Pregledni članak / Review article

Debljina i kardiomiopatija

Obesity related cardiomyopathy

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SAŽETAK: Pretilost predstavlja svjetski epidemijski i veliki zdravstveni problem osobito otkako se povezuje s metaboličkim, kardijalnim i vaskularnim komplikacijama. Prema posljednjim istraživanjima, ektopično visceralno masno tkivo je važan prediktor razvoja kardiovaskularnih bolesti i inzulinske rezistencije, značajnije nego ukupno akumulirano masno tivo. Kardijalno visceralno masno tkivo čine intratorakalne, epikardijalne i intramiokardijalne masne stanice, koje su povezane i s konvencionalnim kardiovaskularnim čimbenicima rizika. Adipociti su aktivne endokrine stanice koje produciraju mnogobrojne adipocitokemokine. Leptin i adiponektin su adipokini sa značajnom ulogom u razvoju kardiovaskularnih bolesti, uključujući aterosklerotske procese, hipertrofiju kardiomiocita i remodelaciju miokardijalnog ekstracelularnog matriksa. U stanju pretilosti koncentracija cirkulirajućeg protektivnog adiponektina je snižena, dok je koncentracija leptina povišena. Zajedno, hipoadiponektinemija i hiperleptinemija imaju proaterosklerotski i proupalni učinak, djelujući na hipertrofični signal u kardiomiocitima putem kompleksnih mehanizama. Može se zaključiti da pretilost, ektopično kardijalno masno tkivo i adipokini utječu na lokalne i sistemske, metaboličke i mehaničke promijene kardiovaskularnog sustava s patohistološkim i patofiziološkim promijenama kardiomiocita i miokarda. Rezultat svih promjena je razvoj debljinom uzrokovane kardiomiopatije s poremećajem miokardijalne relaksacije i dijastoličke funkcije.

KLJUČNE RIJEČI: adiponektin, kardiomiopatija, epikardijalno masno tkivo, leptin, pretilost.

SUMMARY: Obesity is becoming a worldwide epidemic and a major health problem, since its presence is associated with significant adverse effects on health including metabolic, cardiac and vascular complications. According to latest research, ectopic visceral fat accumulation is an important predictor of diseases, particularly of cardiovascular diseases and insulin resistance, carrying more risk than general fat accumulation. Cardiac ectopic fat includes fat deposition around the heart (epicardial and intrathoracic fat) and intra-myocardial fat cells. All ectopic fat depots are related to conventional risk factors for cardiovascular diseases. Adipocytes act as an endocrine organ, producing a number of adipocytokemokines. Leptin and adiponectin are adipokines with a significant role in development of cardiovascular diseases, including atherosclerosis, cardiac hypertrophy and myocardial extracellular matrix remodeling. The level of circulating protective adiponectin is decreased while leptin level is increased in obese patients. Hypoadiponectinemia and hyperleptinemia have proatherosclerotic and proinflammatory effects inducing hypertrophic signal in cardiomyocytes via complex mechanisms. It can be concluded that obesity, cardiac fat, inflammation and adipokines changes contribute to local and systemic, metabolic and mechanical changes in cardiovascular system, with pathohistological and pathophysiological changes of cardiomyocytes and myocardium. The result of all these changes is obesity related cardiomyopathy with disturbances of myocardium relaxation and diastolic dysfunction.

KEYWORDS: adiponectin, cardiomyopathy, epicardial adipose tissue, leptin, obesity.

CITATION: Cardiol Croat. 2012;7(7-8):204-208.

Debljina i visceralno kardijalno masno tkivo

Prema funkciji, masno tkivo dijelimo u supkutano i visceralno masno tkivo[1]. Supkutano masno tkivo ima važnu ulogu u termoregulacijskim procesima, mehaničkoj potpori i zaštiti[2]. Visceralno masno tkivo sadrži značajne lipidne depoe unutar ili oko drugih tkiva i organa s neurohumoralnm aktivnošću i utjecajem na metaboličke i aterosklerotske procese[3].

Ektopično kardijalno masno tkivo je prepoznato kao potencijalni marker za kardiovaskularne bolesti (KVB)[4], ali je još uvijek nepoznanica na koji način utječe na kardiometabolizam i srčanu funkciju[5]. Pretilost je karakterizirana prekomjernom produkcijom brojnih adipokina i citokemokina (povećana koncentracija leptina i brojnih drugih adipokina, IL-1, IL-6, IL-8,

Obesity and cardiac visceral adipose tissue

Adipose tissue can be classified as subcutaneous and visceral ectopic fat according to its function[1]. Subcutaneous adipose tissue has an important role in thermoregulation processes, mechanical support and protection[2]. Visceral obesity, on the other hand, is present in form of significant lipid depots within and around other tissues and organs with neurohumoral activity and influence on metabolic disorders and atherosclerotic processes[3]. Ectopic cardiac adipose tissue has been recognized as a potential marker for cardiovascular diseases (CVD)[4], but its influence on cardiac metabolism and its function is stil unknown[5]. Obesity is characterized by excess production of a large number of adipokines and citokemokines (increased level of leptin, interleukin-1, interleukin-6, interleukin-8, tumor necrosis factor-alpha, monocyte

TNF-alfa, MCP-1, PAI-1; te sniženom koncentracijom protektivnog adiponektina), što uzrokuje kroničnu lokalnu i sistemsku supkliničku upalu visceralnog masnog tkiva, rezultirajući progresijom upale i endotelne disfunkcije[6]. Epikardijalno i miokardijalno masno tkivo rastu sa stupnjem debljine i utječu na kardijalne promijene[7].

Metabolički i mehanički učinak masti

Kardiomiociti i neadipociti kod pacijenata s urednim indeksom tjelesne mase (ITM) imaju malu mogućnost skladištenja masti, dok su pretile osobe izložene visokim koncentracijama lipida koji mogu poticati akumulaciju triglicerida u kardiomiocitima[8,9]. Anatomska pozicija epikardijalnog masnog tkiva također može dodatno, lokalno utjecati na patofiziološke procese u miokardu[10,11]. Visceralno masno tkivo je visoko lipolitično. Neadekvatna supresija slobodnih masnih kiselina inzulinom i visoke koncentracije triglicerida koreliraju s epikardnim masnim tkivom[10,12] značajnije nego s ostalim masnim depoima[11]. Kardijalno masno tkivo predstavlja izvor kardiotoksičnih slobodnih masnih kiselina koje dovode do masne akumulacije[13] uzrokujući miokardnu steatozu s utjecajem na kontraktilnost i smanjenu funkciju[14].

Različite vrste stanica u miokardu: kardiomiociti, fibroblasti, endotelne i glatke mišićne stanice, neovisno reagiraju na autokrini, parakrini i endokrini učinak adipokina i pridonose procesu patološke remodelacije miokardnog matriksa[15]. Remodeliranje ekstracelularnog matriksa je aktivan proces u kojem dolazi do ultrastrukturnih promijena miokarda, doprinoseći razvoju dijastoličke disunkcije[15]. Abnormalnosti matriksa u procesima hipertrofije lijeve klijetke (HLK) uključuje neurohormone, bioaktivne molekule i matricelularne proteine koji reguliraju sintezu i degradaciju ekstracelularnog matriksa putem učinka matriks metaloproteinaze i koncentracije inhibitora matriks metaloproteinaze[16].

Debljinom povezana arterijska hipertenzija i kardijalna funkcija

U stanju pretilosti adipokini utječu na razvoj arterijske hipertenzije (AH) putem prekomjerne simpatičke stimulacije, endotelne disfunkcije i vazokonstrikcije, povećanom retencijom natrija u bubrezima[17]. Zajedno, i hemodinamski (putem AH) i nehemodinamski neurohumoralni čimbenici (adipokini — leptin i adiponektin) utječu na remodelaciju i hipertrofiju miokarda[18-21], djelujući na sistoličku i dijastoličku funkciju. Prema nekim studijama, regionalna redukcija sistoličke funkcije direktno korelira s AH i metaboličkim abnormalnostima, kao posljedica visceralnog masnog tkiva, triglicerida i inzulinske rezistencije[5,22]. Prema rezultatima drugih studija, udio miokardnih triglicerida raste s dobi, doprinoseći razvoju dijastoličke disfunkcije neovisno o ITM i vrijednostima arterijskog tlaka[14,23] mijenjajući miokardnu rastezljivost i bioenergetsku funkcionalnost[24].

Leptin i adiponektin

Leptin je adipokin s glavnom ulogom u procesima održanja homeostaze centralnih i perifernih tkiva. Primarno se sintetizira u adipocitima, a može i u kardiomiocitima. U srcu leptin ostvaruje autokrine, parakrine i endokrine učinke putem leptinskih receptora[25]. Kod većine pretilih osoba, serumska koncentracija leptina je povećana i u korelaciji s ITM. Mnogobrojne kliničke i eksperimentalne studije te *in vitro* analize

chemoatrractant protein-1, plasminogen activator inhibitor-1; decreased level of adiponectin), which causes chronic local and systemic, subclinical inflammation of visceral adipose tissue resulting in development of further inflammatory processes and endothelial dysfunction[6]. Epicardial and myocardial fat depots increase with degree of adiposity and contribute to obesity-associated cardiac changes. Epicardial fat thickness may serve as a predictor of myocardial fat content better than waist circumference or traditional biochemical markers[7].

Metabolic and mechanical effect of fat

Cardiomyocytes and non-adipocytes have low fat-storage capacity in patients with normal body mass index (BMI) values, while in obese patients they are exposed to high levels of plasma lipids, which can lead to accumulation of triglycerides in cardiomyocytes[8,9]. Because of its anatomic location, epicardial adipose tissue can locally modulate the myocardium[10,11]. Ectopic visceral fat tissue are highly lipolytic. Impaired suppression of free fatty acids by insulin and higher triglycerides level correlated with epicardial fat[10,12], more significantly than in other fat depots[11]. Cardiac adipose tissue acts as a source of cardiotoxic free fatty and pro-inflammatory adipokines, which leads to myocardial fat accumulation[13] and causes cardiac steatosis with influence on myocardial contractility and consequentually reduced myocardial function[14].

Various cell types in cardiac tissue namely, cardiomyocytes, fibroblasts, endothelial cells and smooth muscle cells, independently respond to autocrine, paracrine and endocrine effects of adipokines and contribute to the pathologic process of myocardial matrix remodelling[15]. Extracellular matrix remodelling is an active process in which ultrastructure of myocardium is altered, contributing to abnormalities in diastolic fuction[15]. Matrix abnormalities in left ventricular hypertrophy (LVH) process includes neurohormones, bioactive molecules and matricellular proteins that regulate extracellular matrix accumulation, synthesis and degradation through effects on matrix metalloproteinase and tissue inhibitor of metalloproteinase levels[16].

Obesity related hypertension and cardiac function

Adipocytokines contribute to development of hypertension in obesity via sympathetic nervous system overactivity, endothelial dysfunction and vasoconstriction, as well as via increased sodium retention in kidneys[17]. Both, haemodynamic (hypertension) and non-haemodynamic neurohumoral factors (adipokines — leptin and adiponectin) have influence on cardiac muscle remodelling and hypertrophy[18-21] affecting both systolic and diastolic function of the left ventricle. Some studies suggest that reduction of regional systolic function of the heart directly correlates with hypertension parameters of metabolic abnormality, such as epicardial fat accumulation, triglycerides accumulation and insulin resistance[5,22]. Some other studies have shown that myocardial triglycerides content increases with age, thus contributing to development of diastolic heart dysfunction regardless of BMI and blood pressure values[14,23] and causing changes in myocardial stiffness and myocardial energy availability/bioenergetics[24].

Leptin and adiponectin

Leptin is an adipokine which acts as a key factor for maintenance of energy homeostasis in central and peripheral tissues. Leptin is primarily synthesized by adipocyte, and can

su pokazale da leptin igra ključnu ulogu u debljinom povezanim KVB[26]. Prema posljednjim istraživanjima, leptin sudjeluje u regulaciji metabolizma kardiomiocita direktnim i indirektnim mehanizmima, a ima i proaterogenetski i proupalni učinak[25]. Perzistentna hiperleptinemija pridonosi dijelom lipotoksičnosti u miokardu[27], direktno inducirajući hipertrofiju humanih i životinjskih kardiomiocita[28,29], utječući na progresivne promijene kompozicije miokarda te strukturu ekstracelularnog matriksa i fibrozu[27]. Profibrotski efekt leptina u srcu primarno se manifestira predominacijom sinteze kolagena u odnosu na njegovu degradaciju[30], direktno povećavajući aktivnost matriks metaloproteinaze i ekspresiju mRNA putem aktivnosti janus-kinaze, ekstracelularne signalne kinaze i signalnih molekula[15].

Adiponektin je adipokin sintetiziran u masnom tkivu, čiji se receptori nalaze u skeletnim mišićima (AdipoR1) i u jetri (AdipoR2). APPL1 je adaptorna molekula koja je u interakciji s intracelularnim fragmntom AdipoR1 receptora te zbog proširene ekspresije APPL1 u brojnim tkivima, ostvaruju se brojni učinci adiponektina u različitim tkivima[31]. Adiponektin ima veliku kliničku važnost obzirom na antidijabetični, antiinflamatorni i antiaterogeni učinak. Koncentracija adiponektina je obrnuto proporcionalna stupnju debljine, dislipidemiji i KVB[32]. Osim pozitivnog učinka na djelovanje inzulina, adiponektin djeluje kao protektor u aterosklerotskim procesima djelujući na adhezijske endotelne molekule, transformaciju makrofaga u pjenušave stanice, modulaciju proliferacije glatkih mišićnih stanica i inhibiciju sekrecije TNF-alfa[33]. Prema posljednjim eksperimentalnim i klinički istraživanjima, adiponektin ima značajnu protektivnu ulogu u remodelaciji kardiomiocita i hipertrofiji miokarda. Snižena koncentracija adiponektina aktivira hipertrofični signal djelujući na aktivnost AMPK aktivnost[34], HP-EGF aktivaciju[35] i ROS sustav[36], što snižava adiponektin-posredovanu kardioprotekciju. Zaključno, protuupalni efekt je ključni biološki učinak u kardioprotekciji posredovanoj adiponektinom[19].

Prema svim dostupnim podacima, može se zaključiti da još nije do kraja razjašnjen mehanizam utjecaja sistemske debljine i visceralnog kardijalnog masnog tkiva na poremećaj kardiometabolizma i razvoj histoloških i patofizioloških posljedica kardiomiocita i posljedične kardiomiopatije[4].

Diskusija

Multiple sustavne metaboličke promjene (izmijenjen učinak inzulina, glikotokičnost i lipotoksičnost, povećana aktivnost citokina, intrakardiomiocitni i/ili intersticijski depoziti triglicerida[24], aktivirani vaskularni ROS molekularni sustav[4,36], izmijenjena aktivnost adipokina i osobito povećana aktivnost leptina i snižena koncentracija adiponektina[18]) obilježavaju stanje debljine udruženo sa suviškom ektopičnog kardijalnog masnog tkiva. Ovi multipli triger faktori potiču endotelnu disfunkciju sistemskih, koronarnih i malih intramiokardijalnih arterija[37].

Rezerve miokardnih triglicerida su inertne. One infiltriraju kardiomiocite i utječu na molekularnu strukturu i funkciju[38]. S metaboličke strane, hipertrigliceridemija perzistira kao posljedica povećane beta oksidacije masnih kiselina u mitohondrijima i povećane koncentracije slobodnih masnih kiselina, posljedično povećanoj lipolizi visceralne masti[14]. Međuproizvodi masnih kiselina ubrzavaju prirodne procese propadanja kardiomiocita uzrokujući apoptozu, promjene u strukturi i funkciji njihovih membrana, snižavajući funkcionalnost mitohondrija[39]. S druge strane, mehanički učinak se ostvaruje u obliku tzv. pseudoinfiltrativnog učinka, nakuplja-

also be produced in cardiac tissue. In the heart, its effect are mediated trough leptin receptors, via autocrine and paracrine effects[25]. In most obese individuals, serum leptin levels are increased and correlate with the individual's BMI. Abundant investigations ranging from clinical and animal model studies to in vitro analyses show that leptin plays a pivotal role in obesity-related CVD[26]. According to the latest research, leptin regulates metabolism in cardiomyocytes via direct and indirect mechanisms. It has proatherogenic and proinflammatory effect[23]. Persistant hyperleptinemia contribute in part to lipotoxicity in the heart[27], directly induce hypertrophy in humans and rodent cardiomyocytes[28,29], induce progressive changes in the myocardium composition and structure of the extracellular matrix and fibrosis[27]. Profibrotic effects of leptin in the heart manifest primarily trough the predominance of collagen synthesis over degradation[30], directly increase matrix metalloproteinase activity and mRNA expression via Janus kinase activity, extracellular signal regulated-kinase and signalling mechanisms[15].

Adiponectin is an adipokine produced by adipose tissue with receptors in the skeletal muscles ADIPOR1 and in the liver ADIPOR2. APPL1, an adaptor molecule, interacts with the intracellular fragment of AdipoR1. Ubiquitous expression of APPL1 may reflect widespread relevance of adiponectin signalling in various tissues[31]. Adiponectin is of great clinical significance due to its anti-diabetic, anti-inflammatory and anti-atherogenic properties. High adiponectin levels are inversely correlated with obesity, dyslipidemia and CVD[32]. In addition to its insulin sensitizing effects, adiponectin acts as atherosclerosis protector by modulation of endothelial adhesion molecules, transformation of macrophages into foam cells, modulation of vascular smooth muscle cells proliferation and inhibition of TNF-alpha secretion[33]. According to the latest experimental and clinical research, adiponectin can have an important role in protection against cardiomyocyte remodelling and cardiac hypertrophy. Decreased concentration of adiponectins activates hypertrophic signal in cardiomyocytes, acting on adenosine monophosphate-activated protein kinase activity[34], heparin binding-epidermal growth factor activation[35] and reactive oxygen species[36], which decreases adiponectin-mediated cardioprotection. Generally, anti-inflammation is a key biological action of adiponectin in providing cardiovascular protection[19].

To conclude, it remains unclear how obesity, systemic and ectopic cardiac fat tissue along with disturbed cardiac metabolism locally affect histological and pathophysiological changes in cardiomyocites and consequential cardiomyopathy[4].

Discussion

Multiple systemic metabolic changes (including changed insulin signalling, glyco- and lipotoxicity, increased cytokine activity, intra-myocite and/or interstitial deposition of triglycerides[24], activated vascular reactive oxygen molecule system[4,36], changed adipokines activity and, particularly, increased leptin and decreased adiponectin level[18]) occur in obesity accompanied with excess of ectopic cardiac fat. These multiple factors trigger endothelial dysfunction of systemic, coronary and small intramyocardial arteries[37].

Myocardial triglycerides reserves are inert. They infiltrate cardiomyocytes and affect both their molecular structure and function[38]. Hypertriglyceridemia occurs as a consequence of decreased beta oxidation of fatty acids in mitochondria and increased free fatty acids concentration following increased visceral fat lipolysis[14]. Fatty acid intermediates speed up natural processes of cardiomyocytes deteriora-

njem proizvoda lipolize unutar kardiomiocita. Promjene u krutosti i relaksacijskim mogućnostima nastaju kao rezultat promjena sastava i svojstava miokarda, kao što su intersticijska fibroza i remodeliranje matriksa, HLK[24] i masna infiltracija koje zajedno uzrokuju dijastoličku disfunkciju lijeve klijetke.

Epikardijski i intramiokardijalni adipociti imaju značajnu ulogu, osobito otkako je poznat njihov endokrini učinak te mogućnost molekularnog odgovora na poticajne metaboličke signale što rezultira poremećenom produkcijom adipocitokina.

Zaključak

Ektopično visceralno kardijalno masno tkivo dovodi do:

1) mehaničkih posljedica odlaganja triglicerida i slobodnih masnih kiselina u kardiomiocitima — razvoj pseudoinfiltrativne masne kardiomiopatije;

2) remodeliranja miokardnog matriksa, aktivacije hipertrofičnog i profibrotičkog signala u miokardu s razvojem dijastoličke disfunkcije;

3) metaboličkih promijena kardiomiocita — posljedica lokalnog učinka masti te adipocitokinske disregulacije i upale.

Received: 8th June 2012

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tion, causing apoptosis and changing the structure and function of their membranes and decreasing mitochondria functionality[39]. Apart from metabolic effects, there is also mechanical effect in the form of accumulation of lipolysis products within cardiomyocytes and their pseudoinfiltrative effect. Changes in stiffness and relaxation properties may occur as a result of changes in the composition and material properties of the myocardium, such as interstitial fibrosis and matrix remodelling, LVH[24] or fatty infiltration causing diastolic dysfunction of the left ventricle.

Epicardial and intramyocardial adipocytes also have a significant role, since they were proved to be powerful endocrine cells capable of responding to metabolic cues and transducing signals, which results in disturbed production of adipocytokemokines.

Conclusion

Ectopic visceral cardiac fat leads to:

1) mechanical consequences of depositing triglycerides and free fatty acids in cardiomyocytes — development of pseudoinfiltrative fatty cardiomyopathy;

2) myocardium matrix remodelling, activation of hypertrophic and profibrotic effect in cardiomayocytes and myocardium with diastolic dysfunction development;

3) metabolic changes in cardiomyocytes — consequence of cytokemokine disregulation and inflammation.

Literature

1. Rajsheker S, Manka D, Blomkalns AL, Chatterjee TK, Stoll LL, Weintraub NL. Crosstalk between perivascular adipose tissue and blood vessels. Curr Opin Pharmacol. 2010;10(2):191-6.

2. Juqueira LC, Carneiro J, Kelley RO. Osnove histologije. Zagreb: Školska knjiga; 1999. 126p.

3. Montani JP, Carroll JF, Dwyer TM, Antic V, Yang Z, Dulloo AG. Ectopic fat storage in heart, blood vessels and kidneys in the pathogenesis of cardiovascular diseases. Int J Obes Relat Metab Disord. 2004;28 Suppl 4:S58-65.

4. Gastadelli A, Basta G. Ectopic fat and cardiovascular disease: What is the link? Nutr Metab Cardiovasc Dis. 2010;20(7):481-90.

5. Sironi AM, Pingitore A, Ghione S, De Marchi D, Scanttini B, Positano V, et al. Early hypertension is assotiated with reduced regional cardiac function, insulin resistance, epicardial, and visceral fat. Hypertension. 2008;51:282-8.

6. Wang Z, Nakayama T. Inflammation, a link between obesity and cardiovascular diseases. Mediators Inflamm. 2010;2010:535918

7. Malavazos AE, Di Leo G, Secchi F, Lupo EN, Dogliotti G, Coman C, et al. Relation of echocardiographic epicardial fat thickness and myocardial fat. Am J Cardiol. 2010;105(12): 1931-5.

8. Zhou YT, Graybourn P, Karim A, Shimabukuro M, Higa M, Baetens D, et al. Lipotoxic heart disease in obese rats: implications for human obesity. Proc Natl Acad Sci USA. 2009;97:1784-9.

9. Unger RH, Orci L. Lipoapoptosis: its mechaisms and its diseases. Biochim Biophys Acta. 2002;1585:202-12.

10. Sacks HS, Fain JN. Human epicardial adipose tissue: a review. Am Heart J. 2007;153:907-17.

11. Iacobellis G, Corradi G, Sharma AM. Epicardial adipose tissue: anatomic, biomolecular and clinical relationshipwith the heart. Nat Clin Pract Cardiovasc Med. 2005;2:536-43.

12. Iacobellis G, Sharna AM. Epicardial adipose tissue as a new cardio-metabolic risk marker and potential therapeutic target in the metabolic syndrome. Curr Pharm Des. 2007;13:2180-4.

13. Iacobellis G, Gao YJ, Sharma AM. Do cardiac and perivascular adipose tissue play a role in atherosclerosis? Curr Diab Rep. 2008;8:20-4.

14. Van der Meer RW, Rijzewijk LJ, Diamant M, Hammer S, Schär M, Bax JJ, et al. The ageing male heart: myocardial triglyceride content as independent predictor of diastolic function. European Heart J. 2008;29:1516-22.

15. Schram K, Sweeney G. Implications of myocardial matrix remodeling by adipokines in obesity-related heart failure. Trends Cardiovasc Med. 2008;18(6):199-205.

16. Lindsey M.L, Spinale F.G. Targeting matrix remodelin in cardiac hypertrophy and heart failure. Drug Discovery Today: Therapeutic Strategies. 2005;2:253-8.

17. Kotsis V, Stabouli S, Papakatsika S, Rizos Z, Parati G. Mechanisms of obesity-induced hypertension. Hypertens Res. 2010;33(5):386-93.

18. Selthofer-Relatić K, Radić R, Včev A, Steiner R, Vizjak V, Šram M, et al. Low adiponectin serum level-protective effect on the left ventricular wall thicknes. Coll Antropol. 2011;35:787-91.

19. Okamoto Y. Adiponectin Provides Cardiovascular protection in metabolic syndrome. Cardiol Res Pract. 2011;23:313179.

20. Selthofer-Relatić K, Radić R, Vizjak V, Včev A, Kosović P, Bošnjak I, et al. Hyperleptinemia-non-haemodynamic risk factor for the left ventricular hypertrophy development in hypertensive overweight females. Coll Antropol. 2008;32(3):681-5.

21. Vizjak V, Radić R, Selthofer-Relatić K, Ćurković M, Ištvanić T, Buljubašić D. Plasma leptin in obesity related hypertension. Periodicum Biologorum. 2011;113(3):373-6.

22. Stanley WC, Recchia FA, Lopaschuk GD. Myocardial substrate metabolism in the normal and failing heart. Physiol Rev. 2005;85:1093-129.

23. Rijzewijk LJ, Van der Meer RW, Smit JW, Diamant M, Bax JJ, Hammer S, et al. Myocardial steatosis is an independent predictor of diastolic dysfunction in type 2 diabetes mellitus. J Am Coll Cardiol. 2008;52:1793-9.

24. Von Bibra H. Diastolic dysunfction in diabetes and the metabolic syndrome: promising potential for diagnosis and prognosis. Diabetologia. 2010;53:1033-45.

25. S. Shultze PC, Kratzsch J. Leptin as a new diagnostic tool in chronic heart failure. Clin Chim Acta.2005;1:362:1-11.

26. Hou N, Lou JD. Leptin and cardiovascular diseases Clin Exp Pharmacol Physiol. 2011;38(12):905-13.

27. Dale AE, Sweeney G. Modulation of the cardiovascular system by leptin. Biochemie. 2012; Apr 2. [Epub ahead of print]

28. Rajapurohitam V, Javadov S, Purdham DM, Kirshenbaum LA, Karmazyn M. An autocrine role for leptin in mediating the cardiomyocyte hypertrophyc effects of angiotensin II and endothelin-1. J Moll Cell Cardiol. 2006;41:265-74.

29. Rajapurohitam V, Gan XT, Kirshenbaum LA, Karmazyn M. The obesity-associated peptide leptin induces hypertrophy in neonatal rat ventricular myocytes. Circ Res. 2003;93:277-9.

30. Zibadi S, Cordova F, Slack EH, Wattson RR, Larson DF. Leptin's regulation of obesity-induced cardiac extracellular matrix remodeling. Cardiovasc Toxicol. 2011;11(4):325-33.

31. Wang ZV, Scherer PE. Adiponectin, cardiovascular function, and hypertension. Hypertension. 2008;51(1):8-14.

32. Trujillo ME, Scherer PE. Adiponectin-journey from an adipocyte secretory protein to biomarker of the metabolic syndrome. J Intern Med. 2005;257:167-75.

33. Arita Y, Kihara S, Ouchi N, Maeda K, Kuriyama H, Okamoto, et al. Adipocyte-derived plasma protein adiponectin acts as a platelet-derived growth factor-Bb-binding protein and regulates growth factor-induced common postreceptor signal in vascular smooth muscle celll. Circulation. 2002;105:2893-8.

34. Shibata R, Ouchi N, Ito M, Kihara S, Shiojima I, Pimentel DR, et al. Adiponectin-mediated modulation of hypertrophic signals in the heart. Nature Medicine. 2004;10(12):1384-9.

35. Liao Y, Xuan W, Zhao J, Bin J, Zhao H, Asakura M, et al. Antihypertrophic effect of adiponectin on cardiomyocytes are associated with the inhibition of heparin binding epidermal growth factor signalling. Biochem Biophys Res Commun. 2010;393(3):519-25.

36. Essick EE, Ouchi N, Wilson RM, Ohashi K, Ghobrial J, Shibata R, et al. Adiponectin mediates cardioprotection in oxidative stress-induced cardiac myocyte remodeling. Am J Physiol Heart Circ Physiol. 2011:301(3):H984-93.

37. Widlansky ME, Gokce N, Keaney JF Jr, Vita JA. The clinical implications of endothelial dysfunction. J AM Coll Cardioll. 2003;42:1149-60.

38. Schafer J. Lipotoxicity: when tissue overeat. Curr Opin Lipidol. 2003:14;281-287.

39. Murray AJ, Anderson RE, Watson GC, Radda GK, Clake K. Uncoupling proteins in human heart. Lancet. 2004;364:1786-8.

ISBN 978-953-57168-0-8

Tisak: STEGA TISAK d.o.o.

Prodaja: ŠKOLSKA KNJIGA d.d.