Multipli mehanizmi bubrežne bolesti vezane za pretilost

Multiple obesity related mechanisms of kidney disease

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SAŽETAK: Posljednjih desetak godina svjedoci smo da je u središtu medicinske zbilje različitih struka interdisciplinarnost, dominantno gledajući iz perspektive vaskularnoga zdravlja, a zbog razvoja molekularne fiziologije i genetike, što omogućuje translacijski pristup ne samo zbrinjavanja bolesnika nego i prevencije bolesti. Aktualnost problema debljine i uloge bubrega u smanjenju kardiovaskularnog rizika očituje se osnivanjem *The Council on Kidney in Cardiovascular Disease*, u sklopu *American Heart Association* koji pristupa problemu pretilosti kao dijelu translacijske medicine. Rano prepoznavanje problema pretilosti vodi prema smanjivanju posljedica bolesti ne samo bubrega nego i cjelokupnoga kardiovaskularnog sustava uz nastavak liječenja interaktivnim pristupom u kontinuitetu od dječje do zdravstvene zaštite odrasle dobi. Bitno je promijeniti pristup sagledavanju problema vezanih za pretilost, posebice stoga što su masne stanice hormonski živo aktivno tkivo koje luči brojne citokine koji stimuliraju angiogenezu uzrokujući sustavno upalno zbivanje.

SUMMARY: In the last decade, we have witnessed a tendency of various medical professions to focus on an interdisciplinary approach, predominantly from the aspect of vascular health and based on advances in molecular physiology and genetics offering a translational approach not only in patient management but also for prevention of disease. The topical issue of obesity and the role of kidney in cardiovascular risk reduction have manifested through establishment of the Council on Kidney in Cardiovascular Disease at the American Heart Association to tackle the issue of obesity as part of translational medicine. Early recognition of the problem of obesity leads to reducing the sequels of not only kidney disease but also of the entire cardiovascular system, along with continuing treatment with interactive approach from pediatric through adult health care. It is crucial to change approach to the problem of obesity, especially because adipose cells are a hormonally active tissue secreting numerous cytokines that stimulate angiogenesis, thus causing systemic inflammatory event.

KLJUČNE RIJEČI: pretilost, kardiovaskularni rizik, translacijska medicina.

KEYWORDS: obesity, cardiovascular risk, translational medicine.

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Dobitnik Nobelove nagrade za fiziologiju 2016. godine jest istraživač *Yoshinori Ohsumi* koji je otkrio mehanizam autofagije i gene koji kontroliraju bitne fiziološke funkcije degradacije i obnove staničnih komponenti uzrokovane različitim načinima oštećenja stanica (npr. zbog infekcije ili stresa)[1]. Mehanizam autofagije od iznimne je važnosti u svakodnevnom smanjenju negativnih posljedica starenja, a važan je i za staničnu diferencijaciju[2]. Neadekvatan mehanizam autofagije povezuje se s brojnim različitim bolestima kao što su Parkinsonova bolest, šećerna bolest tipa 2, razvoj tumorskih bolesti i brojnim ostalim poremećajima koji se pojavljuju vezani za preuranjeno starenje[3]. U

In 2016, the Nobel Physiology Prize winner was Yoshinori Ohsumi, a researcher, for discovering the mechanism of autophagy and the genes regulating the substantial physiologic functions of degradation and recycling of cellular components induced by different ways of cell damage (e.g., infection or stress)[1]. The mechanism of autophagy is of utmost importance in reducing negative consequences of aging on a daily basis, and is relevant for cell differentiation[2]. Inappropriate mechanism of autophagy has been associated with a variety of diseases such as Parkinson's disease, diabetes mellitus type 2, tumor disease development, and many other disorders related to premature aging[3]. The

eksperimentalnim su istraživanjima opisani mogući načini djelovanja na stanični metabolizam lipida jer smanjeno nakupljanje lipida djeluje na smanjenje glomerularne ozljede[4]. Razumljivo je da su htijenja moderne medicine usmjerena na razvoj potencijalnih lijekova koji će utjecati na mehanizam autofagije i smanjenja ektopičnog gomilanja masnoga tkiva, uspostavljajući ravnotežu na staničnoj razini, odnosno razini lizosoma i mitohondrija[5].

Iako se na prvi pogled sve čini vrlo jednostavno, pojam pretilosti mnogo je kompleksniji problem jer je debljina stanje kroničnoga upalnog odgovora[6]. Neravnoteža leptina i adiponektina osnovni je čimbenik koji je povezan s inzulinskom rezistencijom, srčanožilnom bolešću i glomerularnom ozljedom. Receptor za leptin pretežito se nalazi u bubrežnoj meduli, a pripada obitelji klase I citokinskih receptora koji je povezan s upalnim poremećajem uz pretilost. Adipozno visceralno tkivo proizvodi velike količine interleukina-6, čime se potkrepljuje sveobuhvatna teorija debljine kao stanja sustavnoga upalnog odgovora[7].

Daljnje obilježje pretilosti jesu hipoadiponektinemija, hiperleptinemija i hiperaldosteronizam. Hipoadiponektinemija je regulirana razinom glikoproteina, fetuin-A, koji se sintetizira u jetri, a povezan je s razvojem inzulinske rezistencije, srčanožilnim bolestima i ozljedom glomerula. Hiperleptinemija povisuje tubularnu reapsorpciju soli, dok hiperaldosteronizam djeluje dvojnim putem, bilo uzrokujući glomerularnu hiperfiltraciju (slično djelovanju leptina) bilo izravnom ozljedom podocita zbog nastanka reaktivnih dušičnih spojeva. Sljedeća mogućnost oštećenja vaskulature (ne samo) bubrega jest spoznaja da je pretilost karakterizirana povišenim kalorijskim unosom uz sniženu razinu adiponektina koji snizuje aktivnost „senzora" koji se nalazi u jetrenim stanicama i podocitima (5'-*AMP activated protein kinase*) uzrokujući albuminuriju.

Osobitost poremećaja vezanih za pretilost jest i mehanizam inzulinske rezistencije, izražen u šećernoj bolesti tipa 2, starenju i lipodistrofiji te ektopična akumulacija masnoća koja pridonosi oštećenju organa u kontekstu metaboličkih bolesti, upućujući na to da bi bubrežna bolest vezana z pretilost mogla biti shvaćena kao stanje lipodistrofije, odnosno sustavnih bolesti nakupljanja[8]. Posebnost se očituje u gubitku „bijeloga" masnog tkiva i dislipidemiji uz već navedenu akumulaciju lipida na ektopičnim mjestima[8]. Uz navedeno ektopično nakupljanje masnoća u bubregu dolazi do gomilanja oksidativnoga stresa, što zajedno uzrokuje preuranjeno starenje[9]. Učinak povišene razine oksidativnoga stresa u adipoznome tkivu nastaje zbog smanjenja glutationa koji inhibira preadipocitnu diferencijaciju. Patogenetsku ulogu u povišenome oksidativnom stresu ima asimetrični dimetilarginin (ADMA) koji je endogeni inhibitor dušičnog oksida (NOS). ADMA se razlaže djelovanjem enzima dimetilarginindimetilaminohidrolaze (DDAH) a dokazano je da adipociti proizvode ADMA i DDAH tipa 1 i 2, što uzrokuje poremećeno sazrijevanje, a ne samo gomilanja masnoga tkiva[6].

Osnovni je poremećaj narušena ravnoteža, a taj mehanizam narušene ravnoteže između tjelesne težine i kompozicije tijela danas je prepoznat kao stanje povišenoga upalnog stanja organizma koje utječe i na telomere. Kada govorimo o telomerama, potrebno je navesti da su telomere specijalizirane DNA-proteinske strukture na kraju eukariotičnih kromosoma i markeri su biološke starosti. Oštećenjem telomera ubrzava se starenje[10]. Dokazano je da su kraće telomere udružene s

potential mechanisms influencing cellular lipid metabolism have been described in experimental researches, indicating that decreased lipid accumulation results in lower glomerular injury[4]. It is quite understandable that modern medicine tends to develop drugs with a potential to influence the mechanism of autophagy and reduction of ectopic adipose tissue accumulation, thus resuming balance at the cellular level, i.e. at the lysosomal and mitochondrial level[5].

Although this all may seem quite simple at the first sight, obesity is a much more complex issue because obesity is a state of chronic inflammatory response[6]. The leptin and adiponectin imbalance is the main factor associated with insulin resistance, cardiovascular disease, and glomerular injury. Leptin receptor is found predominantly in renal medulla and belongs to the family of class I cytokine receptors associated with inflammatory response in obesity. Visceral adipose tissue produces large amounts of interleukin-6, supporting the comprehensive theory on obesity as a state of systemic inflammatory response[7].

Other features of obesity include hypoadiponectinemia, hyperleptinemia and hyperaldosteronism. Hypoadiponectinemia is regulated by the level of fetuin-A, a glycoprotein synthesized in the liver and associated with development of insulin resistance, cardiovascular disease and glomerular injury. Hyperleptinemia increases tubular salt reabsorption, whereas hyperaldosteronism exerts dual action, either by inducing glomerular hyperfiltration (similar to leptin action) or by direct podocyte injury due to the formation of nitrogen reactive species. Another potential kidney (not exclusively) vascular damage implies that obesity is characterized by increased calorie intake along with a decreased level of adiponectin, which reduces the activity of 'energy sensor' (5'AMP activated protein kinase) found in hepatocytes and podocytes, thus causing albuminuria.

Furthermore, the impairments related to obesity are characterized by the mechanism of insulin resistance that is pronounced in diabetes mellitus type 2, aging and lipodystrophy, and by ectopic fat accumulation that contributes to organ damage in metabolic diseases. Such a scenario suggests that the obesity related kidney disease might be considered as a state of lipodystrophy, i.e. systemic storage disorder[8]. It is characterized by loss of 'white' adipose tissue and dyslipidemia, along with the mentioned lipid accumulation at ectopic sites[8]. This ectopic fat storage in the kidney is accompanied by increased oxidative stress, which together result in premature aging[9]. The effect of increased oxidative stress on adipose tissue occurs due to the reduced level of glutathione, which inhibits pre-adipocyte differentiation. The pathogenic role in enhanced oxidative stress is played by asymmetric dimethylarginine (ADMA), an endogenous inhibitor of nitric oxide synthase (NOS). ADMA is degraded by the enzyme dimethylarginine dimethylaminohydrolase (DDAH). Adipocytes have been demonstrated to produce ADMA and DDAH type 1 and 2, resulting not only in adipose tissue accumulation but also in impaired maturation[6].

Imbalance is the basic impairment. This mechanism of imbalance between body weight and body composition has been recognized as a state of increased inflammatory state of the body, which also influences telomeres. Considering telomeres, it should be noted that telomeres are specific DNA-protein structures at the end of the eukaryotic chromosomes and are markers of biologic aging. The aging process is ac-

povišenim indeksom tjelesne mase, sklonošću pretilosti, povišenim omjerom struk/bok i povišenom razinom visceralne masti. Mnoge metaboličke komponentne debljine upravo uzrokuju disfunkciju rada bubrega (i drugih organa) zbog ubrzanoga procesa starenja[10].

Stoga je bitno navesti da povezanost lipidnoga poremećenog metabolizma, inzulinske rezistencije i aktivacija upalnoga procesa uzrokuje razvoja glomerulopatije povezane s pretilošću i razvoja ne samo bubrežne nego i srčane i vaskularne bolesti, a osnovica koja sve povezuje jest mehanizam autofagije[11].

Translacijski mehanizmi

Epigenetika u razvoju bubrežnih bolesti i pretilosti te uskog međudjelovanja procesa kontrole ekspresije gena i utjecaja fenotipa na postojeću gensku strukturu (DNA) navodi se kao sve važniji čimbenik nastanka bolesti[12]. Genski čimbenici u međudjelovanju s čimbenicima iz okoliša od najranije dobi dovode do predispozicije za bubrežne bolesti, što se može povezati sa češćom pojavnošću prehipertenzije povezane s pretilošću[12]. Epigenetske promjene uključuju metilaciju DNA i modifikaciju histona u međudjelovanju stabilnog genoma i promjenljivih okolišnih čimbenika. Transformirajući faktor rasta beta (TGFß) glavni je posrednik ubrzanoga starenja, odnosno fibroziranja bubrega, koji stimulira nakupljanje ekstracelularnog matriksa, čime se narušava normalan rad bubrega. Povišena razina TGFß-a nalazi se u stanjima inzulinske rezistencije i pretilosti, a dobro je poznato da leptin stimulira proliferaciju TGFß-a u endotelnim stanicama glomerula[13].

Povezivanjem međudjelovanja svih navedenih čimbenika potencijalno se otvara novo terapijsko mjesto djelovanja prevencije razvoja ne samo bubrežnih nego i kardioloških bolesti ako se stabiliziraju struktura mitohondrija i mehanizam autofagije.

Mjere koje mogu utjecati na smanjenje problema pretilosti

Koliko je aktualan problem liječenja pretilosti u 2017. godini pokazuje važnost koja se pridaje problemu na globalnoj razini jer je debljina bolest 21. stoljeća. Lijekovi koji se primjenjuju za liječenje uključuju one koji suprimiraju têk i inhibitore lipaza te one koji djeluju na reninsko-angiotenzinsko-aldosteronski sustav. Svakako je najvažniji način promjena životnoga stila s individualno usmjerenim nutricijskim režimom prehrane, psihološkom potporom, uz mjere tjelesne aktivnosti.

Dokazano je da unos samo 16 grama žitarica na dan (*Dietary Guidelines for Americans*, AHA, 2016.) kroz određeno razdoblje može dovesti do smanjenja rizika mortaliteta za 7 %, smanjenja srčanožilnih bolesti i smrti vezanih uz njih za 9 %, kao i smanjenja smrti vezanih za tumore za 5 %. Ako se unos žitarica poveća na 48 grama na dan, moguće je smanjiti smrtnost za 20 %, kardiovaskularne bolesti za 25 % te smanjiti smrtnosti vezanu uz tumore za 14 %. Način na koji se mogu objasniti navedene činjenice važne za prehranu i način života leži u dinamičnom međudjelovanju genetike i epigenetike, što je povezano sa složenim procesom starenja[12]. Najvažnije karakteristike preuranjenog starenja stanica i tkiva jesu snižena mogućnost metilacije (hipometilacija) zbog ograničenja u prehrani koja je bogata metilnim skupinama (folati, metionin, biotin, kolin te vitamini B2, B6 i B12). Manjak unosa hrane

celerated by telomere damage[10]. Short telomeres have been demonstrated to be associated with elevated body mass index, proneness to obesity, increased waist-to-hip ratio, and increased level of visceral fat. Indeed, many metabolic components of obesity cause dysfunction of the kidney (and other organs) due to accelerated aging process[10].

Accordingly, it should be emphasized that the synergistic action of impaired lipid metabolism, insulin resistance and inflammatory process activation leads to development of glomerulopathy associated with obesity, as well as to renal and cardiovascular diseases, these all being underlain by the mechanism of autophagy[11].

Translational mechanisms

Epigenetics has been depicted as an ever more relevant factor of disease onset in the development of kidney diseases and obesity, including close interplay of the gene expression regulation and phenotype effect on the existing gene structure (DNA)[12]. The interaction of gene factors and environmental factors from the youngest age leads to predisposition to kidney disease, which can be related to the growing prevalence of prehypertension associated with obesity[12]. Epigenetic alterations include DNA methylation and histone modification through the interplay of stable genome and variable environmental factors. The transforming growth factor beta (TGFβ) is the main mediator of accelerated aging, i.e. kidney fibrozation, which stimulates accumulation of extracellular matrix, thus interfering with normal kidney function. Elevated TGFβ level is found in the states of insulin resistance and obesity, while leptin is known to stimulate TGFβ proliferation in glomerular endothelial cells[13].

Linking the interactions of all the factors mentioned above bears the potential of opening a new therapeutic site of acting to prevent development of not only kidney but also cardiologic diseases if mitochondrial structure and the mechanism of autophagy are properly stabilized.

Measures that may reduce the problem of obesity

The topical issue of obesity management in 2017 is best illustrated by the importance attached to this problem worldwide, as obesity is a disease of the 21st century. Drugs used in the treatment of obesity include appetite suppressants, lipase inhibitors, and those acting on the renin-angiotensin-aldosterone system. However, most important is lifestyle modification with individually focused dietary regimen, psychological support and physical activity.

Daily intake of only 16 grams of cereals (Dietary Guidelines for Americans, AHA, 2016) over a certain period has been demonstrated to reduce the mortality risk by 7 %, the risk of cardiovascular disease and related death by 9 %, and the risk of tumor death by 5 %. If the intake of cereals is increased to 48 grams daily, the risk of mortality can be decreased by 20 %, of cardiovascular disease by 25 % and tumor mortality by 14 %. These facts important for dietary habits and lifestyle can be explained by the dynamic interplay of genetics and epigenetics, which is related to the complex aging process[12]. The most relevant characteristic of premature cell and tissue aging is reduced methylation (hypomethylation) due to restricted dietary intake of foods rich in methyl groups (folate,

bogate metilnim skupinama u dječjoj dobi ima utjecaj na DNA metilaciju i povećava rizik od nepovoljnih ishoda u kasnijoj odrasloj dobi, uključujući i razvoj zloćudnih bolesti, ubrzane ateroskleroze, arterijske hipertenzije i pretilosti. Nedostatna je „metilacija" karakteristika preuranjenoga starenja stanica i bolesti vezanih za pretilost[13].

Zaključak

Razumijevanje međudjelovanja vanjskih podražaja epigenetske kontrole genske ekspresije potpuno novi terapijski način razmišljanja ne samo o bubrežnoj bolesti povezanoj s pretilošću i o njezinu nastajanju nego i o cijelome kardiovaskularnom kontinuumu. U liječenju pretilih bolesnika (ne samo hipertoničara) primarno treba odabrati lijekove koji djeluju inhibitorno na reninsko-angiotenzinsko-aldosteronski sustav smanjujući primarno intraglomerularni tlak (ozljedu podocita), no utječući i na smanjenje fibroziranja tkiva uzrokovano aldosteronom, kao i imunološkim dodatnim mehanizmima koji utječu na smanjenje bubrežne i vaskularne ozljede[14,15].

Pretilost nije samo problem estetske prirode nego ozbiljan javnozdravstveni problem koji može znatno narušiti cjelokupno zdravlje i kvalitetu života. Potrebno je promovirati edukaciju o mogućim štetnim posljedicama pretilosti na zdravlje bubrega, kao i cijelog organizma od najranije dobi, te zagovarati zdrav način života koji primarno uključuje kretanje i bavljenje tjelesnim aktivnostima.

methionine, biotin, choline, and vitamins B2, B6 and B12). Deficient intake of diet high in methyl groups in childhood influences DNA methylation and increases the risk of unfavorable outcomes later in life, including development of malignant diseases, accelerated atherosclerosis, arterial hypertension, and obesity. Inadequate methylation is a characteristic of premature cell aging and obesity related diseases[13].

Conclusion

Understanding the interaction of external stimuli and epigenetic regulation of gene expression implies a completely new therapeutic reasoning on not only obesity related kidney disease and its genesis, but on the overall cardiovascular continuum. In the treatment of obese patients (not only hypertensive ones), the first choice should be drugs that inhibit the renin-angiotensin-aldosterone system and thus primarily decrease the intraglomerular pressure (podocyte lesion), while also reducing tissue fibrozation caused by aldosterone, as well as by additive immune mechanisms that reduce renal and vascular injury[14,15].

Obesity is not just an aesthetic problem but also a serious public health issue that can considerably impair general health and quality of life. Education on the potential harmful consequences of obesity on the health of kidneys and the whole body from earliest childhood should be strongly promoted and healthy lifestyle that primarily involves exercise and physical activity advocated.

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