Vrijednosti serumskog kreatinina, *Cockcroft-Gault* i *Modification of Diet in Renal Diseases* jednadžbi u bolesnika s arterijskom hipertenzijom

Performance of Serum Creatinine, Cockcroft-Gault and Modification of Diet in Renal Disease Study Equations in Assessment of Kidney Function in Patients with Arterial Hypertension

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RECEIVED: April 24, 2021
UPDATED: May 1, 2021
ACCEPTED: May 25, 2021

SAŽETAK: *Cilj:* utvrditi postoje li razlike između vrijednosti kreatinina u serumu, procijenjene stope glomerularne filtracije (eGFR) prema jednadžbi *Modification of Diet in Renal Disease* (MDRD), klirensa kreatinina i eGFR-a dobivenih *Cockcroft-Gault* metodom s obzirom na dob, stupanj i trajanje arterijske hipertenzije (AH).

Bolesnici i metode: istraživanje je obuhvatilo 124 ambulantna bolesnika s AH-om pregledana na Klinici za bolesti srca, krvnih žila i reumatizam Kliničkog centra Univerziteta u Sarajevu. Pregledani su svi bolesnici te su uzeti podatci o trajanju i stupnju AH-a. Bubrežna je funkcija ocijenjena na osnovi serumskog kreatina, procijenjene su stope glomerularne filtracije prema MDRD jednadžbi, klirensom kreatinina procijenjenim *Cockcroft-Gault* jednadžbom ($eCrCl_{CG}$) i njegovim korekcijama za površinu tijela ($eCrCl_{CG1,73}$), za indeks tjelesne mase ($eCrCl_{CGBMI}$), indeks tjelesne mase i površinu tijela ($eCrCl_{CGBMI1,73}$) i procijenjeni GFR primjenom *Cockcroft-Gault* metode ($eGFR_{CGBMI1,73}$).

Rezultati: nađena je značajna razlika u vrijednostima procijenjenog GFR-a MDRD jednadžbom, $eCrCl_{CGBMI}$, $eCrCl_{CGBMI1,73}$ i $eGFR_{CGBMI1,73}$ u bolesnika s različitim stupnjevima i trajanjem AH-a, što nije dobiveno analizom vrijednosti serumskog kreatinina.

Zaključak: procijenjeni GFR i eCrCl osjetljiviji su biljezi oštećenja bubrega od vrijednosti kreatinina u serumu i njihovo određivanje treba biti uvedeno kao rutinski probir u otkrivanju ranih stadija kronične bubrežne bolesti u primarnoj zdravstvenoj zaštiti, posebno u bolesnika s AH-om.

SUMMARY: *Aim:* To determine whether there are differences between serum creatinine levels, estimated glomerular filtration rate (GFR) according to the Modification of Diet in Renal Disease Study (MDRD) equation, creatinine clearance, and estimated GFR obtained by the Cockcroft-Gault method related to age, stage, and duration of arterial hypertension.

Patients and Methods: The study included 124 patients with arterial hypertension who were examined at the Clinic for Heart, Rheumatism and Blood Vessels, Clinical Center University of Sarajevo. All patients were examined, and data about the duration and stage of hypertension were taken. Kidney function was assessed using serum creatinine, estimated GFR according to the MDRD equation, creatinine clearance estimated by the Cockcroft-Gault method ($eCrCl_{CG}$) and its corrections for body surface area ($eCrCl_{CG1.73}$), body mass index ($eCrCl_{CGBMI}$), both body surface area and body mass index ($eCrCl_{CGBMI1.73}$), and estimated GFR using the Cockcroft-Gault method ($eGFR_{CGBMI1.73}$).

Results: There was a significant difference in values in MDRD equation estimated GFR, $eCrCl_{CGBMI}$, $eCrCl_{CGBMI1.73}$, and $eGFR_{CGBMI1.73}$ in patients with different stages and durations of hypertension, which was not found by analysis of serum creatinine values.

Conclusion: Estimated GFR and eCrCl are more sensitive markers of kidney impairment than serum creatinine values, and their assessment should be introduced as a routine screening in the detection of early stages of chronic kidney disease in primary care settings, especially in patients with arterial hypertension.

KLJUČNE RIJEČI: stopa glomerularne filtracije, kardiovaskularne bolesti, probir, primarna zdravstvena zaštita.

KEYWORDS: glomerular filtration rate, cardiovascular diseases, screening, primary health care.

CITATION: Cardiol Croat. 2021;16(7-8):257-63. | https://doi.org/10.15836/ccar2021.257

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TO CITE THIS ARTICLE: Šečić D, Turohan A, Begić E, Sokolović Š, Rebić D. Mušija E, et al. Performance of Serum Creatinine, Cockcroft-Gault and Modification of Diet in Renal Disease Study Equations in Assessment of Kidney Function in Patients with Arterial Hypertension. Cardiol Croat. 2021;16(7-8):257-63. | https://doi.org/10.15836/ccar2021.257

TO LINK TO THIS ARTICLE: https://doi.org/10.15836/ccar2021.257

Uvod

The National Kidney Foundation (NKF) kroničnu bubrežnu bolest (KBB) definira kao oštećenje bubrega koje traje više od 3 mjeseca, a uzrokovano je strukturnim ili funkcionalnim poremećajima bubrega, sa smanjenjem stope glomerularne filtracije (GFR) ili bez njega, manifestirana histološkim abnormalnostima ili poremećajima krvi, mokraće ili bubrežne funkcije. Izraz „kronično zatajenje bubrega" rabi se za opis terminalne (pete) faze kronične bubrežne bolesti.[1] Kronična bolest bubrega jedan je od vodećih uzroka smrtnosti i pobola u svijetu.[1-3] Prevalencija bubrežne bolesti neprestano se povećava u posljednjem desetljeću usporedo s brzim širenjem šećerne bolesti i arterijske hipertenzije (AH) te je glavni javnozdravstveni problem s golemim utjecajem na kvalitetu života i ekonomski status.[1,4,5]

Rano otkrivanje i liječenje smanjuju napredovanje KBB-a prema završnom stupnju zatajenja bubrega.[6-8] Najčešći uzroci smrtnosti i pobola u bolesnika s KBB-om jesu kardiovaskularne bolesti.[9] Arterijska hipertenzija može uzrokovati oštećenje glomerula, mikroalbuminuriju i proteinuriju.[3-5] Povećanje vrijednosti arterijskoga tlaka (AT) povezano je sa znatnim smanjenjem GFR-a (1,1 – 6,2 mL/min/godišnje).[6] Terapija ACE inhibitorima i blokatorima angiotenzin II receptora (ARB) pokazuju renoprotektivni učinak i smanjenje proteinurije u bolesnika s AH-om.[5] Ovakav renoprotektivni učinak temelji se na blokadi pretvorbe angiotenzina I u angiotenzin II i na posljedičnom širenju eferentnih arteriola i smanjenju intraglomerularnog tlaka.[7,10,11]

Rano otkrivanje bubrežne bolesti uz uporabu probirnih testova za otkrivanje visokorizičnih skupina bolesnika, poput onih s AH-om i šećernom bolesti, vrlo je važno i isplativo.[12-14] Vrijednosti klirensa kreatinina uvijek se odnose na prosječnu površinu tijela odraslih (1,73 m^2), ali, budući da se površina tijela znatno razlikuje između pretilih i vitkih osoba, vrijednosti klirensa kreatinina treba ispraviti za stvarnu tjelesnu površinu.[4] U kliničkoj je praksi procjena GFR-a široko prihvaćena kao najbolji pokazatelj funkcije bubrega.[13] Normalni GFR u mladih odraslih osoba veći je od 90 mL/min/1,73 m^2, u prosjeku 125 mL/min/1,73 m^2.[1] Mjerenje klirensa kreatinina i inulina primjenjuje se za procjenu GFR-a.[1] Ocjena bubrežne funkcije može se provesti procjenom glomerularne filtracije prema MDRD (*Modification of Diet in Renal Diseases*) jednadžbi, klirensom kreatinina određenim *Cockcroft-Gault* metodom ($eCrCl_{CG}$) i njegovom korekcijom za površinu tijela ($eCrCl_{CG1,73}$).[1,5,12,13] Osim toga, za ocjenu bubrežne funkcije može se iskoristiti klirens kreatinina određen *Cockcroft-Gault* metodom korigiran za indeks tjelesne mase ($eCrCl_{CGBMI}$), površinu tijela ($eCrCl_{CGBMI1,73}$) i procijenjeni GFR koristeći se *Cockcroft-Gault* metodom ($eGFR_{CGBMI1,73}$).[1,5,13]

Svrha je ovog istraživanja bila je utvrditi postoje li razlike između razine serumskog kreatinina, procijenjene stope glomerularne filtracije (eGFR) prema *Modification of Diet in Renal Disease* (MDRD) jednadžbi, klirensa kreatinina i procijenjenog GFR-a *Cockcroft-Gault* metodom s obzirom na dob te stupanj i trajanje AH-a.

Bolesnici i metode

BOLESNICI I DIZAJN ISTRAŽIVANJA

Ovo presječno istraživanje provedeno je na Klinici za bolesti srca, krvnih žila i reumatizam Kliničkog centra Univerziteta

Introduction

The National Kidney Foundation defines chronic kidney disease as kidney damage that lasts for more than 3 months and is caused by structural or functional disorders of the kidneys, with or without a decrease in glomerular filtration rate (GFR), manifesting as histological abnormalities or disturbances in blood, urine, or kidney function. The term "chronic kidney failure" is used to describe the terminal (fifth) stage of chronic kidney disease.[1] Chronic kidney disease is one of the leading causes of mortality and morbidity in the world.[1-3] The prevalence of kidney disease has been constantly increasing over the last decade, in parallel with the rapid increase in diabetes mellitus and arterial hypertension, representing a major public health problem with enormous impact on quality of life and economic status.[1,4,5]

Early detection and treatment reduce the progression of chronic kidney disease toward end-stage kidney failure.[6-8] The most common causes of morbidity and mortality in patients with chronic kidney disease are cardiovascular ones.[9] Arterial hypertension can cause glomerular damage, microalbuminuria, and proteinuria.[3-5] Increase in blood pressure is associated with a significant decrease in GFR (1.1-6.2 mL/min/year).[6] Therapy with angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs) has shown a renoprotective effect and reduction in proteinuria in patients with arterial hypertension.[5] This renoprotective effect is based on the blockage of the conversion of angiotensin I to angiotensin II and the consequent dilatation of the efferent arterioles and reduction of intraglomerular pressure.[7,10,11]

Early detection of kidney disease with the use of screening tests to reveal high-risk groups of patients, such as those with arterial hypertension and diabetes mellitus, is very important and cost-effective.[12-14] Creatinine clearance values always refer to the average body surface area of adults (1.73 m^2), but because body surface area differs significantly between obese and slim individuals, creatinine values need to be corrected for actual body surface area.[4] In clinical practice, estimation of GFR is widely accepted as the best indicator of kidney function.[13] Normal GFR in young adults is greater than 90 mL/min/1.73 m^2, averaging 125 mL/min/1.73 m^2.[1] Measurement of creatinine and inulin clearance is used to assess GFR.[1] Assessment of kidney function can be done using glomerular filtration, according to the MDRD (Modification of Diet in Renal Disease Study) equation, while clearance of creatinine is determined by the Cockcroft-Gault method ($eCrCl_{CG}$) and its correction for body surface area ($eCrCl_{CG1.73}$).[1,5,12,13] Additionally, creatinine clearance determined by the Cockcroft-Gault method corrected for body mass index ($eCrCl_{CGBMI}$) and body surface area ($eCrCl_{CGBMI1.73}$) and estimated GFR using the Cockcroft-Gault method ($eGFR_{CGBMI1.73}$) can be used for assessment of kidney function.[1,5,13]

The aim of this study was to determine whether there are differences between serum creatinine levels, estimated GFR according to the MDRD equation, creatinine clearance, and estimated GFR obtained by the Cockcroft-Gault method related to age, stage, and duration of arterial hypertension.

Patients and Methods

PATIENTS AND STUDY DESIGN

This cross-sectional study was conducted in the Clinic for Heart, Rheumatism and Blood Vessels, Clinical Center Uni-

u Sarajevu, tijekom ožujka 2019. Istraživanje je uključilo 124 ambulantna bolesnika (n = 124) s dijagnozom AH-a. Svi su bolesnici pregledani, a pri uzimanju anamnestičkih podataka osobita je pozornost, među ostalim, posvećena uzrocima, trajanju bolesti i visini AT-a, kao i uzimanju antihipertenziva i navici pušenja.

Uključni kriteriji za istraživanje bili su dob >18 godina, dijagnoza AH i nalaz vrijednosti kreatinina u serumu. Isključni su kriteriji bili: bolesnici s prije postojećom dijagnozom KBB-a nehipertenzivne etiologije bilo kojeg stupnja, bolesnici na programu kronične dijalize, bolesnici s akutnim i kroničnim zatajivanjem srca, bolesnici s amputacijom donjih ekstremiteta, prisutnost aktivnih ili karcinoma u anamnestičkim podatcima, trudnoća.

Etičko odobrenje dobiveno je od Etičkog odbora Kliničkog centra Univerziteta u Sarajevu.

METODE

Vrijednosti AT-a klasificirane su u sljedeće kategorije: stupanj I., II. i III., prema postojećim smjernicama za arterijsku hipertenziju.[5]

Procjena funkcije bubrega rađena je sa: serumskom razinom kreatinina (µmol/L), MDRD jednadžbom (mL/min/1,73m²), $eCrCl_{CG}$ (mL/min), $eCrCl_{CG1,73}$ (mL/min), $eCrCl_{CGBMI}$ (mL/min), $eCrCl_{BMI1,73}$ (mL/min) i $eGFR_{CGBMI1,73}$ (mL/min/1,73 m²).

STATISTIČKA ANALIZA

Rezultati istraživanja obrađeni su s pomoću deskriptivne i inferencijalne statistike. Kolmogorov-Smirnovljev test primijenjen je za procjenu raspodjele podataka i podatci s normalnom raspodjelom prikazani su prema aritmetičkoj sredini (X) i standardnoj devijaciji (SD). Usporedbe numeričkih podataka među skupinama napravljene su Studentovim t-testom i jednosmjernom analizom varijance (ANOVA). Ocjena povezanosti kategorijskih varijabli provođena je Hi-kvadrat i Fisherovim testom. Svi rezultati statističke analize na razini p<0,05 bili su prihvaćeni kao statistički značajni.

Rezultati

U istraživanje su bila uključena 124 bolesnika, među kojima je bilo 60 (48,4 %) žena prosječne dobi 63,1 ± 8,15 godina i 64 (51,6 %) muškarca prosječne dobi 63,2 ± 11,03. Većina bolesnika, tj. njih 56 (45,2 %) imalo je 56 – 65 godina, među kojima su 29 žena i 27 muškaraca. Najmanji broj bolesnika bio je u dobnoj skupini 35 – 44 godine (njih 7), među kojima 2 žene i 5 muškaraca. Postojala je značajna razlika s obzirom na spol u dobnoj skupini 76 – 85 godina (x^2 = 4,818, p<0,05). Analiza farmakološkog statusa pokazala je da se velik broj bolesnika s AH-om (n = 88) koristio različitim antihipertenzivnim lijekovima, tj. 60 bolesnika uzimalo je dvojnu terapiju ACE inhibitor + diuretik ili ARB + diuretik. ACE inhibitorom koristilo se 55 (44,3 %) bolesnika u monoterapiji i to su bili bolesnici niskog rizika s AH-om uglavnom prvoga stupnja, dok su se 42 bolesnika (33,8 %) koristila je blokatorima kalcijevih kanala (**tablica 1**). Od 36 bolesnika s AH-om i šećernom bolesti, njih 17 rabilo je diuretik s ACE inhibitorom ili ARB-om (**tablica 2**). Zabilježena je značajna razlika u uporabi nitroglicerinskih preparata između bolesnika s AH-om i onih s AH-om i šećernom bolešću, tj. bolesnici s objema bolestima češće su koristili nitroglicerinskim preparatima (x^2 = 6,278; p <0,05). Postojala

versity of Sarajevo, during March 2019. The study included 124 inpatients (n=124) with a diagnosis of arterial hypertension. Among other anamnestic data collected during physical examination, data was also collected from patient medical records on the cause, duration, and stage of arterial hypertension, as well as on antihypertensive therapy and smoking habits.

Criteria for inclusion in the study were: more than 18 years old, diagnosis of arterial hypertension, and measured serum creatinine values during the examination. Criteria for exclusion were: pre-existing diagnosis of chronic kidney disease of non-hypertensive ethology of any stage, chronic dialysis, diagnosis of acute and chronic heart failure, amputation of lower extremities, presence of active cancer or cancer in the anamnestic data, and pregnancy.

Ethical approval was obtained from the Ethical Committee, Clinical Center University of Sarajevo.

METHODS

Assessment of the stage of arterial hypertension (grade I, II, and III) was performed based on the relevant guidelines for the management of arterial hypertension.[5]

Assessment of kidney function was performed with: serum creatinine levels (µmol/L), MDRD equation (mL/min/1.73 m²), $eCrCl_{CG}$ (mL/min), $eCrCl_{CG1.73}$ (mL/min), $eCrCl_{CGBMI}$ (mL/min), $eCrCl_{CGBMI1.73}$ (mL/min), and $eGFR_{CGBMI1.73}$ (mL/min/1.73 m²).

STATISTICAL ANALYSIS

The results of the study were processed using descriptive and inferential statistics. The Kolmogorov-Smirnov test was used to assess the distribution of the data, and the data with the normal distribution was reported as arithmetic mean (X) and standard deviation (SD). Comparisons of numerical data between groups were done using the y Student's t-test and one-way analysis of variance (ANOVA). The chi-square test of Independence and the Fisher's exact test were used for evaluation of the association of categorical variables. All results of the statistical analysis at the level of p<0.05 were accepted as statistically significant.

Results

The study included 124 patients, of whom 60 (48.4%) were women with an average age of 63.1±8.15 and 64 (51.6%) men with an average age of 63.2±11.03. The majority of patients, i.e. 56 (45.2%) of them, were 56-65 years old, of whom 29 were women and 27 were men. The lowest number of patients was in the 35-44 age group (7 of them) – of those 2 women and 5 men. There was a significant difference in sex distribution in the 76-85 age group (x^2=4.818, p<0.05). Analysis of pharmacological status indicated that the vast number of patients with hypertension (n=88) used different types of antihypertensive drugs, i.e. 60 patients used dual therapy with either an ACE inhibitor + diuretic or ARB + diuretic. Fifty five (44.3%) patients used an ACE inhibitor and were low-risk patients with mainly the first-stage arterial hypertension; 42 patients (33.8%) used calcium channel blockers (**Table 1**). Of 36 patients with both arterial hypertension and diabetes mellitus, 17 used a diuretic with an ACE inhibitor or ARB (**Table 2**). There was a significant difference in the usage of nitro-based products between patients with hypertension only and patients with both arterial hypertension and diabetes mellitus, i.e. patients with both diseases used nitro-based products more often (x^2=6.278; p<0.05).

TABLE 1. Distribution of patients according to duration and stage of arterial hypertension.

Hypertension n (%)		Total number of patients (n=124)	Duration of the disease (in years)
		Mean ± SD	
Hypertension duration	<5 years	49 (39.5%)	2.3 ± 0.92
	5-10 years	43 (34.7%)	7.3 ± 2.07
	>10 years	32 (25.8%)	18.4 ± 8.39
Hypertension stage	I	56 (45.2%)	6.8 ± 6.99
	II	56 (45.2%)	8.8 ± 6.37
	III	12 (9.6%)	12.3 ± 13.69

SD=standard deviation

TABLE 2. Frequency of usage of different drugs and drug combinations in the treatment of arterial hypertension in relation to the stage and duration of the disease.

Characteristic		Antihypertensive treatment				
		ACE inhibitor	ARB	Diuretic+ACE inhibitor / Diuretic+ARB	Ca-blocker	Nitro-derivates
		n (%)	n (%)	n (%)	n (%)	n (%)
Disease	HTA	39 (43.8%)	10 (11.2%)	43 (48.3%)	30 (33.7%)	43 (48.3%)
	HTA/DM	16 (45.7%)	4 (11.4%)	17 (48.6%)	12 (34.3%)	29 (82.9%)
Sex	female	26 (43.3%)	8 (13.3%)	27 (45.0%)	24 (40%)	31 (51.7%)
	male	29 (45.3%)	6 (9.4%)	33 (51.6%)	18 (28.1%)	41 (67.2%)
Age (years)	35-45	3 (42.9%)	0 (0.0%)	4 (57.1%)	2 (28.6%)	4 (57.1%)
	46-55	8 (61.5%)	1 (7.7%)	4 (30.8%)	4 (30.8%)	7 (53.8%)
	56-65	28 (50.0%)	6 (10.7%)	25 (44.6%)	18 (32.1%)	30 (53.6%)
	66-75	14 (38.9%)	6 (16.7%)	18 (50.0%)	13 (36.1%)	24 (66.7%)
	76-85	2 (16.7%)	1 (8.3%)	9 (75.0%)	5 (41.7%)	7 (58.3%)
HTA duration (years)	<5	27 (55.1%)	5 (10.2%)	20 (40.8%)	10 (20.4%)	26 (53.1%)
	5-10	17 (39.5%)	6 (13.9%)	19 (44.2%)	16 (37.2%)	29 (67.4%)
	>10	9 (28.1%)	3 (9.4%)	21 (65.6%)	16 (50.0%)	17 (53.1%)
HTA stage	I	29 (51.8%)	3 (5.4%)	23 (41.1%)	12 (21.4%)	31 (55.4%)
	II	22 (39.3%)	10 (17.8%)	30 (53.6%)	20 (35.7%)	33 (58.9%)
	III	4 (33.3%)	1 (8.3%)	7 (58.3%)	10 (83.3%)	8 (66.7%)
Smoking	Yes	41 (47.1%)	9 (10.3%)	41 (47.1%)	34 (39.1%)	54 (62.1%)
	No	14 (37.8%)	5 (13.5%)	19 (51.4%)	8 (21.6%)	18 (48.6%)

ACE inhibitor=angiotensin converting enzyme inhibitor; ARB=angiotensin receptor blocker; Ca blocker=calcium blocker; HTA=hypertension; DM=diabetes mellitus

je značajna povezanost između $eGFR_{CGBMI1,73}$ i dobi (p = 0,001) (**tablica 3**). Kako se dob povećavala za 10 godina, prosječna se vrijednost $eGFR_{CGBMI1,73}$ snizivala za 11,03 mL/min/1,73 m^2. Također, kako se dob povećavala za 10 godina, prosječna vrijednost procijenjenog GFR-a MDRD jednadžbom snizivala se za 5,24 mL/min/1,73m^2. Nadalje, postojala je značajna razlika u vrijednostima prema MDRD jednadžbi procijenjenog GFR-a, $eCrCl_{CGBMI}$, $eCrCl_{CGBMI1,73}$, $eGFR_{CGBMI1,73}$, u ispitanika različitih

There was a significant relation between the $eGFR_{CGBMI1.73}$ and the age (p=0.001) (**Table 3**). For each 10-year age increase, the average value of $eGFR_{CGBMI1.73}$ decreased by 11.03 mL/min/1.73 m^2. Additionally, with each 10-year age increase the average value of the estimated GFR with the MDRD formula decreased by 5.24 mL/min/1.73 m^2. Furthermore, there was a significant difference in the values MDRD formula-estimated GFR, $eCrCl_{CGBMI}$, $eCrCl_{CGBMI1.73}$, and $eGFR_{CGBMI1.73}$ in subjects with

stupnjeva i različita prosječnog trajanja bolesti (**tablica 4**). Ako se rabi serumski kreatinin, ne dobiva se značajna razlika između skupina s obzirom na napredovanje AH-a.

different stages and different average illness duration (**Table 4**). If serum creatinine was used, no significant difference was observed between groups regarding the progression of arterial hypertension.

TABLE 3. Evaluation of kidney function according to sex.

Kidney function	All patients (n=124)	Sex		p
		Women (n=60)	Men (n=64)	
Serum creatinine (μmol/L)	89.7 ± 20.49	84.4 ± 20.97	94.8 ± 19.02	0.005
MDRD (mL/min/1.73 m²)	72.0 ± 18.24	66.4 ± 16.27	77.4 ± 18.65	0.001
$eCrCl_{CG}$ (mL/min)	82.5 ± 28.49	72.3 ± 19.43	92.2 ± 32.39	0.001
$eCrCl_{CG1.73}$ (mL/min)	70.6 ± 19.41	66.6 ± 15.32	74.3 ± 22.20	0.027
$eCrCl_{CGBMI}$ (mL/min)	74.4 ± 24. 27	65.6 ± 17.04	82.6 ± 27.30	0.001
$eCrCl_{CGBMI1.73}$ (mL/min)	63.4 ± 16.96	60.2 ± 14.10	66.5 ± 18.99	0.038
$eGFR_{CGBMI1.73}$ (mL/min/1.73 m²)	50.6 ± 19.04	46.8 ± 15.80	54.3 ± 21.29	0.030

MDRD=estimated glomerular filtration rate according to the MDRD (Modification of Diet in Renal Disease Study) equation; $eCrCl_{CG}$=clearance of creatinine estimated by the Cockcroft-Gault method; $eCrCl_{CG1.73}$=correction for body surface area; $eCrCl_{CGBMI}$=correction for body mass index; $eCrCl_{CGBMI1.73}$=correction for body surface area and body mass index; $eGFR_{CGBMI1.73}$=estimated GFR using the Cockcroft-Gault method; p=level of significance

TABLE 4. Evaluation of kidney function according to sex in relation to the stage of arterial hypertension and average duration of disease.

Kidney function	Average disease duration (in years)			p
	6.8	8.8	12.3	
	Disease stage			
	I (Mean ±SD)	II (Mean ±SD)	III (Mean ±SD)	
Serum creatinine (μmol/L)	87.0 ± 19.19	92.1 ± 20.68	91.9 ± 26.14	0.404
MDRD (mL/min/1.73 m²)	76.5 ± 19.42	68.8 ± 15.65	66.0 ± 21.12	0.039
$eCrCl_{CG}$ (mL/min)	88.7 ± 29.41	78.7 ± 25.71	71.8 ± 33.66	0.071
$eCrCl_{CG1.73}$ (mL/min)	75.1 ± 20.45	67.4 ± 17.15	64.8 ± 22.29	0.060
$eCrCl_{CGBMI}$ (mL/min)	80.5 ± 25.40	70.0 ± 20.83	66.9 ± 29.91	0.038
$eCrCl_{CGBMI1.73}$ (mL/min)	68.1 ± 18.00	59.8 ± 14.30	59.2 ± 20.20	0.024
$eGFR_{CGBMI1.73}$ (mL/min/1.73 m²)	55.6 ± 20.16	46.8 ± 16.21	45.7 ± 22.74	0.031

MDRD=estimated glomerular filtration rate according to the MDRD (Modification of Diet in Renal Disease Study) equation; $eCrCl_{CG}$=clearance of creatinine estimated by the Cockcroft-Gault method; $eCrCl_{CG1.73}$=correction for body surface area; $eCrCl_{CGBMI}$=correction for body mass index; $eCrCl_{CGBMI1.73}$=correction for body surface area and body mass index; $eGFR_{CGBMI1.73}$=estimated GFR using the Cockcroft-Gault method; p=level of significance; SD=standard deviation

Rasprava

Istraživanje je pokazalo da bolesnici najčešće uzimaju više antihipertenzivnih lijekova, što je praksa u suvremenoj kardiologiji.[5] Raspodjela AH-a na stupnjeve s obzirom na vrijednosti AT-a na pregledu nije baš optimalna za kliničku uporabu. Također, u skladu s rezultatima ovog istraživanja trajanje AH-a ne utječe na njezin stupanj. Uporaba je bubrežnozaštitnih i srčanozaštitnih lijekova obvezna.[5] Sporije napredovanje

Discussion

Research has shown that patients predominantly receive polytherapy for arterial hypertension, which is a trend in modern cardiology.[5] Classification of arterial hypertension in stages in relation to blood pressure values on examination is not an optimal clinical approach. Additionally, as demonstrated in this study, the duration of hypertension does not affect the stage of hypertension. The use of renoprotective

bubrežne bolesti pokazano je kod bolesnika sa šećernom bolesti i AH ako su rabljeni ACE inhibitori ili ARB.[14,15] Kada nije moguće uključiti jedan od ovih lijekova u terapiju, preporučuju se nehidropiridinski blokatori kalcijevih kanala.[5] Terapija ACE inhibitorima i blokatorima angiotenzin II receptora (ARB) pokazuje renoprotektivni učinak i smanjenje proteinurije u bolesnika s AH-om. Kombinacije ACE inhibitora i diuretika, te ARB-a i diuretika bile su najpropisivanije. *National Kidney Foundation* preporučujeu uporabu fiksne granične vrijednosti procijenjene GFR za definiranje KBB-a i te su vrijednosti GF <60 mL/min/1,73m^2 s tromjesečnim kronicitetom.[16] Ova preporuka nije obrazložena jer ne uzima u obzir spolne i dobne razlike, što je nedvojbeno. Istraživanje je potvrdilo značajnu razliku u vrijednostima po MDRD jednadžbi procijenjene GFR, $eCrCl_{CGBMI}$, $eCrCl_{CGBMI1,73}$, $eGFR_{CGBMI1,73}$, u ispitanika različitih stupnjeva i različita prosječnog trajanja bolesti, što nije pokazano za serumski kreatinin. Rule *i sur.* proveli su istraživanje s 365 potencijalnih darivatelja bubrega kako bi se definirale dobne i spolne granične vrijednosti za GFR i kreatinin u serumu.[17] Stopa glomerularne filtracije bila je procijenjena primjenom klirensa jodtalamata, skraćene MDRD jednadžbe (eGFR-MDRD) i Cockcroft-Gault metode.[17] Stopa glomerularne filtracije značajno se smanjivala kako se dob povećavala, i to mnogo manje u žena nego muškaraca. Prosječni procijenjeni GFR muškaraca čija je prosječna dob bila 20 godina iznosio je 129 mL/min uz pad od 4,6 ml/min/desetljeće. U žena iste dobi procijenjeni GFR bio je 123 mL/min uz pad od 7,1 mL/min/desetljeće. Vrijednosti GFR-a korigirane za indeks tjelesne mase bile su značajno različite po dobi, ali ne i po spolu.[17] Također, za bolesnike koji su u prosjeku imali 20 godina procijenjeni GFR je bio 111 mL/min/1,73 m^2, uz pad od 4,9 mL/min/1,73 m^2 sa svakim desetljećem.[17]

Velde *i sur.* ispitali su korelaciju procijenjenih GFR-a (za različite metode i dobne skupine) i kardiovaskularnih događaja u 8047 ispitanika.[18] Da bi se procijenio GFR, uporabljene su sljedeće jednadžbe: MDRD,CKD-EPI, cistatin C, kombinirana jednadžba serumskog kreatinina i kvadratne jednadžbe cistatina C i 24 satni klirens kreatinina.[18] Zaključeno je da su sve metode primijenjene za procjenu GFR-a značajno u korelaciji s kardiovaskularnim događajima u bolesnika mlađih od 60 godina, dok je 24-satni klirens kreatinina pokazao značajnu korelaciju s kardiovaskularnim događajima u ispitanika koji imaju 60 ili više godina. Milojković *i sur.* istraživali su korelaciju esencijalne AH i hipertenzivne nefropatije među 283 ispitanika, kao i prevalenciju čimbenika rizika za razvoj aterosklerotskih promjena.[19] Utvrđena je značajna korelacija između pozitivne anamneze, AH-a, pušenja i dislipidemije s obzirom na prevalenciju hipertenzivne nefropatije.[19] Procijenjeni GFR prema MDRD jednadžbi bio je u značajno obrnuto proporcionalnom odnosu s trajanjem i stupnjem AH-a, a jednak je odnos pronađen između $eCrCl_{CGBMI1,73}$ i $eGFR_{CGBMI1,73}$ i trajanja te stupnja AH-a.[19] Istraživanja su pokazala da je navika pušenja i dalje velik problem za bolesnike u Bosni i Hercegovini i preventivni programi sa svrhom smanjenja progresije aterosklerotske bolest trebali bi biti dio svakodnevnog rada liječnika u primarnoj zdravstvenoj zaštiti.

Ograničenja istraživanja bila su, prvo, mali broj bolesnika za procjenu optimalnoga farmakološkog tretmana, drugo, nije uzet u obzir način liječenja šećerne bolesti, što bi moglo utjecati na rezultate. Također bi raspodjela ACE inhibitora ili ARB-a u pojedinih ispitanika, uzimajući u obzir njihovu far-

and cardioprotective drugs is imperative.[5] Slower progression of kidney disease has been demonstrated in patients with diabetes mellitus and arterial hypertension if they used ACE inhibitors or ARBs.[14,15] When it is not possible to include one of these medications in the therapy, non-hydropyridine calcium channel blockers are recommended.[5] Therapy with ACE inhibitors and ARBs shows a renoprotective effect and reduction in proteinuria in patients with arterial hypertension. Combinations of ACE inhibitors and diuretics and ARBs and diuretics were the most-prescribed combinations. The National Kidney Foundation suggests the use of a fixed cut-off value of estimated GFR to define chronic kidney diseases, those values being GF<60 mL/min/1.73 m^2 with a three-month chronicity.[16] This recommendation is not reasonable, as it does not take into account differences in age and sex, which are non-negotiable. Research has verified significant differences in the values of MDRD formula-estimated GFR, $eCrCl_{CGBMI}$, $eCrCl_{CGBMI1.73}$, and $eGFR_{CGBMI1.73}$ in subjects with different stages and different average illness durations, which has not been demonstrated for serum creatinine. Rule *et al.* conducted a study on 365 potential kidney donors to define age- and sex-related reference values for GFR and serum creatinine values.[17] GFR was measured using iothalamate clearance, and the abbreviated MDRD equation (eGFR-MDRD) and the Cockcroft-Gault method were used for its estimation.[17] It decreased significantly with increased age and was much lower in women compared with men. The average estimated GFR of men whose average age was 20 was 129 mL/min with a decline of 4.6 mL/min per decade. In women of the same age, the estimated GFR was 123 mL/min with a decline of 7.1 mL/min/decade. GFR values corrected for body mass index were significantly different for age, but not for sex.[17] Additionally, patients who were on average 20 years old had a GFR of 111 mL/min/1.73 m^2, with a decline of 4.9 mL/min/1.73 m^2 with every decade.[17]

Velde *et al.* examined the correlation of estimated GFRs (for different methods and different age groups) and cardiovascular events in 8047 subjects.[18] The following equations were used to estimate GFR: the MDRD equation, the chronic kidney disease-epidemiology collaboration (CKD-EPI) equation, the cystatin C-based equation, the combined serum creatinine and cystatin C Quadratic Equation, and 24-hours creatinine clearance.[18] They concluded that all of the methods used to estimate GFR were significantly correlated with cardiovascular events in patients who are less than 60 years old, while 24-hour creatinine clearance showed a significant correlation with cardiovascular events in subjects who are 60 or more years old. Milojkovic *et al.* investigated the correlation between essential arterial hypertension and hypertensive nephropathy among 283 subjects as well as the prevalence of risk factors for the development of atherosclerotic changes.[19] A significant correlation was found between a positive anamnesis, arterial hypertension, smoking, and dyslipidemia in relation to the prevalence of hypertensive nephropathy.[19] The estimated GFR according to the MDRD equation was in a significant inversely proportional relationship with duration and stages of arterial hypertension, and the same relationship was found between $eCrCl_{CGBMI1.73}$ and $eGFR_{CGBMI1.73}$ and the duration and stage of arterial hypertension.[19] Research has shown that the habit of smoking is still a large problem for patients in Bosnia and Herzegovina, and preventive programs aiming to reduce progression of atherosclerotic disease should be part of the daily work of medical doctors in primary health care.

makodinamiku i farmakokinetička svojstva, bila važna za procjenu renoprotektivnog učinka lijekova.

Zaključak

Procijenjeni GFR i eCrCl osjetljiviji su biljezi oštećenja bubrega od vrijednosti kreatinina u serumu i njihovo određivanje treba uvesti kao rutinski probir u otkrivanju ranih stadija KBB-a u primarnoj zdravstvenoj zaštiti, posebno u bolesnika s AH-om.

The limitations of the present study were, firstly, the small number of patients used to assess optimal pharmacological treatment, and secondly, the treatment modality of diabetes mellitus was not taken into account, which could have affected the results. Additionally, distribution of ACE inhibitors or ARBs to individual patients while taking into account their pharmacodynamics and pharmacokinetic properties, would be an important approach in assessing the renoprotective effects of the drugs.

Conclusion

Estimated GFR and eCrCl are more sensitive markers of kidney impairment than serum creatinine values, and their assessment should be introduced as a routine screening in the detection of early stages of chronic kidney disease in primary care settings, especially in patients with arterial hypertension.

FUNDING: No specific funding was received for this study.

TRANSPARENCY DECLARATION: Competing interests: none to declare.

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