Bubrežna bolest i pretilost

Kidney Disease and Obesity

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SAŽETAK: Pretilost je globalni problem i ozbiljna kronična bolest. Kronične nezarazne bolesti, među kojima je i pretilost postale su vodeći uzrok pobola i smrtnosti u cijelom svijetu. Pretilost je udružena s različitim poremećajima i bolestima koje izravno utječu na bubrežnu funkciju. To se prije svega odnosi na šećernu bolest, visoki arterijski tlak i metabolički sindrom. Pretilost, bez pridruženih bolesti, pogoduje razvoju kronične bubrežne bolesti (KBB). Pretilost je udružena s različitim bubrežnim bolestima, kao što su glomerulopatije i nefrolitijaza, te utječe na preživljavanje bubrežnog presatka. Metabolički sindrom i šećerna bolest tipa II klasični su čimbenici rizika za razvoj KBB-a i srčanožilne bolesti. Upala je jedna od najvažnijih obilježja KBB-a i pretilosti koja pridonosi razvoju glomeruloskleroze i tubulointersticijske atrofije. Fokalna segmentalna glomeruloskleroza uz glopromerulopatiju udruženu s pretilošću, sa značajnom proteinurijom izravno je povezana s pretilošću. Adipozni bolesnici s IgA nefropatijom imaju lošiju prognozu bolesti.

SUMMARY: Obesity is a global problem and a serious chronic disease. Some non-communicablediseases, includingobesity are among the leadingcauses of morbidity and mortality globally. Obesity is associated with a variety of disorders and diseases that have direct impact on kidney function. This primarily refers to diabetes mellitus, elevated arterial pressure, and metabolic syndrome. Obesity, even without associated diseases, favors development of chronic kidney disease (CKD). Obesity is associated with a number of kidney diseases such as glomerulopathies and nephrolithiasis, and influences kidney graft survival. Metabolic syndrome and diabetes mellitus type 2 are classic risk factors for CKD and cardiovascular disease development. Inflammation is one of the most important CKD and obesity characteristics, contributing to the development of glomerulosclerosis and tubulointerstitial atrophy. Along with glomerulopathy associated with obesity, focal segmental glomerulosclerosis with significant proteinuria is directly related to obesity. Adipose patients with IgA nephropathy have poorer disease prognosis.

KLJUČNE RIJEČI: pretilost, kronična bubrežna bolest, glomerulopatija udružena s pretilošću.

KEYWORDS: obesity, chronic kidney disease, glomerulopathy associated with obesity.

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Pretilost je kronična bolest, a, s obzirom na učestalost, u današnjemu svijetu, jedan je od vodećih javnozdravstvenih problema. Zbog promjena u načinu prehrane i smanjenju tjelesne aktivnosti, broj se oboljelih stalno povećava. Pretilost i metabolički sindrom često su povezani s konvencionalnim čimbenicima rizika za razvoj srčanožilne bolesti, kao što su arterijska hipertenzija, šećerna bolest tipa 2, dislipidemija, hiperuricemija. Prevencija pretilosti kao čimbenika rizika za razvoj šećerne bolesti i arterijske hipertenzije, uključuje sprječavanje razvoja kronične bubrežne bolesti (KBB). Neovisno

Obesity is a chronic disease with a high prevalence worldwide, thus posing one of the leading public health problems in the world. The number of affected individuals is constantly on rise due to unfavorable modifications in dietary habits and decrease in physical activity. Obesity and metabolic syndrome are frequently associated with conventional risk factors for development of cardiovascular diseases such as arterial hypertension, diabetes mellitus type 2, dyslipidemia, and hyperuricemia. Preventing obesity as a risk factor for diabetes mellitus and arterial hypertension also means prevention of

o drugim čimbenicima, pretilost je čimbenik rizika za razvoj KBB-a[1,2].

Glomerulopatija udružena s pretilošću

U izrazito pretilih bolesnika mogu se naći promjene na bubrezima u smislu fokalne segmentalne glomeruloskleroze, odnosno glomerulopatije udružene s pretilošću. Gubitak tjelesne težine povoljno djeluje na ovu bolest[3].

U bubrezima oboljelih od pretilosti mogu se naći različite nespecifične strukturne promjene. Glavno obilježje glomerulopatije udružene s pretilošću jest glomerulomegalija koja se pojavljuje prije pojave znatne proteinurije, odnosno prije KBB-a. Uz glomerulomegaliju, nastaju umnožavanje mezangijskog matriksa, hipertrofija podocita, glomerularna skleroza i proliferacija mezangijskog matriksa[4,5]. Progresija KBB-a u ovom, sekundarnom obliku fokalne segmentalne glomeruloskleroze (FSGS) sporija je od progresije KBB-a u idiopatskim oblicima FSGS-a. Upalni odgovor na početne lezije dovodi do razvoja sekundarne fokalne glomeruloskleroze i progresije KBB-a. Ovakva „hiperfiltracijska teorija" ostavlja brojne dvojbe vezane za činjenicu da svi pretili bolesnici ne obole od bubrežne bolesti i da stupanj pretilosti nije u povezanosti s proširenošću strukturnih promjena glomerula. Metabolički zdravi pretili bolesnici obično ne obole od glomerulopatije udružene s debljinom[6]. Dakle, uz debljinu utjecaj na nastanak i progresiju KBB-a mogli bi imati i neki genski i okolišni čimbenici.

Debljina i kronična upala

Masno je tkivo endokrini organ koji posreduje u patogenetskim mehanizmima koji djeluju na inzulinsku rezistenciju i vaskularnu ozljedu[7,8].

Leptin je, uglavnom proizvod masnoga tkiva. U pretilih je osoba povećana količina leptina, ali i rezistencija na leptin. Receptori za leptin dio su razreda I. citokinskih receptora pa postoji mišljenje da su oni odgovorni za pokretanje upalnoga procesa u bubrezima. Djelovanjem leptina na bubrežne tubule dolazi do povećane reapsorpcije natrija u tubulima i porasta glomerularne filtracije[9]. Glomerularna hiperfiltracija ima utjecaj na inzulin, angiotenzin II i aldosteron. Neravnoteža leptina i adiponektina u vezi je s inzulinskom rezistencijom, srčanožilnom bolešću i glomerularnom ozljedom. Smanjena razina adiponektina posljedica je djelovanja fetuina-A. Znatan gubitak na tjelesnoj težini uzrokuje smanjenje razine leptina i povišenje razine adiponektina te posljedično smanjenje albuminurije[10,11]. U pretilih je bolesnika povišena i razina aldosterona, neovisno o reninsko-angiotenzinskom sustavu. Aktivacija reninsko-angiotenzinsko-aldosteronskog sustava dovodi do razvoja glomerularne hiperfiltracije i porasta reaposrpcije vode i natrija u tubulima, preglomerularne vazodilatacije i posljedične hipertenzije.

Zbog povišene razine aldosterona različitim mehanizmima nastaje ozljeda podocita. Uz centralni tip debljine vezane su inzulinska rezistencija i hiperinzulinemija te veća učestalost nastanka šećerne bolesti. U visceralnom masnom tkivu povećana je proizvodnja interleukina-6, što dovodi do stanja sustavne upale[12].

Pretile osobe imaju poremećaje crijevne mikroflore, što dovodi do otpuštanja upalnih čimbenika iz crijeva, narušavanja crijevne homeostaze i pojačanja upalnog odgovora u bolesnika s KBB-om[13]. Upala u KBB-u izravno djeluje na migraciju i

chronic kidney disease (CKD) development. Obesity is a risk factor for CKD independent of other risk factors[1,2].

Glomerulopathy associated with obesity

Kidney lesions in the form of focal segmental glomerulosclerosis (FSGS) and glomerulopathy associated with obesity are found in very obese patients. Weight loss has favorable effects on this disease[3].

In obese patients, kidneys show various nonspecific structural changes. The main characteristic of glomerulopathy associated with obesity is glomerulomegaly, which precedes the occurrence of pronounced proteinuria, i.e. before CKD. Besides glomerulomegaly, mesangial matrix proliferation, podocyte hypertrophy and glomerulosclerosis are also observed[4,5]. In this secondary form of FSGS, CKD progression follows slower course as compared with CKD progression in idiopathic forms of FSGS. Inflammatory response to initial lesions leads to development of secondary focal glomerulosclerosis and CKD progression. This 'hyperfiltration theory' leaves numerous dilemmas related to the fact that not all obese patients develop kidney disease and that there is no correlation between the degree of obesity and extension of glomerular structural alterations. Metabolically healthy obese individuals generally do not develop glomerulopathy associated with obesity[6]. Accordingly, besides obesity, some genetic and environmental factors may also be involved in the onset and progression of CKD.

Obesity and chronic inflammation

Adipose tissue is an endocrine organ involved in the pathogenic mechanisms that influence insulin resistance and vascular injury[7,8].

Leptin is mostly a product of adipose tissue. In obese individuals, both the level of and resistance to leptin are increased. Leptin receptors are members of class I cytokine receptors, thus being considered responsible for triggering inflammatory process in the kidneys. Leptin action on kidney tubules leads to increased tubular sodium reabsorption and increased glomerular filtration[9]. Glomerular hyperfiltration then influences insulin, angiotensin II and aldosterone. The leptin to adiponectin imbalance is associated with insulin resistance, cardiovascular disease, and glomerular injury. Decreased adiponectin level is the result of fetuin-A activity. Significant weight loss leads to leptin level decrease and adiponectin level increase with consequential albuminuria reduction[10,11]. In obese patients, the level of aldosterone is also elevated, independently of the rennin-angiotensin system. Activation of the rennin-angiotensin-aldosterone system results in glomerular hyperfiltration and increased tubular water and sodium reabsorption, pre-glomerular vasodilatation, and consequential hypertension.

Elevation of aldosterone level *via* various mechanisms results in podocyte injury. Central type obesity is associated with insulin resistance and hyperinsulinemia, as well as an increased prevalence of diabetes mellitus. The interleukin-6 production in visceral adipose tissue is increased, leading to the state of systemic inflammation[12].

Obese persons suffer from intestinal microflora impairments that result in the release of inflammatory factors into the intestine, impaired intestinal homeostasis, and increased inflammatory response in patients with CKD[13]. In CKD, in-

aktivaciju imunosnih stanica u masnome tkivu, aktiviraju se i proinflamatroni adipociti. Restrikcijska dijeta, lijekovi i drugi potencijalni načini liječenja debljine trebali bi djelovati na prisutnost i funkciju crijevne flore.

Proučavanje pretilosti dovelo je do povećanog zanimanja za ektopične lipide akumulirane u nemasnome tkivu. Ektopični se lipidi dovode u vezu sa strukturnim i funkcijskim promjenama mezangijskih stanica, podocita i stanica proksimalnih tubula, a time i s razvojem bubrežne bolesti udružene s pretilošću[14]. Novija su istraživanja usmjerena na pronalaženje odgovarajućih metoda koje bi pratile metabolizam ektopičnih lipida i njihov utjecaj na komplikacije u vezi s pretilošću.

U današnjemu svijetu pretilost je znatan problem. Javnozdravstveni sustavi stvorili su različite programe za prevenciju debljine i promociju zdravog načina života. Pretilost je kronična bolest i teško se liječi. Smanjenje tjelesne težine u bolesnika s KBB-om dovodi do smanjenja glomerularne hiperfiltracije i proteinurije, ali istodobno djeluje na arterijsku hipertenziju, poremećaje metabolizma lipida, inzulinsku rezistenciju i upalu[15,16]. Dokazano je da niskokalorijska dijeta uzrokuje smanjenje razine fetuina-A s povišenjem razine adiponektina i do zaustavljanja ozljede podocita.

Uz niskokalorijsku dijetu najveći je problem održavanje smanjene tjelesne težine. Uporaba lijekova – orlistat ili sibutramin u kombinaciji s niskokalorijskom dijetom i pojačanom tjelesnom aktivnošću može dovesti do znatnog broja nuspojava, posebice u bolesnika s povećanim srčanožilnim rizikom. Bolesnici podvrgnuti operacijskim zahvatima radi liječenja pretilosti mogu popraviti bubrežnu funkciju, ali i smanjiti progresiju već postojeće KBB. Iako kirurški pristup smanjuje rizik od razvoja bolesti udruženih s pretilošću, sam je operacijski zahvat povezan je s povećanim rizikom od akutnoga bubrežnog zatajenja[17,18].

U liječenju pretilosti u bolesnika s KBB-om svoje mjesto imaju lijekovi koji djeluju na reninsko-angiotenzinsko-aldosteronski sustav.

Inhibitori reninsko-angiotenzinski sustava smanjuju intraglomerularni tlak, a time i ozljedu podocita. Hiperaldosteronizam pogoduje razvoju hiperfiltracije, ozljedi podocita i upalnom odgovoru, tako da inhibitori aldosterona imaju renoprotektivni učinak. Uporaba inhibitora aldosterona sprječava fibrozu uzrokovanu aldosteronom. Inhibitori aldosterona s ACE inhibitorima ili blokatorima angiotenzinskih II receptora djeluju na smanjenje proteinurije, ali ne poboljšavaju bubrežnu funkciju. U eksperimentalnim istraživanjima traže se načini djelovanja na stanični metabolizam lipida jer smanjeno nakupljanje lipida djeluje na smanjenje glomerularne ozljede[19].

Unatoč brojnim istraživanjima, još nije prepoznat ključni čimbenik (proces) koji utječe na bubrežnu funkciju u oboljelih od pretilosti.

Cilj daljnjih istraživanja jest pronalaženje novih, nefarmakoloških postupaka koji mogu poboljšati bubrežnu funkciju. U dosadašnjim epidemiološkim istraživanjima pokazane su bitne spolne i etničke razlike u incidenciji i prevalenciji debljine, KBB-a i završnoga stupnja kroničnoga bubrežnog zatajenja, što se može objasniti genskim i okolišnim čimbenicima.

Potrebna su i dodatna objašnjenja u vezi s djelovanjem probiotika, postbiotika i dijete na upalu i metaboličke poremećaje, kao i istraživanja povezanosti apneje u spavanju, hipoksije i

flammation acts directly on the migration and activation of immune cells in adipose tissue, along with proinflammatory adipocyte activation. The presence and function of intestinal flora are to be regulated by restriction diet, drugs and other potential modes of obesity treatment.

Obesity research has instigated interest in ectopic lipids accumulated in non-adipose tissue. Ectopic lipids have been related to structural and functional changes in mesangial cells, podocytes and proximal tubular cells, and thus to the development of kidney disease associated with obesity[14]. Recent studies have been focused on developing appropriate methods to monitor ectopic lipid metabolism and their influence on obesity complications.

Obesity poses a major problem in the world today. Public health systems have created various programs for obesity prevention and healthy lifestyle promotion. Obesity is a chronic disease that is difficult to treat. In CKD patients, weight loss results in decreased glomerular hyperfiltration and proteinuria, while acting favorably on arterial hypertension, lipid metabolism impairments, insulin resistance, and inflammation[15,16]. Low-calorie diet has been demonstrated to reduce fetuin-A level, along with increasing the level of adiponectin and preventing podocyte injury.

With low-calorie diet, a major problem is maintaining body weight reduction. Using drugs such as orlistat or sibutramine in combination with low-calorie diet and enhanced physical activity may lead to a number of complications, in particular in patients at a high cardiovascular risk. In patients undergoing operative procedures for the treatment of obesity, it can improve their kidney function and slow down progression of the existing CKD. Although surgical approach reduces the risk of diseases associated with obesity, the procedure itself is associated with an increased risk of acute renal failure[17,18].

Drugs acting on the rennin-angiotensin-aldosterone system can also be used in the treatment of obesity in CKD patients.

Inhibitors of the rennin-angiotensin system decrease intraglomerular pressure and thus podocyte injury. Since hyperaldosteronism favors development of hyperfiltration, podocyte injury and inflammatory response, aldosterone inhibitors have a renoprotective effect. Aldosterone induced fibrosis is suppressed by aldosterone inhibitors. Aldosterone inhibitors with angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers result in proteinuria reduction but do not improve kidney function. There are experimental studies investigating the potential modes of acting on the intracellular lipid metabolism because reduced lipid accumulation decreases glomerular injury[19].

In spite of numerous studies, the key factor (process) influencing kidney function in obese patients has not yet been identified.

The aim of future research is establishment of novel nonpharmacological procedures to improve kidney function. Previous epidemiological studies have demonstrated significant gender and ethnic differences in the incidence and prevalence of obesity, CKD and end-stage chronic renal failure, which can be explained by genetic and environmental factors.

Additional explanations are needed concerning the action of probiotics, postbiotics and diet on inflammation and metabolic impairments, and so are studies of the association

KBB-a[20]. Pristup liječenju ovakvih bolesnika mora biti individualan.

Budući da je bolje spriječiti nego liječiti, na prvo mjesto treba staviti promjene životnoga stila u djece koje će prevenirati razvoj pretilosti.

of sleep apnea, hypoxia and CKD[20]. These patients require individualized therapeutic approach.

As prevention is better than cure, favorable lifestyle modifications in children to prevent development of obesity should come first.

LITERATURE

1. Aune D, Sen A, Prasad M, Norat T, Janszky I, Tonstad S, et al. BMI and all cause mortality: systematic review and non-linear dose-response meta-analysis of 230 cohort studies with 3.74 million deaths among 30.3 million participants. BMJ. 2016 May 4;353:i2156. https://doi.org/10.1136/bmj.i2156
2. Kramer H, Luke A, Bidani A, Cao G, Cooper R, McGee D. Obesity and prevalent and incident CKD: the Hypertension Detection and Follow-Up Program. Am J Kidney Dis. 2005;46:587-94. https://doi.org/10.1053/j.ajkd.2005.06.007
3. Kambham N, Markowitz GS, Valeri AM, Lin J, D'Agati VD. Obesity-related glomerulopathy: an emerging epidemic. Kidney Int. 2001;59(4):1498-509. https://doi.org/10.1046/j.1523-1755.2001.0590041498.x
4. Danilewicz M, Wagrowska-Danielwicz M. Morphometric and immunohistochemical insight into focal segmental glomerulosclerosis in obese and non-obese patients. Nefrologia. 2009;29:35-41. https://doi.org/10.3265/Nefrologia.2009.29.1.35.1.en.full.pdf
5. Darouich S, Goucha R, Jaafoura MH, Zekri S, Ben Maiz H, Kheder A. Clinicopathological characteristics of obesity-associated focal segmental glomerulosclerosis. Ultrastruct Pathol. 2011;35(4):176-82. https://doi.org/10.3109/01913123.2011.584657
6. Hashimoto Y, Tanaka M, Okada H, Senmaru T, Hamaguchi M, Asano M, et al. Metabolically healthy obesity and risk of incident CKD. Clin J Am Soc Nephrol. 2015;10:578-83. https://doi.org/10.2215/CJN.08980914
7. Hutley L, Prins JB. Fat as an endocrine organ: relationship to the metabolic syndrome. Am J Med Sci. 2005;330:280-9. https://doi.org/10.1097/00000441-200512000-00005
8. Fontana L, Eagon JC, Trujillo ME, Scherer PE, Klein S. Visceral fat adipokine secretion is associated with systemic inflammation in obese humans. Diabetes. 2007 Apr;56(4):1010-3. https://doi.org/10.2337/db06-1656
9. Declèves AE, Sharma K. Obesity and kidney disease: differential effects of obesity on adipose tissue and kidney inflammation and fibrosis. Curr Opin Nephrol Hypertens. 2015;24:28-36. https://doi.org/10.1097/MNH.0000000000000087
10. Sharma K, Ramachandrarao S, Qiu G, Usui HK, Zhu Y, Dunn SR, et al. Adiponectin regulates albuminuria and podocyte function in mice. J Clin Invest. 2008;118:1645-56. https://doi.org/10.1172/JCI32691
11. Ix JH, Sharma K. Mechanisms linking obesity, chronic kidney disease and fatty liver disease: the roles of fetuin-A, adiponectin, and AMPK. J Am Soc Nephrol. 2010;21:406-12. https://doi.org/10.1681/ASN.2009080820
12. Elsayed EF, Sarnak MJ, Tighiouart H, Griffith JL, Kurth T, Salem DN, et al. Waist-to-hip ratio and body mass index as risk factors for cardiovascular events in CKD. Am J Kidney Dis. 2008 Jul;52(1):49-57. https://doi.org/10.1053/j.ajkd.2008.04.002
13. Anders HJ, Andersen K, Stecher B. The intestinal microbiota, a leaky gut, and abnormal immunity in kidney disease. Kidney Int. 2013;83(6):1010-6. https://doi.org/10.1038/ki.2012.440
14. de Vries AP, Ruggenenti P, Ruan XZ, Praga M, Cruzado JM, Bajema IM, et al; ERA-EDTAWorking Group Diabesity. Fatty kidney: emerging role of ectopic lipid in obesity-related renal disease. Lancet Diabetes Endocrinol. 2014;2:417-26. https://doi.org/10.1016/S2213-8587(14)70065-8
15. Afshinnia F, Wilt TJ, Duval S, Esmaeili A, Ibrahim HN. Weight loss and proteinuria: systematic review of clinical trials and comparative cohorts. Nephrol Dial Transplant. 2010;25:1173-83. https://doi.org/10.1093/ndt/gfp640
16. Ray Krishnamurthy VM, Wei G, Baird BC, Murtaugh M, Chonchol MB, Raphael KL, et al. High dietary fiber intake is associated with decreased inflammation and all-cause mortality in patients with chronic kidney disease. Kidney Int. 2012 Feb;81(3):300-6. https://doi.org/10.1038/ki.2011.355
17. Serra A, Granada ML, Romero R, Bayés B, Cantón A, Bonet J, et al. The effect of bariatric surgery on adipocytokines, renal parameters and other cardiovascular risk factors in severe and very severe obesity: 1-year follow-up. Clin Nutr. 2006;25:400-8. https://doi.org/10.1016/j.clnu.2005.11.014
18. Chang AR, Chen Y, Still C, Wood GC, Kirchner HL, Lewis M, et al. Bariatric surgery is associated with improvement in kidney outcomes. Kidney Int. 2016;90:164-71. https://doi.org/10.1016/j.kint.2016.02.039
19. Chagnac A, Weinstein T, Herman M, Hirsh J, Gafter U, Ori Y. The effects of weight loss on renal function in patients with severe obesity. J Am Soc Nephrol. 2003;14:1480-6. https://doi.org/10.1097/01.ASN.0000068462.38661.89
20. Câmara NO, Iseki K, Kramer H, Liu ZH, Sharma K. Kidney disease and obesity: epidemiology, mechanisms and treatment. Nat Rev Nephrol. 2017;13:181-90. https://doi.org/10.1038/nrneph.2016.191