POVEZANOST IZMEĐU INDEKSA TELESNE MASE I JAČINE GLOMERULSKE FILTRACIJE

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Sažetak: UVOD: Rastuća prevalenca hronične bubrežne bolesti (HBB) je veliki zdravstveni problem. Prevalenca gojaznosti, takođe, rađa raste širom sveta. Mali broj studija je ispitivao povezanost između prekomernih težina i rizika za HBB. CILJ: Ispitivanje mogućeg doprinosa povišenog indeksa telesne mase (ITM) poremećaju funkcije bubrega u uzorku opštine populacije. METOD: Studija je obuhvatila 500 ispitanika starijih od 30 godina (228 muškaraca, 272 žene, starosti 57,58±13,68) koji su posetili izabranog lekara u Domu zdravlja „Dr Simo Milošević“. Svim ispitanicima su uzeti uzorci krvi za laboratorijske analize, izmeren crveni pritisak i određene su antropometrijske mere. Jačina glomerulске filtracije je određena koristeći skraćenu formulu iz MDRD studije ("The Modification of Diet in Renal Disease Study"), a HBB je definisana kao JGF manja od 60 ml/min/1,73m2. Za statističku analizu podatka je korišćen SPSS 19.0 softver (IBM, Somers, Njujork, SAD). REZULTATI: Srednja vrednost ITM je bila 25,09±3,54 kg/m2 sa 0,6% osoba u kategoriji pothranjenih ITM<18,5 kg/m2), 17,6% u grupi sa teškom masom u opsegu niže normalne (ITM 18,5 do 21,9 kg/m2), 33,2% u grupi sa visokom normalnom telesnom masom (ITM od 22,0 do 24,9 kg/m2) i 48,6% u grupi prekomernog uhraženih ili gojaznih (ITM>25,0 kg/m²). Srednja vrednost JGF je bila 100,33±0,78 ml/min/1,73m2 sa 112±8,6 kod pothranjenih, 116,9±3,8 u kategoriji sa normalnom, 102,37±2,99 u kategoriji sa visokom normalnom telesnom masom i 92,78±1,72 u kategoriji prekomerne vecenje vrednosti JGF, naročito kod osoba u kategoriji sa višom normalnom u poređenju sa nižom normalnom telesnom masom (p<0,001) i u grupi prekomerno uhraženih i gojaznih u poređenju sa grupom sa nižom normalnom telesnom masom (p<0,001). U poređenju sa ispitanicima u grupi sa nižom normalnom telesnom masom, nepriklazeni odnos šans (the non-adjusted odds ratio - OR) za blago ili umerno redukovana blagim (GF od 99 ml/min/1,73m2) je bio 2,54 (95% CI 1,41-4,56) za ispitanike sa višom normalnom i 3,26 (95% CI 1,88-5,70) u grupi prekomernih uhraženih i gojaznih ispitanika. Nakon prilagođavanja u odnosu na potencijalne doprinos u faktore (starost, pol, dijabetes melitus, hipertenzija, hipercolesterolemija, hipertrofijerađemija i pušački status) OR za blago ili umerno redukovao blagim (GF od 99 ml/min/1,73m2) je bio 2,23 (95% CI 1,41-4,10) u grupi sa višom normalnom telesnom masom, a 2,65 (95% CI 1,44-4,87) u kategoriji prekomerne vecenje vrednosti JGF u kategoriji sa normalnom telesnom masom (p<0,001). Naša studija je pokazala da postoji jaka povezanost između viših vrednosti ITM i snižene JGF u opštoj populaciji nezavisno od tradicionalnih faktora rizika za HBB. Tačan mehanizam ove povezanosti kao i da li aktivnosti preuzete u cilju redukcije ITM dovode do smanjenja učestalosti HBB ostaje da bude proučen.

Ključne reči: indeks telesne mase, jačina glomerulске filtracije, hronična bolest bubrega, bubrežna funkcija, opšta populacija

UVOD
Hronična bubrežna bolest (HBB) je globalni zdravstveni problem i predstavljaj veliko ekonomsko opterećenje za zdravstvene sisteme. Globalna prevalenca HBB je između 11 i 13% sa najvećim udelem trećeg stadijuma. Svi stadijumi HBB su povezani sa povećanim rizikom za kardiovaskularni morbiditet, preranu smrt i/ili snižen kvalitet života [1]. Prevalenca gojaznosti, takođe, rađa raste širom sveta, pa je gojaznost poprimila razmere globalne epidemije hronične nezarazne

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THE RELATIONSHIP BETWEEN BODY MASS INDEX AND ESTIMATED GLOMERULAR FILTRATION RATE

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Abstract: INTRODUCTION: The increasing prevalence of chronic kidney disease (CKD) is a major health problem. The prevalence of obesity has also been rapidly increasing worldwide. Few studies have examined the relationship between excess body weight and CKD risk. Aim: To evaluate the possible contribution of increased body mass index (BMI) to impaired renal function in the general population sample. METHODS: The study involved 500 participants older than 30 years (228 men, 272 women, age 57.58±13.68) who visited their general practitioner in Health Center „Dr Simo Milosevic”. Blood samples, blood pressure anthropometric measures were performed on each participant. Estimated glomerular filtration rate was calculated using the abbreviated equation from MDRD study ("The Modification of Diet in Renal Disease Study") and CKD was defined as eGFR less than 60 ml/min/1.73m². Statistical analysis was performed using SPSS 19.0 software (IBM, Somers, New York, USA). RESULTS: The mean BMI was 25.09±3.54 kg/m² with 0.6% in underweight (BMI<18.5 kg/m²), 17.6% in lower normal (BMI 18.5 to 21.9 kg/m²), 33.2% in upper normal (BMI 22.0 to 24.9 kg/m²) and 48.6% in overweight or obese (BMI≥25.0 kg/m²) body mass category. The mean eGFR was 100.33±30.78 ml/min/1.73m² with 112±8.62 in underweight, 116.94±3.8 in lower normal, 102.37±2.39 in upper normal and 92.78±1.72 in overweight or obese category. Estimated GFR values decreased significantly with increasing BMI specially in those in upper normal compared to lower normal (p<0.001) and overweight and obese compared to lower normal body mass category (p<0.001). Compared with participants with lower normal body mass, the non-adjusted odds ratio (OR) for mildly or moderately reduced renal function (eGFR<90 ml/min/1.73m²) was 2.54 (95% CI 1.41-4.56) for upper normal and 3.26 (95% CI 1.88-5.70) for overweight and obese participants. After adjusting for potential confounding variables (age, sex, diabetes mellitus, hypertension, hypercholesterolemia, hypertriglyceridemia and smoking status) OR for mildly or moderately reduced renal function was 2.23 (95% CI 1.21-4.10) for upper normal 2.65 (95% CI 1.44-4.87) for overweight or obese participants compared to those in lower normal body mass category. CONCLUSION: Estimated GFR values decreased significantly with increasing BMI specially in those in upper normal compared to lower normal and overweight and obese compared to lower normal body mass category (p<0.001). This study showed that increasing BMI is strongly associated with decreasing eGFR in the general population. The underlying mechanism behind this association remains to be investigated through prospective population-based studies. Key words: body mass index, estimated glomerular filtration rate, chronic kidney disease, renal function, general population

INTRODUCTION

Chronic kidney disease (CKD) is a global health problem and represents a big economic burden for health systems. Global prevalence of CKD lies between 11 and 13% with the third stadium having the largest share. All CKD stadiums are related to the increased risk for cardiovascular morbidity, early death and/or poorer quality of life [1]. The prevalence of obesity has also been rapidly increasing worldwide so much that obesity acquired the proportions of a global epidemic of chronic noncommunicable disease of the 21st century. The prevalence of obesity (body mass index ≥30 kg/m²) almost doubled in the period between 1980 and 2008. In 1980 5% of men and 8% of women were obese while in 2008 it was 10% of men and 14% of women which makes more than half a billion people [2]. If this secular trend continues it is estimated that by 2030 38% of adult world population will be overweight while 20% will be obese [3]. Overweight and obesity have adverse metabolic effects on blood pressure, leading to
bolesti 21. veka. Prevalenca gojaznosti (indeks telesne mase ≥ 30 kg/m²) se skoro udvostručila u periodu između 1980. i 2008. godine. U 1980. godini 5% muškaraca i 8% žena je bilo gojazno, a 2008. godine 10% muškaraca i 14% žena što je više od pola milijarde ljudi [2]. Ukoliko se sekularni trend nastavi, procenjuje se da će do 2030. godine 38% odrasle svetske populacije biti prekomerno uhranjeno, a 20% će biti gojazno [3].

Prekomerna uhranjenost i gojaznost imaju neželjene metaboličke efekte na krvni pritisk, dovode do hiperholesterolemije, hipertriglicerideremije i insuliinske rezistencije. Rizik za koronarnu bolest, ishemijski moždani udar i dijabetes melitus tip 2 raste proporcionalno sa porastom ITM. Povišen ITM, takođe, povećava rizik za nastanak kancerne dojke, kolona, prostate, endometrijuma, bubrega i žučne kese [4].

Širom sveta bar 2,8 miliona ljudi umre svake godine od posledica prekomerne uhranjenosti ili gojaznosti [2]. Gojaznost je veliki faktor rizika za razvoj bubrežne bolesti. Ona povećava rizik za razvoj “major” faktora rizika za HBB kao što su dijabetes i hipertenzija i ima direktni uticaj na razvoj HBB i terminalne bubrežne insuficijencije [5].

Cilj studije je ispitivanje mogućeg doprinosa povišenog indeksa telesne mase (ITM) poremećaju funkcije bubrega u uzorku opšte populacije. Testirana je hipoteza da je povišen ITM povezan sa sniženjem jačine glomerulske filtracije. Prema našim saznanjima, ovo je prva studija koja je ispitivala povezanost između indeksa telesne mase i jačine glomerulske filtracije na našim prostorima u uzorku populacije u primarnoj zdravstvenoj zaštiti.

**MATERIJAL I METOD**

Studija je sprovedena kao opservaciona analitička studija preseka. U studiji su učestvovalo osobe starije od 30 godine koje su posetile svog izabranog lekara u Domu zdravlja „Dr Simo Milošević“. Prikupljanje podataka je završeno nakon mesec dana nakon što je formiran uzorak od 500 ispitanika. Svim ispitanicima su uzeti uzorci krvi, krvni pritisak i telesna masa i visina su merene u ordinaciji,

Laboratorijska analiza, izmeren je krvni pritisak i određene su antropometrijske mere. Laboratorijska merenja su podrazumevala određivanje koncentracije glukoze, uree, kreatinina, ukupnog holesterola i triglicerida i urađena su svakom od ispitanika. Krvni pritisak je meren na levoj nadlaktici u sedečem položaju. Telesna masa i visina su merene u ordinaciji, a ITM je računan kao količnik telesne mase izražene u kilogramima i kvadrata visine izražene u metrima. Na osnovu vrednosti ITM ispitanici su svrstani u kategorije prikazane u tabeli 1 [6].

| Kategorija          | ITM (kg/m²) |
|---------------------|-------------|
| neuhranjenost       | < 18,5      |
| niža normalna telesna masa | 18,5 do 21,9 |
| viša normalna telesna masa | 22,0 do 24,9 |
| prekomerna uhranjenost | 25,0 do 29,9 |
| gojaznost           | > 30        |

Ispitanici su se izjasnili da li su nepušači, bivši ili aktivni pušači. Jačina glomerularne filtracije je određena koristeći skraćenu formulu iz “The Modification of Diet in Renal Disease Study” [7].

\[
eGFR = 32788 \times \frac{\text{Serum Creatinine}^{-1.154} \times \text{Age}^{-0.083} \times [1.210 \text{ if Black}] \times [0.742 \text{ if Female}]}{[1.003^{7.42 - 1.21 \text{ Age}]} - 1]
\]

Stadijumi bubrežne slabosti su navedeni u tabeli 2 [8].

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hypercholesterolaemia, hypertriglyceridaemia and insulin resistance. Coronary disease risk, ischemic stroke and diabetes mellitus type 2 increases proportionally with the increase of BMI. Increased BMI also increases the risk of developing breast, colon, prostate, endometrial, kidney and gallbladder cancers [4].

All over the world at least 2.8 million people die each year from overweight and obesity [2].

Obesity is a big risk factor for the development of a renal disease. It increases the risk for the development of “major” risk factors for CKD such as diabetes and hypertension and has a direct impact on the development of CKD and terminal renal insufficiency [5].

Purpose of the study is examination of possible contribution of increased body mass index (BMI) to the impaired renal function in the general population sample. The hypothesis that the increased BMI is associated with glomerular filtration rate decrease was tested. According to our knowledge, this is the first study which examined the correlation between body mass index and glomerular filtration rate in these regions in the population sample in primary health care.

MATERIAL AND METHOD
The study was conducted as an observational analytical cross sectional study. The study involved participants older than 30 years who visited their general practitioner in Health Center ‘Dr Simo Milošević’. Data collection was completed a month after the sample of 500 participants was formed. Blood samples, blood pressure and anthropometric measures were performed on each participant. Laboratory measurements involved determining of glucose, urea, creatinine, total cholesterol and triglyceride concentrations and were performed on each of the participants. Blood pressure was measured on the left upper arm in a sitting position. Body mass and height were measured in the office and BMI was calculated as the quotient of body mass expressed in kilograms and square height expressed in meters. Based on the BMI values, the participants were classified into the categories shown in Table 1 [6].

| Table 1. BMI categorization |
|----------------------------|
| Category | BMI (kg/m²) |
|----------|-------------|
| malnutrition | <18.5 |
| lower normal body mass index | 18.5 - 21.9 |
| upper normal body mass index | 22.0 - 24.9 |
| overweight | 25.0 - 29.9 |
| obesity | > 30 |

Participants stated whether they were non-smokers, former or active smokers. Glomerular filtration rate was determined using the shortened formula from “The Modification of Diet in Renal Disease Study” [7].

\[ eGFR = 32788 \times \text{Serum Creatinine}^{-1.154 \times \text{Age}^{-0.203 \times [1.210 \text{ if Black} \times 0.742 \text{ if Female}]}} \]

Stadiums of renal insufficiency were given in the table 2 [8].

| Table 2. Classification of chronic kidney disease |
|-------------------------------------------------|
| Stadium | GFR | Description |
|---------|-----|-------------|
| 1 | >90 | Normal renal function but pathological urine findings or structural abnormalities or genetic traits indicate kidney disease |
| 2 | 60-89 | Slightly reduced renal function and other findings (as for stadium 1) indicate renal disease |
| 3A | 45-59 | Moderately reduced renal function |
| 3B | 30-44 | Moderately reduced renal function |
| 4 | 15-29 | Seriously reduced renal function |
| 5 | <15 | Very severe renal impairment or end-stage renal insufficiency |

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**Tabela 2. Klasifikacija hronične bubrežne bolesti**

| Stadijum | JGF   | Opis                                                   |
|---------|-------|--------------------------------------------------------|
| 1       | >90   | Normalna bubrežna funkcija ili patološki nalaz u urinu ili strukturne abnormalnosti ili genetske osobine ukazuju na bubrežnu bolest |
| 2       | 60-89 | Blago redukovana bubrežna funkcija i drugi nalazi (kao za stadijum 1) ukazuju na bubrežnu bolest |
| 3A      | 45-59 | Umereno redukovana bubrežna funkcija                   |
| 3B      | 30-44 |                                                        |
| 4       | 15-29 | Ozbiljno redukovana bubrežna funkcija                  |
| 5       | <15 ili dijaliza | Veoma ozbiljno redukovana bubrežna funkcija ili terminalna bubrežna insuficijencija |

**REZULTATI**

U studiju je učestvovalo 500 ispitanika, 228 (45,6%) muškaraca i 272 (54,4%) žene. Srednja vrednost ITM je bila 25,09±3,54 kg/m² sa 0,6% osoba u kategoriji pothranjenih (ITM<18,5 kg/m²), 17,6% u grupi sa telesnom masom u opsegu niže normalne (ITM 18,5 do 21,9 kg/m²), 33,2% u grupi sa višom normalnom telesnom masom (ITM od 22,0 do 24,9 kg/m²) i 48,6% u grupi prekomerno uhranjenih ili gojaznih (ITM≥25,0 kg/m²).

**Grafikon 1. Distribucija ispitanika prema stepenu uhranjenosti**

| Kategoriya prema ITM | JGF (ml/min/1,73m²) |
|----------------------|---------------------|
| pothranjenost        | 112 ± 8,62          |
| niža normalna        | 116,94 ± 3,8        |
| viša normalna        | 102,37 ± 2,39       |
| prekomerno uhranjeni i gojazni | 92,78 ± 1,72       |

Srednja vrednost JGF je bila 100,33 ± 30,78 ml/min/1,73m². Srednje vrednosti JGF u kategorijama prema ITM su prikazane u tabeli 3.

**Tabela 3. JGF u pojedinim kategorijama prema ITM**

JGF je značajno opadala sa povećanjem vrednosti ITM, naročito u kategoriji prekomerno uhranjenih i gojaznih ispitanika u poređenju sa ispitanicima sa nižom normalnom telesnom masom (p<0,001), kao i u grupi sa višom normalnom u poređenju sa grupom sa nižom normalnom telesnom masom (p<0,001). U poređenju sa ispitanicima u grupi sa nižom normalnom masom, neprilagođeni odnos šansi- (the non-adjusted odds ratio-OR) za blago ili umereno redukovani bubrežni funkciju.
CKD is defined as GFR less than 60 ml/min/1.73m². SPSS 19.0 software (IBM, Somers, New York, USA) was used to create the database and analyze it. For testing of correlation between body mass index and glomerular filtration rate with adjusting in relation to the associated variable logistical regression was used. The level of significance was 0.05.

RESULTS

The study involved 500 participants, 228 (45.6%) men and 272 (54.4%) women. BMI mean value was 25.09±3.54 kg/m² with 0.6% participants in the category of malnourished (ITM < 18.5 kg/m²), 17.6% in the group of body mass in the range of lower normal (BMI 18.5 up to 21.9 kg/m²), 33.2% in the group with upper normal body mass (BMI from 22.0 to 24.9 kg/m²) and 48.6% in the group of overweight or obese (ITM > 25.0 kg/m²).

Graph 1. Body mass distribution of participants

GFR mean value was 100.33 ± 30.78 ml/min/1.73m². GFR mean values in categories according to BMI are presented in table 3.

Table 3. eGFR in BMI categories

| BMI categories     | GFR (ml/min/1.73m²) |
|--------------------|---------------------|
| Malnourished       | 112±8.62            |
| Lower normal       | 116.94±3.8          |
| Upper normal       | 102.37±2.39         |
| Overweight and obese| 92.78±1.72        |

GFR considerably decreased with the increase of the BMI values particularly in the category of overweight and obese participants compared to the participants with lower normal body, (p<0.001) as well as in the group with upper normal body mass compared to the group of lower normal body mass (p<0.001). In comparison to the participants in the group with lower normal body mass, the non-adjusted odds ratio (OR) for mild or moderately reduced renal function (GFR<90 ml/min/1.73m²) was 2.54 (95% CI 1.41-4.56) for participants with upper normal body mass and 3.26 (95% CI 1.88-5.70) for participants in the group of overweight and obese.

After adjustment in relation to potential contributing factors (age, gender, diabetes mellitus, hypertension, hypercholesterolaemia, hypertriglyceridemia and smoking status) OR for mild or moderately reduced renal function was 2.23 (95% CI 1.21-4.10) in the group with upper normal body weight while it was 2.65 (95% CI 1.44-4.87) in the category of overweight and obese participants compared to those in the category with lower normal body mass.

DISCUSSION

Several previous studies pointed to the significance of the increased body mass index in the development of chronic renal disease. A cross-sectional study conducted in general population in Japan showed that the increased BMI is associated with the decrease of GFR only in men [9]. In the study conducted by Fox et al. OR for the development of new CKD was 23% (OR, 1.23; 95% CI, 1.08–1.41) for the BMI increase by one SD [10]. Gelber et al. showed that the initial increased BMI as well as its increase during the follow-up period of 14 years is associated with increased risk from CKD [11].
(JGF=90 ml/min/1,73m²) je bio 2,54 (95% CI 1,41-4,56) za ispitnike sa višom normalnom i 3,26 (95% CI 1,88-5,70) za ispitnike u grupi prekomerno uhranjenih i gojaznih.

Nakon prilagođavanja u odnosu na potencijalne doprinose faktore (starost, pol, dijabetes melitus, hipertenzija, hiperholesterolemija, hipertrigliceridemija i pušački status) OR za blago ili umereno redukovano bubrežnu funkciju je bio 2,23 (95% CI 1,21-4,10) u grupi sa višom normalnom telesnom masom, a 2,65 (95% CI 1,44-4,87) u kategoriji prekomerno uhranjenih i gojaznih ispitanika u poređenju sa onima u kategoriji sa nižom normalnom telesnom masom.

**DISKUSIJA**

Nekoliko ranije sprovedenih studija je ukazalo na značaj povišenog indeksa telesne mase u razvoju hronične bubrežne bolesti. Studija preseka sprovedena u opštoj populaciji u Japanu je pokazala da je povišen ITM povezan sa smanjenjem JGF samo kod muškaraca [9]. U studiji koju je sprovede Fox sa saradnicima OR za razvoj novonastale HBB je bio 23% (OR, 1,23; 95% CI, 1,08–1,41) za porast ITM od jedne SD [10]. Gelber i saradnici su pokazali da je početni povišen ITM kao i njegovo povećanje tokom perioda praćenja od 14 godina povezano sa povećanim rizikom od HBB [11].

Ostale studije koje su ispitivale povezanost između gojaznosti i HBB su prikazane u tabeli 4.

| Studija | Ispitanici | Faktori rizika | Ishod | Rezultati | Komentar |
|---------|------------|----------------|-------|-----------|-----------|
| PREVEND studija[12] | 7676 Danaca bez dijabetesa | Povišen ITM, hipertenzija, hipertrigliceridemija | Albuminurija 30-300 mg/24h | Gojaznost + centralna distribucija: veći rizik za albuminuriju | Studija preseka |
| CARDIA[13] | 2 354 osoba iz opšte populacije na normalnom bubrežnom funkcijom starosti 28-40 godina | Gojaznost (ITM>30 kg/m²), Faktori rizika povezani sa ishranom i načinom života | Incidentna mikroalbuminurija | Gojaznost (OR 1,9) i nezdrava ishrana (OR 2,0) su povezani sa albuminurijom | Maša učestalost događaja |
| Nacionalna populaciona studija u Švedskoj [14] | 926 Švedana sa užetnom/uzna predovalom HBB u poređenju sa 988 kontrola | ITM ≥ 25 nasuprot<25 kg/m² | HBB nasuprot odsustva HBB | Viši ITM povezan sa 3x većim rizikom od HBB | - Rizik najveći kod dijabetičara ali značajno povisena i kod nedijabetičara - Studija preseka |
| Nacionalna populaciona studija u Izraelu [15] | 1 194 704 muških i ženskih adolescenata, kandidata za prijem u vojsku | Povišen ITM, hipertenzija, hipertrigliceridemija | Incidenta terminalne HBB | Prekomerna uhranjenosti i gojaznost povezani sa većim rizikom za terminalnu HBB | Povezanost najača za dijabetičku HBB ali i značajno veća za ne-dijabetičku HBB |
| Nord-Trøndelag Health Study (HUNT-1)[16] | 74 986 odraslih Norvežana | Kategorije ITM | Incidenta terminalne bubrežne insuficijencije ili renalne smrti | ITM> 30 kg/m²: povezan sa nepovoljnijim ishodom | Povezanost nije prisutna kod osoba sa TA<120/80 mHg |

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Other studies that examined the relationship between obesity and CKD are presented in Table 4.

Table 4. Studies that examined the association between obesity and chronic kidney disease

| Study                                      | Participants                                                                 | Risk factors                                                                 | Outcome                                      | Results                                                                                     | Comment                                                                 |
|--------------------------------------------|------------------------------------------------------------------------------|------------------------------------------------------------------------------|----------------------------------------------|--------------------------------------------------------------------------------------------|------------------------------------------------------------------------|
| PREVEND study [12]                         | 7676 Danish people without diabetes                                         | Increased BMI (overweight obesity) and central distribution of fat (waist / hip circumference ratio) | Albuminuria 30-300 mg/24h increased or decreased GFR | Obesity + central distribution: higher risk for albuminuria Obesity +/− central distribution: higher risk for increased GFR Central distribution +/− obesity associated with decreased GFR | Cross-sectional study                                                  |
| CARDIA [13]                                | 2354 people from general population aged 28-40                              | Obesity (ITM>30 kg/m²) Risk factors associated with nutrition and the way of life | Incidental microalbuminuria                  | Obesity (OR 1.9) and unhealthy diet (OR 2.0) are associated with albuminuria                 | Low-frequency                                                         |
| National population study in Sweden [14]   | 926 Swedish people with mild/advanced CKD compared to 988 control            | BMI ≥ 25 against<25 kg/m²                                                    | CKD against absence of CKD                   | Higher BMI associated with 3x higher risk from CKD                                             | - The greatest risk lies with diabetic participants but it is also significantly increased in the nondiabetic participants - Cross-sectional study |
| National population study in Israel [15]   | 1194704 male and female adolescents/candidates for joining the Army         | Increased BMI (overweight and obesity) compared to normal BMI                | Incidence of terminal CKD                   | Overweight and obesity associated with higher risk for terminal CKD                            | Strongest correlation for diabetic CKD but also significantly higher for nondiabetic CKD |
| Nord-Trøndelag Health Study (HUNT-1)[16]   | 74986 of adult Norwegian people                                              | BMI categories                                                               | Incidence of terminal renal insufficiency or renal death | BMI > 30 kg/m² associated with more unfavorable outcome                                        | Correlation not present in participants with TA (?)<120/80 mmHg          |
| National cohort of American veterans [17]  | 453 946 veterans with the initial GFR 60 ml/min/1.73 m²                     | BMI categories from < 20 to 50 kg/m²                                        | Incidence of tCKD Doubling of serum creatinine Decrease of GFR | Mild and severe overweight are associated with major kidney impairment                           | Correlation present but weaker in participants with advanced CKD       |
| Kaiser Permanente Northern California study [18] | 320252 adults with/without CKD                                                | Overweight, categories I, II and extreme obesity compared to normal BMI       | Incidence of terminal renal disease          | Linearly higher risk in higher BMI categories                                                  | Correlation still exists after adjustment for the presence of diabetes, hypertension, and initial CKD |

Most studies showed existence of a higher risk for CKD in participants with the BMI which is equal to or greater than 25 kg/m² while results of our study show increased risk for mild and moderately impaired renal function in the group of participants with upper normal body mass (BMI 22.0 to 24.9 kg/m²) as well as in the category of overweight and obese (BMI≥25 kg/m²) compared to the participants from the category of lower normal body mass.

The exact mechanism of contribution of obesity to the development or worsening of CKD
| Nacionalna kohorta američkih veterana [17] | 453 946 veterana sa početnom GFR < 60 ml/min/1,73 m² | Kategorije ITM-e od < 20 do 50 kg/m² |
|---|---|---|
| Incidenca tHBB Dupliranje serumskog kreatinina PadjGF | Umerena i ozbiljna gojaznost su povezani sa većim bubrežnim oštećenjem |
| Povezanost prisutna ali slabija kod ispitivanja sa uznemiravanjem HBB |
| Kaiser Permanente Northern California study [18] | 320 252 odraslih sa/bez HBB | Prekomerna uhranjenost, kategorija I, II i ekstremna gojaznost nasuprot normalnog ITM |
| Incidenca terminalne bubrežne bolesti | Linearno viši rizik kod viših kategorija ITM |
| Povezanost i dalje postoji nakon prilagođavanja u odnosu na prisustvo dijabetesa, hipertenzije i požećen HBB |

Većina studija je pokazala postojanje povećanog rizika za HBB kod osoba sa ITM koji je jednak ili veći od 25 kg/m² dok rezultati naše studije ukazuju na povećanje rizika za blago i umereno oštećenje bubrežne funkcije i u grupi ispitivanih sa višom normalnom (ITM 22,0 do 24,9 kg/m²) kao i u kategoriji prekomerno uhranjenih i gojaznih (ITM≥25 kg/m²) u poređenju sa ispitivanima iz kategorije niže normalne telesne mase.

Tačan mehanizam doprinosa gojaznosti nastanku ili pogoršanju HBB je još uvek nedovoljno poznat. U prilog tome da gojaznost nije dovoljna za razvoj HBB govori podatak da većina gojaznih osoba nikad ne razvija HBB, a čak 25% gojaznih nema metaboličke poremećaje [19]. Međutim, učestalost tzv. glomerulopatište povezane sa gojaznošću (obesity-related glomerulopathy) za koju je u opservacionim studijama pokazano da utiče na razvoj HBB je porasla 10 puta u periodu od 1986. do 2000. godine [20]. Masno tkivo ima svoju endokrinu funkciju kroz produkciju adiponektina [21], leptina [22], rezistina [23] i brojnih drugih mediatora što dovodi do oksidativnog stresa [24], inflamacije [25], insulinske rezistencije [26], aktivacije RAAS-a [27] i poremećenog metabolizma masti [28]. Uticaj navedenog na bubrege se ogleda kroz ekstipčnu akumulaciju masti i povećanu depoziciju masnoće u renalnim sinusima [29], razvoj glomerulске hipertenzije kao i hiperfiltracije sa posledičnim oštećenjem glomerulске bazalne membrane i povećanjem permeabilnosti što rezultira glomerulomegalijom i fokalnom segmentnom glomerulosklerozom [20].

Gojaznost je takođe povezana sa povećanim rizikom za nefrolitijazu. Veća telesna težina je povezana sa nižim pH urina [30] i povećanom ekskrecijom oksalata [31], mokraćne kiseline, natrijuma i fosfata [32]. Ishrana sa dosta proteina i soli snižava pH urina i koncentraciju citrata što doprinosi stvaranju kamena. Takođe, insulinska rezistencija preko uticaja na tubularni Na-H transport i amonioogenezu može doprineti kiselosti urina što favorizuje nefrolitijazu [33].

Osim direktnog uticaja gojaznosti na bubrege u patofiziologiji HBB veliku ulogu imaju tradicionalni faktori rizika kao što su dijabetes melitus, arterijska hipertenzija i hronične vaskularne bolesti koje su dokazano češće kod gojaznih osoba.
is still insufficiently known. In support of the claim that obesity itself is not responsible for the development of CKD is the fact that most obese people never develop CKD and as many as 25% of obese people do not have metabolic disorders [19]. However, the frequency of so-called glomerulopathy associated with obesity (obesity-related glomerulopathy) which in the observational studies was proven to affect the development of CKD increased by 10 times in the period from 1986 to the year 2000 [20]. Adipose tissue has its endocrine function through the production of adiponectin [21], leptin [22], resistin [23] and numerous other mediators which leads to oxidative stress [24], inflammation [25], insulin resistance [26], RAAS activation [27] and impaired fat metabolism [28]. The effect of the above on the kidneys is reflected through ectopic fat accumulation and increased fat deposition in the renal sinuses [29], development of glomerular hypertension as well as hyperfiltration with consequent damage to the glomerular basement membrane and increased permeability resulting in glomerulomegaly and focal segmental glomerulosclerosis [20].

Obesity is also associated with increased risk for nephrolithiasis. Higher body weight is associated with lower urine pH [30] and increased oxalate excretion [31], uric acid, sodium and phosphate [32]. A diet with a lot of proteins and salt decreases urine pHand citrate concentration, which contributes to the formation of stone. Also, through effects on tubular Na-H transporter and ammoniogenesis, insulin resistance may contribute to urinary acidity favouring nephrolithiasis [33].

Apart from obesity having a direct impact to kidneys in pathophysiology of CKD, traditional risk factors such as diabetes mellitus, arterial hypertension and chronic vascular diseases proven to be more frequent in obese persons play a major role here.

Figure 1. Assumed mechanisms of the role of obesity in the development of chronic kidney disease
Slika 1. Pretpostavljeni mehanizam uloge gojaznosti u nastanku hronične bubrežne bolesti

Gojaznost

- Lipodistopenija, fleptina, Trehzistina, Tvisfatina, drugih adipokina

- Insulinske rezistencije
  - Konc. insulina
  - RAAS
  - Inflamacije
  - Oksidativnog stresa

poremećaj metabolizma masti

HBB

DM

HVB

HTA


- pH urina
  - Oksalata u urinu
  - Mokračne kiseline
  - Urinarnih citrata

Nefrolitijaza

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CONCLUSION

Estimated GFR values decreased significantly with increasing BMI specially in those in upper normal compared to lower normal (p<0.001) and overweight and obese compared to lower normal weight category (p<0.001). This study showed that increasing BMI is strongly associated with decreasing eGFR in the general population. The underlying mechanism behind this association remains to be investigated through prospective population-based studies.

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