Pretilost u dječjoj dobi i zdravlje bubrega

Childhood obesity and kidney health

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SAŽETAK: Prevalencija kronične bubrežne bolesti povećava se usporedo s porastom prevalencije pretilosti upozoravajući na jasnu uzročno-posljedičnu vezu debljine i bubrežne bolesti. Danas znamo kako prenatalni čimbenici, gestacijska dob i porođajna masa, kao i prehrana od najranije dobi imaju dugoročne učinke na sklonost pojedinca da se u njega razviju pretilost, dijabetes, kardiovaskularne bolesti i kronična bubrežna bolest. Pretilost nepovoljno djeluje na primarnu bolest bubrega, povezana je s ranom pojavom glomerulomegalije i hemodinamskih promjena u hiperfiltrirajućem bubregu, pojavom albuminurije i povišenoga arterijskoga tlaka, a u pretilih osoba, uz dodatne čimbenike rizika, moguć je razvoj glomerulopatije povezane s debljinom. Posljednjih se godina razvijaju metode za rano otkrivanje bubrežnog oštećenja vezanog za pretilost, temeljene na spoznaji da se tubularne lezije razvijaju prije pojave albuminurije, tj. prije glomerularnog oštećenja. Glavna mjera liječenja bubrežnih komplikacija zbog pretilosti jest redukcija, tj. normalizacija tjelesne mase.

SUMMARY: The prevalence of chronic kidney disease increases in parallel with the growing prevalence of obesity, indicating an overt causal relationship of obesity and kidney disease. Nowadays, it is well known that prenatal factors, gestational age and birth mass, as well as dietary pattern from the earliest childhood have long-term effects on the individual's susceptibility to develop obesity, diabetes mellitus, cardiovascular disease and chronic kidney disease. Obesity exerts unfavorable impact on primary kidney disease and is related to early onset of glomerulomegaly and renal hemodynamic changes due to glomerular hyperfiltration, albuminuria and elevated arterial pressure. Obese individuals with additional risk factors may develop obesity-related glomerulopathy. Recently, methods have been developed for early detection of kidney injury related to obesity, based on the fact that tubular lesions precede the onset of albuminuria, i.e. prior to glomerular injury. Body mass reduction, i.e. normalization, is the basic method in the treatment of renal complications of obesity.

KLJUČNE RIJEČI: pretilost, bubreg, djeca, glomerulopatija, arterijska hipertenzija.

KEYWORDS: obesity, kidney, children, glomerulopathy, arterial hypertension.

CITATION: Cardiol Croat. 2017;12(7-8):307-310. | https://doi.org/10.15836/ccar2017.307

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RECEIVED:
June 7, 2017

ACCEPTED:
June 20, 2017

Uvod

Globalno povećanje broja bolesnika s kroničnom bubrežnom bolešću događa se usporedo s epidemijom pretilosti u svijetu upozoravajući na jasnu uzročno-posljedičnu vezu debljine i bubrežne bolesti[1]. Učestalost pretilosti među djecom gotovo se utrostručila od 1980. godine, ostvarujući tako veći porast nego u odrasloj populaciji[2]. Osobito zabrinjava porast pretilosti u najmlađim dobnim skupinama, kao i novi trend porasta broja djece s teškom debljinom u sve ranijoj dobi[3]. U pretile djece pedijatrijski je nefrolog najčešće suočen s trima mogućim problemima: problemom progresije primarne bubrežne bolesti, problemom

Introduction

The worldwide increase in the number of patients with chronic kidney disease is paralleled by the epidemic of obesity in the world, pointing to the overt causal relationship of obesity and renal disease[1]. The prevalence of obesity in children has almost tripled since 1980, and this increase exceeds the rise recorded in adult population[2]. The growing prevalence of obesity in the youngest age groups and the new increasing trend in the number of children with severe obesity at ever-younger age are the causes of deep concern[3]. In obese children, pediatric nephrologist generally encounters three potential problems,

arterijske hipertenzije te glomerulopatijom povezanom s debljinom.

Glomerulopatija povezana s pretilošću

Učinci su pretilosti na bubreg višestruki. Bubreg pritom može biti oštećen primarno (hemodinamske, strukturne i metaboličke promjene) ili sekundarno (npr. uz dijabetes tipa 2 koji je često udružen s debljinom)[4]. Pretilost potiče progresiju gotovo svih primarnih bubrežnih bolesti, no također potiče nastanak tipičnih bubrežnih lezija. Tako je unatrag nekoliko desetljeća u populaciji pretilih osoba, uključujući i djecu, potvrđen poseban oblik glomerularne bolesti koja se pojavljuje neovisno o dijabetičkoj ili hipertenzivnoj nefropatiji, a naziva se glomeuolopatija povezanom s debljinom ili sekundarnom fokalnom segmentalnom glomerulosklerozom (FSGS) povezanom s debljinom. Očekivano, povećanjem broja pretilih ljudi raste i incidencija te bolesti. Ipak, pretilost nije jedini medijator nastanka ove nefropatije jer se neće razviti u svih osoba s prekomjernom tjelesnom masom[5]. Smatra se da je pretilost vjerojatno dodatno opterećenje za bubreg pojedinaca s kongenitalno ili stečeno reduciranim brojem nefrona i/ili nasljednom genskom vulnerabilnošću na metaboličke posljedice djelovanja citokina proizvedenih u masnome tkivu[6]. Kako reduciran broj nefrona vodi u bubrežno oštećenje? U ljudi se broj nefrona konačno definira trenutkom rođenja. U fetusa je razvoj bubrega dovršen oko 34.–36. tjedna gestacije. Nakon toga, moguć je samo gubitak mase nefrona kao dio procesa starenja ili zbog bolesti, traume ili kirurške ablacije. Djeca rođena prije puna 32 tjedna gestacije imat će smanjen broj nefrona razmjerno skraćenju trajanja gestacije[7]. U djece niske porođajne mase reduciran je broj nefrona, a zbog prakse hranjenja takve djece visokokalorijskim formulama i s nadoknadnim ubrzanim rastom, postoji i povećana sklonost za ranu pojavu inzulinske rezistencije, arterijske hipertenzije i pretilosti, kao i razvoja metaboličkog sindroma, što ih čini glavnom rizičnom skupinom za kroničnu bubrežnu bolest. S druge strane, veća porođajna masa, izloženost majčinu dijabetesu i brzi postnatalni prirast na tjelesnoj masi također su čimbenici rizika za razvoj pretilosti u dječjoj dobi koji mogu rezultirati pojavom proteinurije i bubrežne bolesti poslije u životu.

Glavna strukturna obilježja glomerulopatije povezane s pretilošću jesu povećanje bubrežne mase (i do 40 %) te glomerulomegalija[8], dok je osnovna hemodinamska promjena pojava hiperflitracije. Naime, kako u pretilosti postoji stanje povećanih metaboličkih zahtjeva na bubreg, nastaje adaptivna glomerularne hiperfiltracije koja vodi u maladaptivna glomerularna oštećenja[9]. Kako je broj nefrona zadan u trenutku rođenja i ne može se povećavati, okolnosti povećanih metaboličkih zahtjeva i hiperperfuzije dodatno su opterećenje na svaki postojeći nefron koji se, da bi ispunio svoju ulogu, povećava, što to ga ujedno čini i vulnerabilnijim za moguće daljnje oštećenje i propadanje. Na koncept da hiperfiltrirajući glomeruli progrediraju do glomerularne skleroze u okolnostima smanjenoga broja glomerula prvi je upozorio *Brenner* u tzv. hipotezi o ozljedi zbog hiperperfuzije[10]. U radu se iznosi teza da se u stanjima hiperfiltracije glomerula, koja može nastati kao posljedica različitih stanja, primjerice reduciranog broja nefrona, unilateralne bubrežne ageneze, stanja nakon unilateralne nefrektomije i metaboličke promjene, pogoršava bubrežna funkcija te pojavljuje glomerularna, a zatim i sustavna arterijska hipertenzija. Navedena stanja povećanog rizika za bubrežnu bolest dobivaju dodatno na svojoj važnosti u okolno-

i.e. progression of primary kidney disease, arterial hypertension, and obesity-related glomerulopathy.

Obesity-related glomerulopathy

Obesity exerts multiple effects on the kidney, which may cause primary (hemodynamic, structural and metabolic changes) or secondary (e.g., in diabetes mellitus type 2, which is frequently associated with obesity) kidney injury[4]. Obesity favors progression of nearly all primary kidney diseases, as well as the onset of typical kidney lesions. For decades now, a special form of glomerular disease has been demonstrated in the population of obese individuals including children, which develops independently of diabetic or hypertensive nephropathy and is known as obesity-related glomerulopathy or secondary focal segmental glomerulosclerosis (FSGS) associated with obesity. As expected, the increased proportion of obese individuals is accompanied by the growing incidence of this disorder. Yet, obesity is not the only mediator in the onset of this nephropathy because not all overweight persons will develop this disease[5]. It is believed that obesity most likely exerts additional burden upon the kidney in the individuals with congenital or acquired reduction in nephron number and/or inherited genetic vulnerability to metabolic sequels of the action of cytokines produced in adipose tissue[6]. How does a reduced nephron number lead to kidney injury? In humans, nephron number is definitely defined at birth. Fetal kidney development is completed by 34th-36th week of gestation. After that, nephron mass can only decline as part of the aging process or due to disease, trauma or surgical ablation. Children born before 32 weeks of gestation will have a reduced nephron number proportionate to reduction in the length of gestation[7]. Low birth weight children have a reduced nephron number, while the usual practice of feeding them with high-calorie formulas and consequential catch-up growth fast growth compensation result in greater susceptibility to early occurrence of insulin resistance, arterial hypertension and obesity, as well as to developing metabolic syndrome, making these children the main risk group for chronic kidney disease. On the other hand, greater birth mass, exposure to maternal diabetes and fast postnatal weight gain are also risk factors for developing obesity in childhood, which may result in the occurrence of proteinuria and renal disease later in life.

The main structural features of obesity-related glomerulopathy include kidney mass increase (up to 40 %) and glomerulomegaly[8], while hyperfiltration is the major hemodynamic alteration. In obesity, metabolic requirements from the kidney are increased, resulting in adaptive glomerular hyperfiltration, which in turn leads to maladaptational glomerular lesions[9]. As the number of nephrons is given at birth and cannot be increased, the state of greater metabolic requirements and hyperperfusion exerts additional burden upon each of the existing nephrons; then it undergoes enlargement to fulfill its role, which renders it more vulnerable to further damage and destruction. In his hyperperfusion injury hypothesis, Brenner was the first to point to the concept according to which hyperfiltrating glomeruli progress to glomerular sclerosis in the situation of reduced nephron number[10]. It is hypothesized that in glomerular hyperfiltration, which may occur consequentially to different states such as reduced nephron number, unilateral kidney agenesis, post-unilateral nephrectomy state and metabolic changes, deterioration of renal function occurs along with glomerular and then systemic arterial hy-

stima pretilosti. Klinička prezentacija glomerulopatije povezane s pretilošću uključuje proteinuriju, normalne serumske albumine i odsutnost edema uz blaži klinički tijek i sporiju progresiju u usporedbi s primarnom FSGS-om[5].

Pretilost i arterijska hipertenzija

Još prije 15-ak godina u nekoliko ključnih radova potvrđena je jasna veza arterijske hipertenzije i prekomjerne tjelesne mase u djece i adolescenata[11-13]. Tako je dokazano da se rizik od arterijske hipertenzije u djece linearno povećava porastom indeksa tjelesne mase (ITM) kroz cijeli percentilni raspon, da djeca s prekomjernom tjelesnom masom imaju 4,5, odnosno 2,4 puta veći rizik za povišen sistolički, odnosno dijastolički arterijski tlak te da je prevalencija hipertenzije triput veća u pretilih u odnosu prema nepretilim adolescentima. Slična se opažanja mogu naći i u sasvim recentnoj literaturi prema kojoj se bilježi snažna, statistički značajna povezanost između porasta centile ITM-a i centile arterijskoga tlaka, a u velikim populacijskim studijama dokazuje kako su tjelesna masa ili ITM važan prediktor vrijednosti arterijskoga tlaka u djece[14,15]. Čimbenici okoliša (prehrana, tjelesna aktivnost, razina stresa), neki fiziološki i genski čimbenici određuju koliki će biti utjecaj debljine na arterijski tlak. Mehanizmi nastanka arterijske hipertenzije vezane za pretilost kompleksni su i međudjelujući, a uključuju retenciju natrija u bubregu, pojačanu aktivnost simpatičkoga živčanog sustava, povišenu razinu cirkulirajućeg renin-angiotenzina i poremećnu funkciju endotela[16]. Retencija natrija u bubregu jedan je od potvrđenih mehanizama, a povećana tubularna reapsorpcija natrija pripisuje se povećanoj aktivnosti simpatikusa u bubregu. Također se smatra da povišen intrarenalni tlak zbog pritiska okolnoga masnoga tkiva narušava natriurezu. Uzroci aktivacije simpatikusa u pretilih osoba još su nejasni i vjerojatno su višestruki. Mogući mehanizmi uključuju inzulinsku rezistenciju, sustav reninsko-angiotenzinski sustav, leptin ili druge adipokine, opstruktivnu apneju u spavanju, kao i psihološki stres. Aktivacija reninsko-angiotenzinskog sustava vjerojatno je posljedica povišene simpatičke aktivnosti. Poremećena funkcija endotela veže se za brojne čimbenike kardiovaskularnog rizika, uključujući i pretilost.

Metode rane detekcije bubrežnog oštećenja

Mehanizmi kojima pretilost može uzrokovati bubrežnu bolest nisu potpuno razjašnjeni, a rani klinički biomarkeri razvoja glomerulopatije povezane s debljinom nisu još standardizirani. Jedna od najčešće primjenjivanih metoda rane detekcije bubrežne lezije jest albuminurija, koja je primarno rezultat glomerularnog oštećenja. Međutim, istraživanja pokazuju da su tubularne lezije prisutne i prije pojave proteinurije[17]. Stoga se danas u procjeni bubrežne tubularne lezije određuju vrijednosti nekoliko urinarnih enzima. Jedan od biljega tubularne lezije jest N-acetil-beta-D-glukozaminidaza (NAG) koja se rabi za određivanje opsega tubularnog oštećenja uzrokovanog raznim noksama[18]. Nadalje, potencijalno dobar tubularni biljeg jest i KIM-1 (*kidney injury molecule-1*) čija se razina povećava pri oštećenju proksimalnih tubularnih stanica[19]. U jednoj recentnijoj studiji uspoređivane su urinarne razine NAG i KIM-1 između skupina pretile djece te njihovih kontrola s normalnim vrijednostima ITM-a[20]. Vrijednosti obaju biljega bile su statistički značajno više u skupini pretile djece čineći ih potencijalno dobrim biljezima ranoga bubrežnog oštećenja.

pertension. These states of increased risk for kidney disease are of particular importance in obesity. Clinical presentation of obesity-related glomerulopathy includes proteinuria, normal serum albumin and absence of edema, with mild clinical course and slower progression as compared with FSGS[5].

Obesity and arterial hypertension

Clear association of arterial hypertension and excess body mass in children and adolescence was demonstrated in several pivotal studies as early as some 15 years ago[11-13]. The risk of arterial hypertension in children was confirmed to increase linearly with body mass index (BMI) increase across the percentile range. The risk of systolic and diastolic arterial pressure elevation was 4.5-fold and 2.4-fold greater, respectively, in children with excess body mass. In obese adolescents, the prevalence of hypertension was 3-fold prevalence recorded in non-obese adolescents. Similar observations can also be found in recent literature reporting on strong, statistically significant correlation between BMI increase percentile and arterial pressure percentile, whereas large population-based studies have shown that body mass or BMI is a major predictor of arterial pressure level in children[14,15]. Environmental factors (diet, physical activity, stress, etc.), as well as some physiologic and genetic factors determine the extent to which obesity will influence arterial pressure. The mechanisms of arterial hypertension development related to obesity are complex and interacting, and include renal sodium retention, enhanced activity of the sympathetic nervous system, elevated level of circulating renin-angiotensin, and impaired endothelial function[16]. Renal sodium retention is one of the confirmed mechanisms, while increased sodium tubular reabsorption is ascribed to the enhanced renal sympathetic activity. Elevated intrarenal pressure due to pressure exerted by the surrounding adipose tissue is also believed to interfere with natriuresis. The causes of sympathetic activation in obese persons have not yet been fully clarified, and are likely to be manifold. The potential mechanisms involve insulin resistance, renin-angiotensin system, leptin or other adipokines, obstructive sleep apnea, and psychological stress. Activation of the renin-angiotensin system probably results from enhanced sympathetic activity. Impaired endothelial function has been related to numerous cardiovascular risk factors including obesity.

Methods for early detection of kidney injury

The mechanisms by which obesity can cause kidney disease have not been fully elucidated and early clinical biomarkers of obesity-related glomerulopathy have not yet been standardized. One of the most frequently used methods for early detection of kidney injury is albuminuria, which primarily results from glomerular damage. However, studies show that tubular lesions are present even before the occurrence of proteinuria[17]. Therefore, the values of several urinary enzymes are currently determined in the assessment of renal tubular lesion. One of the tubular lesion markers is N-acetyl-beta-D-glucosaminidase (NAG), which is used to determine the extent of tubular lesion caused by various noxae[18]. Furthermore, the kidney injury molecule-1 (KIM-1) is a potentially useful tubular marker, as its level increases in proximal tubular cell damage[19]. A recent study compared urinary levels of NAG and KIM-1 between the groups of obese children and control children with normal BMI values[20]. The values of both markers

Liječenje

Osnovu liječenja bubrežnih komplikacija vezanih uz pretilost čini normalizacija tjelesne mase koja se prije svega postiže promjenama životnih navika koje uključuju promjenu u načinu prehrane, intenziviranje tjelesne aktivnosti i smanjenje unosa soli. U osoba s glomerulopatijom povezanom s pretilošću povoljan učinak smanjenja prekomjerne tjelesne mase očituje se u smanjenju albuminurije, klirensa kreatinina i hiperfiltracije[21]. Normalizacija tjelesne mase čini također osnovu nefarmakološkog liječenja arterijske hipertenzije u pretile djece, a udružena s redovitom tjelesnom aktivnošću uglavnom je dostatna terapijska mjera za regulaciju arterijskoga tlaka u takve djece[22,23].

were statistically significantly higher in the group of obese children, confirming them to be potentially useful markers of early kidney injury.

Treatment

The basic therapeutic option for renal complications related to obesity is body mass normalization, primarily by lifestyle modifications that include dietary habits, intensified physical activity and reduction of salt intake. In persons with obesity-related glomerulopathy, the favorable effect of excess body mass reduction manifests as a decrease in albuminuria, creatinine clearance and hyperfiltration[21]. Body mass normalization also is the basis of nonpharmacological treatment of arterial hypertension in obese children, and together with regular physical activity generally proven as an adequate therapeutic measure for arterial pressure regulation in these children[22,23].

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