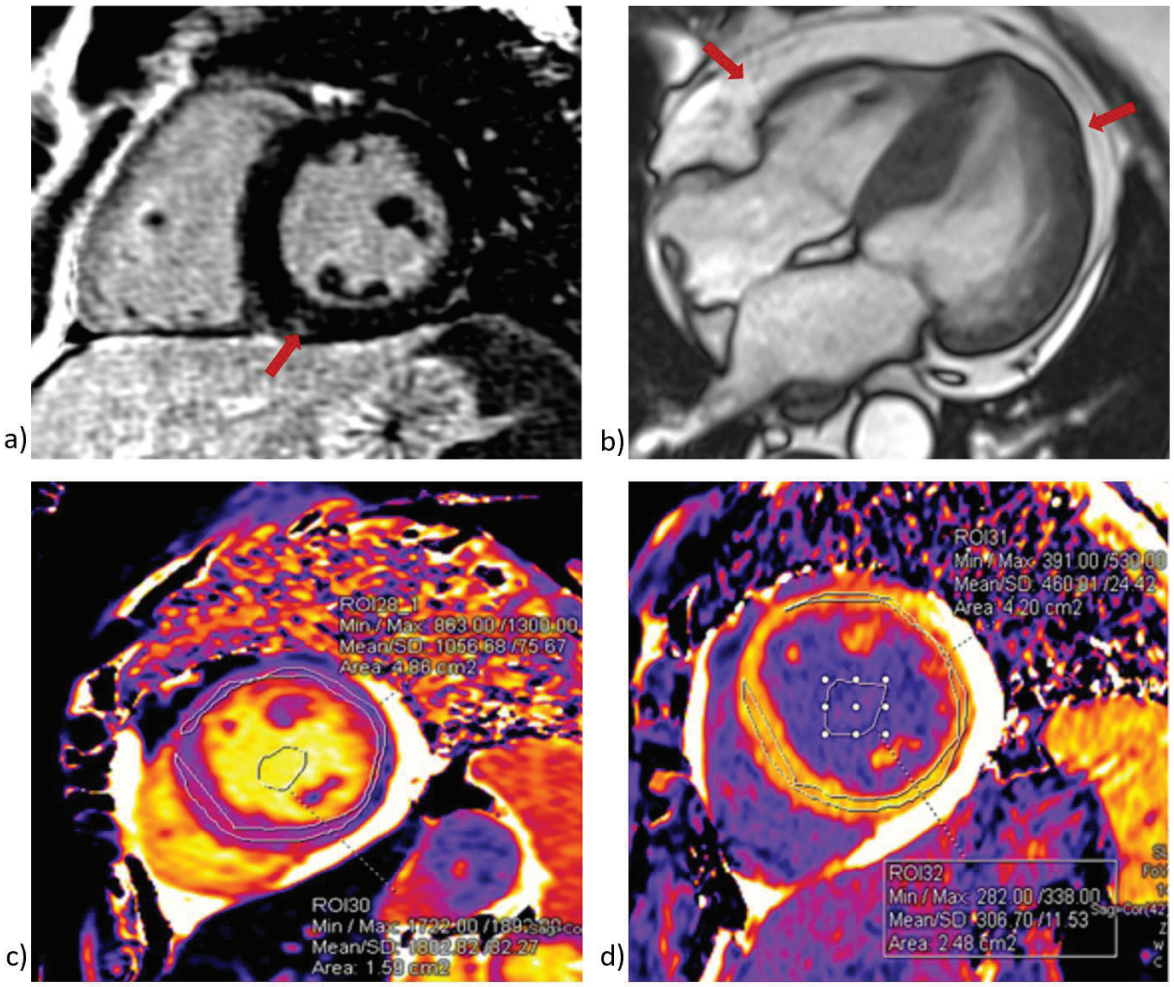
Visceral adipose tissue, which is most prevalent in obese individuals, functions as an endocrine organ that secretes pro-inflammatory cytokines such as interleukin-6, interleukin-1, and tumor necrosis factor-α, all of which contribute to systemic inflammation. Oxidative stress promotes the formation of large numbers of free radicals, leading to structural and functional mitochondrial changes, reduced oxidative phosphorylation, decreased ATP production in the myocardium, impaired calcium homeostasis, and consequently reduced cardiomyocyte contractility. These processes impair the heart's ability to generate sufficient energy for both relaxation and contraction, thereby contributing to diastolic dysfunction in HFpEF. At the same time, nitric oxide levels decrease and vascular resistance increases, which further impairs endothelial function and promotes the development of atherosclerotic changes. As a result, myocardial perfusion worsens and local ischemia develops, which in turn stimulates the production of additional reactive oxygen species [15,16].

The end result is myocardial remodeling, during which a collagen-rich extracellular matrix is deposited, leading to the development of fibrosis. As a consequence of fibrosis, left ventricular wall stiffness increases, myocardial relaxation is impaired, and filling pressures rise, which further compromises myocardial

(pozitivni inotropni efekat), povećane brzine sprovodjenja impulsa i ekscitabilnosti, povećane periferne vazokonstrikcije, povećanih metaboličkih zahteva, povećane potrošnje kiseonika. Na kraju, hronična aktivnost simpatikusa stimuliše fibrozu. Istovremeno, aktivacija RAAS-a kod metaboličkog sindroma dovodi do zadržavanja natrijuma i vode, povišenog krvnog pritiska i dodatnog opterećenja srca [18].

Magnetna rezonanca srca je moderan, neinvazivni dijagnostički alat koji može pružiti detaljne informacije o zapreminama leva komore i karakterizaciji tkiva uključujući kvantifikaciju fibroze i ožiljaka. Stepen fibroze kvantifikovan CMR tehnikama pokazuje povezanost sa stepenom gojaznosti. U jednoj studiji, koju su objavili Roy C., Slimani A. i saradnici, kod gojaznih pacijenata miokardijalna fibroza procenjena pomoću T1-MRI perfusion. Over time, the myocardium is exposed to recurrent ischemic episodes, ultimately contributing to the progression of HFpEF [17].

Obesity leads to disturbances in neurohumoral balance, with increased activity of the sympathetic nervous system and the renin–angiotensin system (RAAS). Enhanced sympathetic activity results in increased heart rate (positive chronotropic effect), increased contractility (positive inotropic effect), faster impulse conduction and excitability, peripheral vasoconstriction, elevated metabolic demands, and increased oxygen consumption. Ultimately, chronic sympathetic activation also promotes fibrosis. In parallel, activation of the RAAS in metabolic syndrome contributes to sodium and water retention, increased blood pressure, and an additional hemodynamic burden on the heart [18].



Slika 1. Nalaz magnetne rezonance srca kod gojaznog pacijenta sa HFpEF, hipertenzijom i dijabetes melitusom: a) LGE PSIR sekvenca, presek kratka osa; mrljasta fibroza u bazalnom inferoseptalnom segmentu, na mestu insercije desne komore (posledica opterećenja pritiskom/volumenom; b) Cine sekvenca, presek četiri šupljine; hipertrofija miokarda leve komore, izraženo epikardno masno tkivo; c, d) nativna T1 mapa i postkontrastna T1 mapa, povišene vrednosti ekstracelularnog volumena kao markera intersticijalne fibroze miokarda

Figure 1. Cardiac magnetic resonance findings in an obese patient with HFpEF, hypertension, and diabetes mellitus: (a) LGE PSIR sequence, short-axis view, demonstrating patchy fibrosis in the basal inferoseptal segment at the right ventricular insertion point, consistent with pressure/volume overload; (b) cine sequence, four-chamber view, showing left ventricular hypertrophy and prominent epicardial adipose tissue; (c, d) native T1 map and post-contrast T1 map demonstrating increased extracellular volume, indicative of myocardial interstitial fibrosis

korelira sa povišenim nivoima inflamatornih citokina IL-1β i IL-18 u plazmi, što povezuje inflamatorni proces sa fibrozom u srčanom mišiću [19,20] (Slika 1).

Na Albert Einstein koledžu na modelu gojaznog dijabetičara, na leptin rezistentnom mišu (laboratorijski soj miša koji je homozigot za mutaciju u genu leptinskog receptora), dokazana je dijastolna disfunkcije uz očuvanu EF, hipertrofija kardiomiocita i difuzna intersticijska fibroza. Takodje, pokazano je da su srčani fibroblasti pojačano proizvodili kolagen i ekstracelularni matriks bez klasične proliferacije u miofibroblaste, što sugeriše da metabolički stres aktivira alternativne profibrotičke puteve [21].

Novo područje istraživanja HFpEF-a ističe značaj limfnog sistema u funkcionisanju srčanog mišića. Studije pokazuju da je metabolički sindrom povezan sa smanjenim brojem malih kapilarnih limfnih sudova kao i njihovim strukturnim i funkcionalnim abnormalnostima. Dolazi do dilatacije i hiperpermeabilnosti početnih limfnih sudova, ali i do njihove smanjene kontraktilnosti. Rezultat ovih promena je smanjen kapacitet limfne drenaže zbog čega izostaje efikasno uklanjanje intersticijalne tečnosti i inflamatornih medijatora iz srčanog tkiva. Posledično nastaje mikroedem miokarda i zadržavanje tečnosti, što podiže pritiske punjenja i može pogoršati simptome srčane slabosti. U radu Cuijpers i saradnika istaknuta je veza udružene disfunkcije koronarnih mikrovaskularnih krvnih sudova sa lošom limfnom drenažom na stvaranje uslova za hroničnu kongestiju i zapaljenske reakcije i posledični nastanak fibroze miokarda [22].

DIJAGNOSTIKA I FENOTIPIZACIJA GOJAZNOG HFPEF PACIJENTA

Kod gojaznih bolesnika natriuretski peptidi BNP/NT-proBNP mogu biti lažno niski usled hemodilucije, pojačanog klirensa i povećane ekspresije neprilizina u adipoznom tkivu. Takođe dispneja, ortopneja i znaci kongestije kao što su periferni edemi često su zamaskirani zbog gojaznosti, što otežava kliničku procenu. H_2FPEF skor, koji uključuje vrednost telesne težine, može proceniti verovatnoću srčane insuficijencije sa očuvanom EF kod osoba kod kojih je dispneja primarno posledica gojaznosti [23].

Transtorakalni ultrazvuk srca ipak predstavlja zlatni standard dijagnostike pružajući uvid u funkciju i strukturne karakteristike srčanih šupljina. Glavni parametri koji se odredjuju kod gojaznih jesu ejekciona frakcija leve komore, globalni longitudinalni strain leve komore (GLS), dijametri levih srčanih šupljina, masa leve komore i dijastolna funkcija. Iako je ejekciona frakcija očuvana, GLS je često snižen, naročito sa porastom BMI. Šestominutni test hoda (6MWT) predstavlja jed-

Cardiac magnetic resonance imaging (CMR) is a modern, non-invasive diagnostic tool that provides detailed information on left ventricular volumes and enables tissue characterization, including quantification of fibrosis and scarring. The degree of fibrosis assessed by CMR techniques correlates with the degree of obesity. In a study by Roy C., Slimani A. et al., myocardial fibrosis measured by T1-mapping MRI in obese patients was associated with elevated plasma levels of the inflammatory cytokines IL-1β and IL-18, thereby linking systemic inflammation with myocardial fibrosis [19,20] (Figure 1).

At Albert Einstein College, in an experimental model of obesity and diabetes using leptin-resistant mice (a laboratory strain homozygous for a mutation in the leptin receptor gene), diastolic dysfunction with preserved ejection fraction, cardiomyocyte hypertrophy, and diffuse interstitial fibrosis were demonstrated. It was also shown that cardiac fibroblasts exhibited increased production of collagen and extracellular matrix without classical differentiation into myofibroblasts, suggesting that metabolic stress activates alternative profibrotic pathways [21].

A new area of HFpEF research highlights the importance of the lymphatic system in myocardial function. Studies show that metabolic syndrome is associated with a reduced number of small capillary lymphatic vessels, as well as structural and functional abnormalities. These include dilation and hyperpermeability of initial lymphatic vessels, along with reduced contractility. The result of these changes is a reduced capacity for lymphatic drainage, leading to impaired removal of interstitial fluid and inflammatory mediators from cardiac tissue. This causes myocardial microedema and fluid retention, which increases filling pressures and may worsen symptoms of heart failure. In the study by Cuijpers et al., the combined dysfunction of coronary microvascular circulation and impaired lymphatic drainage was highlighted, creating conditions for chronic congestion and inflammatory activation, and ultimately contributing to the development of myocardial fibrosis [22].

DIAGNOSIS AND PHENOTYPING IN AN OBESE HFPEF PATIENT

In obese patients, natriuretic peptides (BNP/NT-proBNP) may be falsely low due to hemodilution, increased clearance, and increased expression of neprilysin in adipose tissue. In addition, symptoms such as dyspnea and orthopnea, as well as signs of congestion including peripheral edema, are often obscured by obesity, which complicates clinical assessment. The H_2FPEF score, which incorporates body weight, can help es-

nostavan test za procenu podnošenja fizičkog napora. Kod gojaznih HFpEF pacijenata beleže se manje pređene distance, usled udruženih efekata kardijalnih ograničenja i smanjene kondicije zbog viška kilograma a što sve otežava interpretaciju testa. Ipak 6MWT ima prognostički značaj kod HFpEF i može poslužiti za praćenje efekta terapije [24].

Danas se sve više koristi fenotipska klasifikacija gojaznog HFpEF pacijenta. Izdvajaju se 3 fenotipa.

U metaboličko-inflamatornom fenotipu dominiraju insulinska rezistencija, dijabetes melitus, dislipidemija, povišeni zapaljenski i adipokinski markeri (IL-6, hsCRP, leptin, nizak adiponektin). Kod ovih pacijenata se očekuje dobar terapijski odgovor, koja se bazira na redukciji telesne težine [23].

Drugi je sarkopenično-gojazni fenotip prisutan kod starijih bolesnika sa visokim BMI, ali sa smanjenom mišićnom masom i snagom. Oni imaju izraženu netoleranciju napora i slabiju fizičku kondiciju. Terapijski pristup pored kardiološke terapije, uključuje i fizički trening do granica mogućeg uz adekvatan proteinski unos [25].

Treći je hipertenzivni fenotip i krakteriše ga dugotrajna arterijska hipertenzija, koncentrična hipertrofija leve komore i miokardna fibroza, sa relativno manjim stepenom inflamacije. Terapijski fokus u ovoj grupi je na agresivnoj kontroli pritiska uz optimizaciju volumena [23].

TERAPIJSKI PRISTUP GOJAZNOM HFPEF PACIJENTU

Terapijski plan se mora sprovoditi individualno za svakog pacijenta, multidisciplinarno, kombinujući nefarmakološke i farmakološke mere.

NEFARMAKOLOŠKE MERE

Osnova nefarmakološke terapije jeste promena načina života, koja podrazumeva regulisan način ishrane i fizičku aktivnost.

Hipokalorijske dijete dovode do smanjenja telesne težine, što prati pad krvnog pritiska (prosečno za 3–5 mmHg). Dijete koje se baziraju na mediteranskom načinu ishrane značajno snižavaju dijastolni krvni pritisak [26,27].

Redovan trening takodje ima udela u snižavanju krvnog pritiska za oko 3–5 mmHg dugoročno, ali može da poboljša i insulinsku senzitivnost, pa samim tim utiče i na snižavanje nivoa glikemije, kao i na gubitak telesne težine. Naročito su intenzivne aerobne vežbe (npr. biciklizam) koje su u sklopu dijetetskog režima povezane sa najizraženijim koristima po kardiovaskularni sistem. Ovako se popravlja lipidni profil, snižavaju se trigliceridi i ukupni LDL holesterol uz porast HDL holesterola, a poboljšava se i glikoregulacija [28].

timate the likelihood of heart failure with preserved ejection fraction (HFpEF) in individuals whose dyspnea is primarily attributable to obesity [23].

Transthoracic echocardiography remains the gold standard for diagnosis, providing detailed information on both the functional and structural characteristics of the cardiac chambers. In obese patients, key parameters assessed include left ventricular ejection fraction, left ventricular global longitudinal strain (GLS), left atrial and left ventricular chamber dimensions, left ventricular mass, and indices of diastolic function. Although ejection fraction is typically preserved, GLS is often reduced, particularly with increasing BMI. The six-minute walk test (6MWT) is a simple method for assessing functional exercise capacity. In obese patients with HFpEF, shorter walking distances are typically observed, reflecting the combined effects of cardiac limitation and reduced physical fitness associated with excess body weight, which complicates interpretation of the results. Nevertheless, the 6MWT has prognostic value in HFpEF and can be used to monitor treatment response [24].

Today, phenotypic classification of obese patients with HFpEF is increasingly used, with three main phenotypes identified.

The metabolic-inflammatory phenotype is characterized by insulin resistance, diabetes mellitus, dyslipidemia, and elevated inflammatory and adipokine markers, including IL-6, hsCRP, and leptin, along with reduced adiponectin levels. In these patients, a favorable therapeutic response is generally expected, particularly with interventions aimed at weight reduction [23].

The second is the sarcopenic-obese phenotype, which occurs in elderly patients with a high BMI but reduced muscle mass and strength. These patients exhibit marked exercise intolerance and poor physical condition. The therapeutic approach, in addition to standard cardiological treatment, includes structured physical training tailored to individual tolerance, along with adequate protein intake [25].

The third is the hypertensive phenotype, characterized by long-standing arterial hypertension, concentric left ventricular hypertrophy, and myocardial fibrosis, with a relatively lower degree of systemic inflammation. The therapeutic focus in this group is on strict blood pressure control and careful volume optimization [23].

THERAPEUTIC APPROACH TO AN OBESE HFPEF PATIENT

The therapeutic plan should be individualized for each patient and implemented in a multidisciplinary manner, combining both non-pharmacological and pharmacological approaches.

Dugoročan kombinovan pristup ipak pokazuje najbolje rezultate. Studije pokazuju da osobe koje se zdravo hrane i imaju redovnu fizičku aktivnost imaju za 50% manji kardiovaskularni morbiditet i mortalitet. Tome doprinose i prestanak pušenja i konzumiranja alkohola. Zajednička preporuka endokrinologa i kardiologa je promena stila života kao prve terapijske linije u prevenciji i lečenju gojaznosti i njenih komplikacija [29].

FARMAKOTERAPIJA

Prema aktuelnim preporukama farmakoterapija gojaznosti je indikovana kod svih pacijenata sa BMI ≥ 30 kg/m^2 ako nemaju komorbiditete, a njena primena se savetuje svim pacijentima sa prekomernom telesnom težinom i BMI ≥ 27 kg/m^2 uz prisustvo komorbiditeta (npr. dijabetes tip 2, dislipidemija, hipertenzija) [30].

Izbor farmakoterapijskog agensa treba pažljivo individualno razmotriti u odnosu na komorbiditete i dominantan fenotip bolesnika, kao i u odnosu na cilj koji se želi postići.

SGLT2 inhibitori: Ova klasa antidijabetika pokazala je iznenađujuće povoljan efekat kod HFpEF. U velikim studijama DELIVER i EMPEROR-Preserved dokazano je smanjenje rizika od kardiovaskularne smrti ili pogoršanja srčane insuficijencije u odnosu na placebo (ukupno 16,4% u odnosu na 19,5% za dapagliflozin i 13,8% u odnosu na 17,1% za empagliflozin). Ovi lekovi deluju diuretski i metabolički povoljno (redukuju telesnu masu i poboljšavaju glikoregulaciju), a korisni efekti uočeni su i kod bolesnika bez dijabetesa [31,32].

Istraživanja su ukazala na mehanizam dejstva SGLT2 inhibitora na preusmeravanje energetskog metabolizma kardiomiocita ka korišćenju ketona na račun oksidacije piruvata umesto masnih kiselina, što sve utiče na poboljšanje bioenergetskog i kardiovaskularnog kapaciteta u srčanoj insuficijenciji [33].

GLP-1 receptor agonisti: Glukagonu slični peptid-1 agonisti primarno su antidijabetici i lekovi za gubitak telesne težine, ali su nedavno ispitani kod gojaznih HFpEF bolesnika. U studiji STEP-HFpEF semaglutid (primena leka 2,4 mg nedeljno) doveo je do značajnog poboljšanja simptoma i fizičke kondicije u poređenju sa placebom – prosečno poboljšanje KCCQ-CSS skora bilo je +16,6 poena (naspram +8,7 na placebu) uz prosečni gubitak težine od 13% tokom prve godine terapije. Zabeleženo je takođe i poboljšanje rezultata testa šestominutnog hoda (+21,5 m u odnosu na +1,2 m u placebo grupi) i smanjenje NT-proBNP za 20,9%. GLP-1 receptor agonisti su posebno korisni kod pacijenata sa dijabetesom i/ili indeksnom telesne mase (BMI) > 30, a studija SELECT je takođe pokazala redukciju kardiovaskularnih događaja semaglutidom kod gojaznih visokog rizika [34,35].

NON-PHARAMACOLOGICAL APPROACHES

The cornerstone of non-pharmacological therapy is lifestyle modification, including a balanced diet and regular physical activity.

Hypocaloric diets lead to weight reduction, which is associated with a decrease in blood pressure (on average by 3–5 mmHg). Diets based on the Mediterranean dietary pattern significantly reduce diastolic blood pressure [26,27].

Regular exercise also contributes to a long-term reduction in blood pressure by approximately 3–5 mmHg. It can additionally improve insulin sensitivity, thereby lowering glycaemic levels and promoting weight loss. In particular, high-intensity aerobic activities (e.g., cycling) are associated with the most pronounced cardiovascular benefits when combined with dietary measures. Such interventions improve the lipid profile by reducing triglycerides and total LDL cholesterol while increasing HDL cholesterol, and they also enhance glycemic control [28].

However, a long-term combined approach yields the best outcomes. Studies show that individuals who adhere to a healthy diet and engage in regular physical activity have approximately 50% lower cardiovascular morbidity and mortality. Smoking cessation and alcohol avoidance further contribute to these benefits. The consensus recommendation of endocrinologists and cardiologists is lifestyle modification as the first-line therapy in the prevention and treatment of obesity and its complications [29].

PHARMACOTHERAPY

According to current recommendations, pharmacological treatment of obesity is indicated for all patients with a BMI ≥ 30 kg/m^2 in the absence of comorbidities, and is recommended for overweight patients with a BMI ≥ 27 kg/m^2 when comorbidities are present (e.g., type 2 diabetes, dyslipidemia, or hypertension) [30].

The choice of pharmacotherapeutic agents should be carefully individualized, considering comorbidities, the patient's dominant phenotype, and the specific therapeutic goals to be achieved.

SGLT2 inhibitors: This class of antidiabetic drugs has demonstrated unexpectedly beneficial effects in HFpEF. In the large DELIVER and EMPEROR-Preserved trials, a reduction in the risk of cardiovascular death or worsening heart failure was observed compared with placebo (overall 16.4% vs. 19.5% for dapagliflozin and 13.8% vs. 17.1% for empagliflozin). These agents exert both diuretic and metabolically favorable effects, including reductions in body weight and improvements in glycaemic control, with benefits also seen in patients without diabetes [31,32].

Međunarodna dvostruko slepa, randomizovana, placebo-kontrolisana studija od 731 pacijenta SUMMIT pokazala je da je tirzepatid (dualni agonist GIP/GLP-1 receptora) u dozi do 15 mg jednom nedeljno subkutano značajno smanjio rizik od ishoda kardiovaskularne smrti ili pogoršanja srčane insuficijencije kod pacijenata sa HFpEF (ejekciona frakcija ≥ 50 %) i gojaznošću (BMI ≥ 30) – sa 15,3 % u kontrolnoj grupi na 9,9 % u grupi koja je primala tirzepatid [36].

BARIJATRIJSKA HIRURGIJA

Kod pacijenata sa morbidnom gojaznošću i teškom HFpEF, barijatrijska hirurgija se može razmatrati nakon iscrpljivanja konzervativnih mera. Studije su pokazale da 6 meseci nakon barijatrijske intervencije dolazi do pada telesne težine i do 30% od početne, poboljšanja dijastolne funkcije srca i značajnog smanjenja dijametra leve komore. Prosek rezultata MHLHF skora pokazao je početne vrednosti 27±6, a nakon barijatrijske hirurgije zabeležen je pad na 7 ± 6 nakon gubitka telesne težine, a to je sve poboljšalo NYHA klasu. Kod ovih pacijenata je došlo je do značajnog smanjenja stope hospitalizacije zbog pogoršanja srčane slabosti i smanjenja incidence atrijalne fibrilacije u operisanoj grupi [37].

Po najnovijim ADA smernicama iz 2025. godine razmatra se hirurgija kao pristup za kontrolu telesne težine i glikemije sa pacijentima koji imaju BMI ≥ 30 kg/m^2 (odnosno ≥ 27,5 kg/m^2 za osobe azijskog porekla) [38].

Važeće NICE smernice postavljaju indikaciju za barijatrijsku hirurgiju ako je BMI ≥ 40 kg/m^2 ili između 35–39,9 kg/m^2 uz prisustvo komorbiditeta čije stanje bi se moglo poboljšati sa gubitkom telesne mase (kardiovaskularna bolest, HTA, OSA, NASH, T2D.). Takođe, pristanak na intervenciju je pristanak na doživotne, godišnje kontrole [39].

KONTROLA KOMORBIDITETA

Lečenje pridruženih bolesti od suštinskog je značaja za uspešan ishod kod gojaznih HFpEF pacijenata.

Što se tiče Dijabetes melitusa tip 2, metformin je obično terapija prvog izbora kod gojaznih dijabetičara zbog povoljnog metaboličkog profila i potencijalno blagog gubitka telesne težine. Na Zhejiang univerzitetu u Kini u istraživanju koje je obuhvatilo 372 pacijenata pokazano je da je metformin bio povezan sa nižim mortalitetom kod dijabetičara sa HFpEF. SGLT2i i GLP-1 receptor agonisti su gore već navedeni [40].

Neadekvatno kontrolisan krvni pritisak jedan je od glavnih uzroka HFpEF i razlog je pogoršanja kardiovaskularnog i bubrežnog sistema. Cilj terapije je održavanje krvnog pritiska u optimalnom opsegu radi sprečavanja daljeg remodelovanja miokarda. Gubitak telesne

Research has shown that SGLT2 inhibitors may shift cardiomyocyte energy metabolism toward increased utilization of ketone bodies, with a relative reduction in pyruvate oxidation and fatty acid metabolism. This metabolic reprogramming is thought to improve myocardial bioenergetics and enhance overall cardiovascular function in heart failure [33].

GLP-1 receptor agonists: Glucagon-like peptide-1 receptor agonists are primarily used as antidiabetic and weight-reducing agents, but have recently been studied in obese patients with HFpEF. In the STEP-HFpEF trial, semaglutide (2.4 mg once weekly) led to significant improvements in symptoms and physical function compared with placebo. The mean improvement in the KCCQ-CSS score was +16.6 points (vs. +8.7 with placebo), accompanied by an average weight loss of 13% over the first year of treatment. Improvements were also observed in the six-minute walk test (+21.5 m compared with +1.2 m in the placebo group), along with a 20.9% reduction in NT-proBNP levels. GLP-1 receptor agonists appear particularly beneficial in patients with diabetes and/or a body mass index (BMI) > 30. The SELECT trial further demonstrated a reduction in cardiovascular events with semaglutide in high-risk individuals with obesity [34,35].

The international double-blind, randomized, placebo-controlled SUMMIT trial involving 731 patients showed that tirzepatide, a dual GIP/GLP-1 receptor agonist administered subcutaneously at doses of up to 15 mg once weekly, significantly reduced the risk of cardiovascular death or worsening heart failure in patients with HFpEF (ejection fraction ≥ 50%) and obesity (BMI ≥ 30), from 15.3% in the control group to 9.9% in the tirzepatide group [36].

BARIATRIC SURGERY

In patients with morbid obesity and severe HFpEF, bariatric surgery may be considered after failure of conservative treatment. Studies have shown that within 6 months after bariatric intervention, body weight can decrease by up to 30% from baseline, accompanied by improvement in diastolic function and a significant reduction in left ventricular dimensions. The mean MHLHF score decreased from initial values of 27 ± 6 to 7 ± 6 following weight loss, with corresponding improvement in NYHA functional class. In these patients, a significant reduction in hospitalizations due to worsening heart failure and a lower incidence of atrial fibrillation were also observed in the surgical group [37].

The latest 2025 ADA guidelines consider surgery as an option for weight and glycaemic control in patients with a BMI ≥ 30 kg/m^2 (or ≥ 27.5 kg/m^2 in Asian populations) [38].

težine sam po sebi smanjuje krvni pritisak i povećava osetljivost na antihipertenzivne lekove. Ishrana i fizička aktivnost su glavne intervencije, ali su ograničene jer je dugoročno pridržavanje terapije pacijenata loše. Kod gojaznih bolesnika prednost se daje antihipertenzivima koji ne pogoršavaju insulinsku rezistenciju i ne dovode do porasta telesne mase, kao što su ACE-inhibitori, ARB, ili dugodelujući blokatori kalcijumskih kanala. Diuretici i mineralokortikoidni antagonisti se često dodaju zbog poboljšanja kontrole krvnog pritiska i volumena. Beta blokatori se uključuju ako je prisutna koronarna bolest ili visoka srčana frekvenca, a ako je niska, mogu se dati vazodilatatori. U slučaju hipertenzije otporne na lekove, renalna denervacija je tretman izbora [41].

Opstruktivna sleep apneja je izuzetno česta kod gojaznih HFpEF bolesnika i doprinosi pogoršanju HF kroz mehanizme intermitentne hipoksije, simpatičke aktivacije i skoka krvnog pritiska tokom noći. Lečenje potvrđene umerene do teške OSA CPAP uređajem može značajno poboljšati kliničku sliku ovih bolesnika. Pokazano je da HFpEF pacijenti sa OSA koji su adherentni na CPAP terapiju imaju manje pogoršanje srčane slabosti i bolju funkciju kardiovaskularnog sistema tokom praćenja [42].

NAFLD (nealkoholna masna bolest jetre) je često prisutna kod metaboličkog fenotipa HFpEF zbog visceralne gojaznosti i insulinske rezistencije. Gubitak težine za ≥ 10% telesne težine može ostvariti histološko poboljšanje NAFLD i time smanjiti inflamatorne medijatore koji deluju na miokard. Terapija NAFLD zasniva se na terapiji osnovnih patofizioloških mehanizama i komorbiditeta, uključujući gojaznost, insulinsku rezistenciju, dijabetes, dislipidemiju i hipertenziju [43].

TERAPIJSKE PERSPEKTIVE

Terapija gojaznog HFpEF pacijenta sve se više unapređuje kako dolazi do novih saznanja imunometaboličkih mehanizama ove bolesti. Nekoliko inovativnih terapijskih pristupa mogli bi da predstavljaju budućnost.

U DHART studiji pokazano je poboljšanje fizičke spremnosti i kardiovaskularnih kapaciteta kod pacijenata koji su dobijali antagonist IL-1 receptora, što govori da bi terapijski modaliteti usmereni na inflamaciju (anti-citokinska terapija) mogli biti budućnost. Posebno je interesantan interleukin-6 (IL-6), jer je on glavni modulator inflamacije, i njegov visok nivo korelira sa lošijom toleranicijom napora i povećanim pritiskom punjenja leve komore. Pokazane su povišene koncentracije IL6 i hs-CRP sa lošijim ishodom gojaznih pacijenata, a bili su u korelaciji sa povišenim NTproBNP i hs-TnT. U DAPA-HF istraživanju autori su ispitivali odnos IL6 i hsCRP sa efektima dapagliflozina. Pokazano je da dapagliflozin smanjuje rizik od neželjenih ishoda kod

Current NICE guidelines recommend bariatric surgery for patients with a BMI ≥ 40 kg/m^2, or a BMI of 35–39.9 kg/m^2 in the presence of comorbidities that could be improved with weight loss (e.g., cardiovascular disease, hypertension, obstructive sleep apnoea, non-alcoholic steatohepatitis, or type 2 diabetes). In addition, consent to surgery includes acceptance of lifelong annual follow-up and monitoring [39].

COMORBIDITY CONTROL

Effective management of comorbidities is essential for achieving successful outcomes in obese patients with HFpEF.

Regarding type 2 diabetes mellitus, metformin is typically the first-line therapy in obese patients with diabetes due to its favorable metabolic profile and potential for modest weight reduction. A study from Zhejiang University in China involving 372 patients showed that metformin was associated with reduced mortality in diabetic patients with HFpEF. SGLT2 inhibitors and GLP-1 receptor agonists have already been discussed above [40].

Poorly controlled blood pressure is one of the main contributors to HFpEF and is associated with progressive deterioration of both cardiovascular and renal function. The therapeutic goal is to maintain blood pressure within the optimal range in order to prevent further myocardial remodeling. Weight loss itself reduces blood pressure and improves sensitivity to antihypertensive therapy. Dietary modification and physical activity remain the cornerstone of intervention; however, long-term adherence is often limited in clinical practice. In obese patients, antihypertensive agents that do not worsen insulin resistance or promote weight gain are preferred, such as ACE inhibitors, angiotensin receptor blockers (ARBs), and long-acting calcium channel blockers. Diuretics and mineralocorticoid receptor antagonists are frequently added to optimize blood pressure and volume control. Beta-blockers are indicated in the presence of coronary artery disease or elevated heart rate, while vasodilators may be used when heart rate is low. In cases of drug-resistant hypertension, renal denervation may be considered as a therapeutic option [41].

Obstructive sleep apnea is highly prevalent in obese patients with HFpEF and contributes to heart failure progression through intermittent hypoxia, sympathetic activation, and nocturnal blood pressure surges. Treatment of confirmed moderate to severe OSA with CPAP can significantly improve the clinical condition of these patients. HFpEF patients with OSA who are adherent to CPAP therapy have been shown to experience slower heart failure progression and improved cardiovascular function at follow-up [42].

srčane insuficijencije nezavisno od nivoa početnog IL6 I hsCRP. Dapagliflozin nije imao značajni efekat na koncentracije IL6 ili hsCRP [44,45].

U toku je veliko kliničko ispitivanje HERMES koje procenjuje efekat ziltivekimaba (monoklonalno antitelo na IL-6) na ishode kod bolesnika sa srčanom insuficijencijom sa očuvanom ejekcionom frakcijom. Rezultati ovog i sličnih ispitivanja pokazaće da li ciljano suzbijanje inflamatornih puteva (IL-6, IL-1, TNF-α) može dovesti do trajnog poboljšanja dijastolne funkcije i simptoma srčane slabosti [46].

ZAKLJUČAK

Može se reći da je gojaznost značajan komorbiditet kod srčane slabosti sa očuvanom ejekcionom frakcijom (HFpEF) – čak oko 80% pacijenata sa HFpEF ima prekomernu telesnu masu ili gojaznost, i možemo slobodno reći da rizik od kardijalne dekompenzacije i rehospitalizacije raste linearno sa BMI. Pored toga, gojazni HFpEF pacijenti pokazuju izrazito smanjenje funkcionalnog kapaciteta i fizičke tolerancije napora.

Visceralno masno tkivo je glavni izvor inflamacije koja igra centralnu ulogu u patogenezi HFpEF, koja dovodi do oksidativnog stresa, endotelne disfunkcije koronarne mikrocirkulacije, ishemije miokarda, i na kraju do njegovog remodelovanja i do fibroze.

Zbog svega toga, možemo reći da gojaznost, inflamacija i HFpEF čine patofiziološki „trougao" u kojem svaki element pojačava negativne efekte ostalih, formirajući začarani krug.

Promena životnog stila i farmakoterapija usmerena na redukciju telesne težine mogu prekinuti ovaj circulus vitiosus i poboljšati ishod bolesnika sa HFpEF.

Relativno mali gubitak težine od 5–10% koji je održiv donosi bolji funkcionalni kapacitet i poboljšanje simptoma pacijenata, smanjenje faktora rizika i kontrolu komorbiditeta, te generalno bolje preživljavanje.

Uspešno lečenje gojaznog HFpEF pacijenta zahteva timski rad koji uključuje kardiologa, endokrinologa, nutricionistu, svakako psihologa kako bi uticao na motivaciju pacijenta i specijalistu fizikalne medicine ili sportskog lekara i fizičkog trenera koji bi napravio i kontrolisao plan vežbanja. Najvažnija je naravno pre svega spremnost i volja pacijenta.

U narednim godinama terapijski pristup gojaznom HFpEF pacijentu će se verovatno pomeriti ka još individualizovanijim strategijama lečenja. Kombinovanjem intervencija usmerenih na životni stil sa novim farmakoterapijama otvara se mogućnost za značajnije poboljšanje prognoze ove velike populacije pacijenata čiji broj se sa godinama sve više povećava.

Sukob interesa: Nije prijavljen.

Non-alcoholic fatty liver disease (NAFLD) is frequently present in the metabolic phenotype of HFpEF, driven by visceral obesity and insulin resistance. A weight reduction of ≥10% of body weight can lead to histological improvement in NAFLD and thereby reduce inflammatory mediators that may affect the myocardium. Management of NAFLD is based on addressing the underlying pathophysiological mechanisms and associated comorbidities, including obesity, insulin resistance, diabetes, dyslipidemia, and hypertension [43].

THERAPEUTIC PERSPECTIVES

Therapy for obese patients with HFpEF is continuously improving as new insights into the immunometabolic mechanisms of the disease emerge. Several innovative therapeutic approaches may represent future treatment options.

The DHART study demonstrated improvements in physical fitness and cardiovascular capacity in patients receiving an interleukin-1 receptor antagonist, suggesting that anti-inflammatory (anti-cytokine) therapies may represent a future therapeutic direction. Of particular interest is interleukin-6 (IL-6), a key mediator of inflammation, with elevated levels correlating with reduced exercise tolerance and increased left ventricular filling pressures. Higher concentrations of IL-6 and hs-CRP have been associated with poorer outcomes in obese patients and have been linked to increased NT-proBNP and hs-TnT levels. In the DAPA-HF study, the relationship between IL-6, hs-CRP, and the effects of dapagliflozin was also investigated. Dapagliflozin has been shown to reduce the risk of adverse outcomes in heart failure independently of baseline IL-6 and hs-CRP levels. It was also found to have no significant effect on IL-6 or hs-CRP concentrations [44,45].

The large clinical trial HERMES is ongoing and is evaluating the effect of ziltivekimab, a monoclonal antibody targeting IL-6, on outcomes in patients with heart failure with preserved ejection fraction (HFpEF). The results of this and similar studies will clarify whether targeted suppression of inflammatory pathways (including IL-6, IL-1, and TNF-α) can lead to sustained improvements in diastolic function and heart failure symptoms [46].

CONCLUSION

It can be stated that obesity is a significant comorbidity in heart failure with preserved ejection fraction (HFpEF), with up to 80% of patients being overweight or obese. The risk of cardiac decompensation and rehospitalization appears to increase progressively with BMI. In addition, obese patients with HFpEF demonstrate marked reductions in functional capacity and exercise tolerance.

Visceral adipose tissue is a major source of inflammatory mediators that play a central role in the pathogenesis of HFpEF. It contributes to oxidative stress, endothelial dysfunction of the coronary microcirculation, myocardial ischemia, and ultimately cardiac remodeling and fibrosis.

Taken together, these mechanisms suggest that obesity, inflammation, and HFpEF form a pathophysiological "triangle" in which each component amplifies the detrimental effects of the others, creating a self-perpetuating vicious cycle.

Lifestyle modification and pharmacotherapy aimed at reducing body weight can interrupt this circulus vitiosus and improve outcomes in patients with HFpEF.

A relatively modest, sustained weight loss of 5–10% is associated with improved functional capacity and symptom relief, better control of risk factors and comorbidities, and improved overall survival.

Successful management of an obese patient with HFpEF requires a multidisciplinary team, including a cardiologist, endocrinologist, nutritionist, psychologist to support motivation and behavioral change, and a specialist in physical medicine or sports medicine together with a physical trainer to design and supervise an exercise programme. Ultimately, patient engagement and willingness remain essential for achieving optimal outcomes.

In the coming years, the therapeutic approach to obese patients with HFpEF is likely to shift toward more individualized treatment strategies. The combination of lifestyle interventions and emerging pharmacotherapies offers the potential to significantly improve outcomes in this growing patient population, whose prevalence increases with age.

Conflict of interest: None declared.

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