

Utjecaj varijacija dobi i spola na stopu glomerularne filtracije izračunate jednadžbom MCQE

Influence of age and gender variations on glomerular filtration rate estimated by the MCQE formula

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Sažetak

Uvod: U kliničkoj se praksi stopa glomerularne filtracije (engl. *glomerular filtration rate*, GFR) rutinski određuje jednadžbom temeljenoj na koncentraciji kreatinina u serumu, razvijenoj i potvrđenoj u okviru studije MDRD (engl. *Modification of Diet in Renal Disease Study*, MDRD). Međutim, budući da jednadžba podcjenjuje smanjenje GFR, razvijena je jednadžba MCQE (engl. *Mayo Clinic Quadratic Equation*, MCQE).

Ispitanici i metode: Svrha ovoga istraživanja bila je analizirati utjecaj varijacije dobi i spola kod određivanja GFR pomoću jednadžbe MCQE. Iz baze podataka našega laboratorijskog informatičkog sustava uzeti su rezultati 16.631 određivanja koncentracije kreatinina u serumu provedenih na uzastopnim ispitanicima.

Rezultati: Razlika u određivanju GFR između muškaraca i žena bila je statistički značajna kod računanja objema jednadžbama (MDRD i MCQE). Statistički značajne razlike zabilježene su kod svih dobnih skupina u razredima od po deset godina kod računanja jednadžbom MCQE, a kod računanja jednadžbom MDRD samo kod ispitanika starijih od 51 godine. Zabilježena je i statistički značajna razlika u srednjoj vrijednosti GFR određenoj objema jednadžbama između različitih dobnih skupina u razredima od po deset godina kod oba spola.

Zaključak: Rezultati ove epidemiološke analize potvrđuju da se niti jednadžbom MCQE ne mogu nadomjestiti varijacije dobi i spola.

Ključne riječi: kreatinin; stopa glomerularne filtracije; bubrežna funkcija; MDRD; MCQE

Abstract

Background: In clinical practice, the glomerular filtration rate (GFR) is routinely estimated by the creatinine-based equation developed and validated from the Modification of Diet in Renal Disease (MDRD) Study. However, since this formula estimates the rate of decline in GFR, the Mayo Clinic Quadratic Equation (MCQE) has been developed.

Petients and methods: The purpose of this study was to assess the influence of age and gender variations on GFR estimated by this new equation. Results of 16,631 serum creatinine tests performed in consecutive outpatients were retrieved from the database of our Laboratory Information System. GFR was estimated by both the MDRD and MCQE formulas.

Results: The difference in the estimated GFR between males and females was significantly different when calculated with either MDRD or MCQE formula. Significant gender differences were observed in all age decades by MCQE and in subjects aged >51 years by MDRD. A significant difference in the mean GFR values estimated by either formula was also observed between different age decades in both genders.

Conclusions: The results of this epidemiological analysis indicated the MCQE formula also fail to compensate for age and gender variations.

Key words: creatinine; glomerular filtration rate; kidney function; MDRD; MCQE

Uvod

Stopa glomerularne filtracije (engl. *glomerular filtration rate*, GFR) smatra se najboljim pokazateljem bubrežne funkcije, pa ju Američke nacionalna bubrežna zaklada (engl. *National Kidney Foundation*, NKF) inicijative i različiti programi usavršavanja (engl. *Kidney Disease Outcomes Quality Initiative*, K/DOQI; *National Kidney Disease Education Program*, NKDEP) preporučuju za dijagnosticiranje oštećenja bubrega i kategorizaciju težine bolesti (1). Tradicionalno se GFR ne može izmjeriti izravno, već se određuje mjerenjem mokraćnog klirensa egzogenih biljega filtracije. Međutim, zbog komplicirane uporabe, troškova, izloženosti radijaciji i administrativnih zahtjeva u radu s radionuklidima, te metode imaju ograničenu uporabu i svode se na istraživačku aktivnost (2). Stoga se danas preporuča određivanje GFR jednadžbama temeljenim na koncentraciji kreatinina u serumu u oba slučaja, kod analiziranja bubrežne funkcije (2) ili predviđanja kardiovaskularnih oštećenja (3). Dosada je predloženo nekoliko jednadžba, a trenutno se preporuča jednadžba razvijena u okviru studije MDRD (engl. *Modification of Diet in Renal Disease*, MDRD) (2). Ova je jednadžba prihvatljivija od tradicionalne Cockcroft-Gaultove jednadžbe za predviđanje GFR vrijednosti manje od 60 mL/min/1,73 m² (izmjerene upotrebom radionuklida) i točnija je od slučajeva kada su izmjerene koncentracije kreatinina u serumu manje od 60 μmol/L ili ispravljene na 60 μmol/L ili isključene iz računanja GFR (4). Međutim, naglašava se da bi ova jednadžba mogla imati nekih nedostataka, budući da ne uspijeva korigirati rezultate za dob i spol (5) i nije uspješno ispitana na djeci, starijim osobama, trudnicama, bolesnicima s ozbiljnim komorbiditetima ili osobama ekstremne tjelesne veličine (1). Štoviše, budući da se pokazalo kako bi jednadžba MDRD mogla statistički značajno podcijeniti smanjenje GFR kad se ona mjeri referentnom metodom, razvijena je nova jednadžba MCQE (engl. *Mayo Clinic Quadratic Equation*, MCQE) (6). Stoga je glavna svrha ovoga istraživanja bila analizirati utjecaj varijacija dobi i spola na određivanje GFR ovom novom jednadžbom.

Ispitanici i metode

Ispitanici

Kod uzastopnih ispitanika, što su ih njihovi liječnici opće prakse uputili na rutinsku pretragu krvne slike, koncentracije kreatinina u serumu dobivene su iz baze podataka našega laboratorijskog informatičkog sustava u Sveučilišnoj bolnici u Veroni. Uzorci venske krvi su se rutinski prikupljali ujutro natašte.

Metode

Koncentracija kreatinina u serumu izmjerena je sustavom Roche/Hitachi Modular System P (Roche Diagnosti-

Introduction

Glomerular filtration rate (GFR) is considered the best index of kidney function, which is also recommended by the National Kidney Foundation (NKF), the Kidney Disease Outcomes Quality Initiative (K/DOQI) and the National Kidney Disease Education Program (NKDEP) for diagnosing renal damage and classifying the severity of kidney disease (1). Traditionally, GFR cannot be measured by direct means, but it can be assessed by measuring urinary clearance of exogenous filtration markers. However, due to difficulty in use, expenses, radiation exposure, and radionuclide regulatory requirements, these methods have limited use and are typically confined to the research setting (2). Therefore, it is now recommended to estimate GFR by equations based on serum creatinine, either to assess renal function (2) or to predict cardiovascular outcome (3). Several formulas have been proposed so far, but the currently recommended equation is that developed and validated from the Modification of Diet in Renal Disease (MDRD) Study (2). This formula is superior to the traditional Cockcroft-Gault equation for prediction of radionuclide determined GFR of < 60 mL/min/1.73 m² and is more accurate when creatinine results lower than 60 μmol/L are either corrected to 60 μmol/L or excluded from GFR calculations (4). However, it has also been highlighted that this formula might have some drawbacks, since it fails to correct results for age and gender (5), and it has not been sufficiently tested in children, the elderly, pregnant women, patients with serious comorbidities, or persons with extremes of body size (1). Moreover, since it has also been demonstrated that the MDRD formula might significantly underestimate the rate of decline in GFR when measured by a reference method, the new Mayo Clinic Quadratic Equation (MCQE) has been developed (6). Therefore, the main purpose of this study was to assess the influence of age and gender variations on GFR estimated by this new equation.

Patients and methods

Patients

Results of serum creatinine tests, which were performed in consecutive outpatients referred by general practitioners for routine blood testing over the past year, were retrieved from the database of our Laboratory Information System at the University Hospital of Verona. Fasting venous blood was routinely collected from outpatients in the morning.

Methods

Serum creatinine was measured on a Roche/Hitachi Modular System P (Roche Diagnostics GmbH, Mannheim, Germany) by creatinine Jaffe, rate blanked and compen-

cs GmbH, Mannheim, Njemačka) Jaffeovom kinetičkom metodom za određivanje kreatinina. Kvaliteta rezultata tijekom istraživanja ocjenjivala se redovnom unutarnjom kontrolom kvalitete te sudjelovanjem u programu vanjske procjene kvalitete rada.

Procjena GFR se u cijelom istraživanju računala jednadžbom MDRD (2):

$$\text{GFR} = 186 \times (\text{koncentracija kreatinina u serumu}^{-1,154}) \times (\text{dob}^{-0,203}) \times 1,212 \text{ (ako je Afroamerikanac)} \times 0,742 \text{ (za ženski spol);}$$

i jednadžbom MCQE:

$$\text{GFR} = \exp [1,911 + (5,249/\text{koncentracija kreatinina u serumu}) - (2,114/\text{koncentracija kreatinina u serumu}^2) - 0,00686 \times \text{dob}^{-0,205} \text{ (za ženski spol)}].$$

Ako je koncentracija kreatinina u serumu <71 $\mu\text{mol/L}$, zamjenjuje se vrijednošću 71 $\mu\text{mol/L}$ (6).

Statistička analiza

Shapiro-Wilkinsonovim testom ispitana je normalnost razdiobe, a kako bi se ona poboljšala prije same analize su varijable logaritamski transformirane. Kruskal-Wallisovim testom ispitano je postojanje statistički značajne razlike između GFR u podskupinama prema dobnim razredima. Statističke su analize napravljene pomoću statističkog programskog paketa SPSS verzija 12.0 (SPSS, Chicago, IL, SAD), a razina statističke značajnosti postavljena je na 0,05. Podaci su prikazani kao geometrijska sredina s intervalom pouzdanosti 95% (engl. *confidence interval*, CI).

Rezultati

Ukupni rezultati mjerenja koncentracije kreatinina u serumu dobiveni su za 16.631 ispitanika tijekom razdoblja od 1 godine (M/Ž = 7.231/9.400; dob 57 ± 15 godina; raspon: 21–79 godina). Srednje vrijednosti (95% CI) kreatinina, GFR izračunate iz koncentracije kreatinina jednadžbama MDRD i MCQE iznosile su 72 $\mu\text{mol/L}$ (48–128 $\mu\text{mol/L}$), 78 mL/min/1,73 m² (38–129 mL/min/1,73 m²) i 94 mL/min/1,73 m² (35–134 mL/min/1,73 m²). Razlika u izračunatoj GFR između muškaraca i žena bila je statistički značajna, bez obzira kojom se jednadžbom računala [srednja vrijednost (95% CI)]: MDRD [91 (44–127) prema 87 (48–138) mL/min/1,73 m²; P < 0,001] ili MCQE [109 (46–142) prema 95 (65–120) mL/min/1,73 m²; P < 0,001]. Zabilježena je statistički značajna razlika između muškaraca i žena u svim dobnim skupinama u razredima od po deset godina kod izračuna jednadžbom MCQE i kod ispitanika starijih od 51 godine kod izračuna jednadžbom MDRD (Tablica 1.). Statistički značajna razlika između različitih dobnih razreda kod oba spola zabilježena je također kod srednjih vrijednosti GFR izračunatih objema jednadžbama (svi P < 0,001).

sated assay. The quality of results throughout the study was validated through regular internal quality control procedures and participation in an External Quality Assessment Scheme. GFR was estimated on the entire study population by the MDRD (2):

$$\text{GFR} = 186 \times (\text{serum creatinine}^{-1,154}) \times (\text{age}^{-0,203}) \times 1,212 \text{ (if African-American)} \times 0,742 \text{ (if female);}$$

and MCQE:

$$\text{GFR} = \exp [1,911 + (5,249/\text{serum creatinine}) - (2,114/\text{serum creatinine}^2) - 0,00686 \times \text{age}^{-0,205} \text{ (if female)}].$$

If serum creatinine value is < 71 $\mu\text{mol/L}$ it is replaced by 71 $\mu\text{mol/L}$ (6).

Statistical analysis

The Shapiro-Wilkinson test was used for assessment of normality of variable distributions. Variables were logarithmically transformed to improve normality prior to analysis. The Kruskal-Wallis test was used to evaluate the existence of statistically significant difference in GFR according to age decades. Statistical analyses were performed using the statistical package SPSS version 12.0 (SPSS, Chicago, IL) and the level of statistical significance was set at 0.05. Data are presented as geometric mean and 95% confidence interval (CI).

Results

Cumulative results for serum creatinine levels were retrieved for 16,631 outpatients over the 1-year period (M/F=7,231/9,400; age 57 ± 15 years; range 21–79 years). The mean values (95% CI) of creatinine, MDRD- and MCQE-estimated GFR were 72 $\mu\text{mol/L}$ (48–128 $\mu\text{mol/L}$), 78 mL/min/1.73 m² (38–129 mL/min/1.73 m²) and 94 mL/min/1.73 m² (35–134 mL/min/1.73 m²), respectively. Gender difference in the estimated GFR was significantly different when calculated with either the MDRD [mean (95% CI)]: [91 (44–127) vs. 87 (48–138) mL/min/1.73 m²; P < 0.001] or MCQE [109 (46–142) vs. 95 (65–120) mL/min/1.73 m²; P < 0.001] formula. Significant gender differences were observed in all age decades by MCQE and in subjects older than 51 by MDRD (Table 1). A significant difference in the mean GFR values estimated by either formula was also observed between different age decades in both genders (P < 0.001 all). Linear regression analysis revealed an inverse association between age and estimated GFR by both the MDRD (males: standardized beta coefficient = –0.384; P < 0.001; females: standardized beta coefficient = –0.437; P < 0.001) and MCQE (males: standardized beta coefficient = –0.639; P < 0.001; females: standardized beta coefficient = –0.816; P < 0.001) formulas, with a constant mean decrease of 7% for each decade increase in age, in both genders and for either equation.

TABLICA 1. Vrijednosti stope glomerularne filtracije (geometrijska srednja vrijednost i 95% interval pouzdanosti) izračunate jednadžbom MDRD i jednadžbom MCQE prema dobi i spolu**TABLE 1.** Values of glomerular filtration rate (geometric mean and 95% confidence interval) estimated by Modification of Diet in Renal Disease (MDRD) or Mayo Clinic Quadratic Equation (MCQE) formulas and stratified according to age and sex

Age (yrs)	MDRD				MCQE	
	Females (N)	Males (N)	Females (mL/min/1.73 m ²)	Males (mL/min/1.73 m ²)	Females (mL/min/1.73 m ²)	Males (mL/min/1.73 m ²)
21–30	637	347	107 (77–181)	108 (76–154)	119 (112–124)	141 (100–152) [†]
31–40	1093	768	101 (70–151)	102 (68–157)	112 (103–116)	132 (89–142) [†]
41–50	1342	1056	94 (64–138)	97 (63–141)	104 (93–108)	124 (80–132) [†]
51–60	1954	1506	88 (56–131)	92 (49–136) [†]	97 (79–101)	115 (56–123) [†]
61–70	2532	2055	81 (45–122)	86 (43–126) [†]	90 (59–94)	105 (45–115) [†]
71–79	1842	1499	76 (40–120)	79 (33–124) [†]	85 (49–88)	95 (30–108) [†]

[†] P < 0,01 razlika brzine glomerularne filtracije između spolova unutar iste dobne grupe od deset godina izračunate istim jednadžbama.

Regresijskom raščlambom otkrila se obrnuta povezanost između dobi i izračunate GFR objema jednadžbama: MDRD (muškarci: standardizirani beta koeficijent: -0,384; P < 0,001; žene: standardizirani beta koeficijent = -0,437; P < 0,001) i MCQE (muškarci: standardizirani beta koeficijent = -0,639; P < 0,001; žene: standardizirani beta koeficijent = -0,816; P < 0,001) s konstantnom srednjom vrijednošću pada od 7% za svako slijedeće desetljeće dobi kod oba spola za obje jednadžbe.

Rasprava

Kronična bubrežna bolest predstavlja velik zdravstveni problem diljem svijeta; broj slučajeva i prevalencija su se učetverostručili u zadnjih dvadesetak godina (1,2). GFR se smatra najboljim sveobuhvatnim pokazateljem bubrežne funkcije za potrebe dijagnosticiranja, klasifikacije i odgovarajućeg liječenja kronične bubrežne bolesti. Zbog dobro poznatih ograničenja određivanja koncentracije kreatinina u serumu kao pokazatelja funkcije bubrega, međunarodne organizacije preporučuju jednadžbu za procjenu GFR temeljenu na koncentraciji kreatinina u serumu te na drugim demografskim i kliničkim varijablama. Također se kliničkim laboratorijima preporuča da izdaju nalaz procjene GFR kadgod se zatraži provjera koncentracije kreatinina u serumu (7). Prema tome, stručnjaci u laboratorijima moraju prihvatiti važnost pouzdanog određivanja GFR, kako bi se poboljšala i dijagnostika i liječenje bolesnika. Iako je izračun GFR jednadžbom MDRD u širokoj uporabi, (ta je jednadžba izvedena iz mokraćnog klirensa ¹²⁵I-iothalamata na velikom uzorku gdje su se uzele u obzir razlike u koncentraciji kreatinina između spolova), pokazano je

Discussion

Chronic kidney disease is a major public health problem worldwide, whose incidence and prevalence have more than quadrupled over the last 2 decades (1,2). GFR is considered the best overall index of kidney function for diagnosing, staging, and appropriately treating kidney disease. Due to well-recognized limitations of serum creatinine concentration as an index of kidney function, international organizations now recommend the use of GFR estimating equations based on serum creatinine and other demographic and clinical variables, and that clinical laboratories report estimated GFR whenever serum creatinine is ordered (7). Accordingly, laboratory professionals must clearly acknowledge the importance of a reliable estimation of GFR to improve both the diagnosis and treatment of patients. Although calculation of GFR by the MDRD equation is widely used, since the formula is derived from the urinary clearance of ¹²⁵I-iothalamate on a large sample size where gender differences in creatinine levels have been taken into consideration, it has been demonstrated that the recently developed MCQE formula might improve prediction of GFR, especially in diabetic subjects (8). Current reports suggest the same cut-off (60 mL/min 1.73 m²) of GFR when estimated by MDRD and MCQE formulas in both genders. Recently, Khatami *et al.* have highlighted that a univocal threshold for MDRD derived GFR cannot be used throughout different genders and ages (9), since the difference between the men and women is significantly different and there is an inverse association between age and GFR in both genders. However, no information is available on the potential influence

da bi nedavno izvedena jednadžba MCQE mogla poboljšati predviđanje GFR, osobito kod ispitanika sa šećernom bolešću (8). Novija izvješća ukazuju na činjenicu da se izračunom objema jednadžbama (MDRD i MCQE) dobije ista granična vrijednost GFR (60 mL/min 1,73 m²) kod oba spola. Nedavno su Khatami i sur. naglasili da se jednoznačno određena GFR izračunata jednadžbom MDRD ne može rabiti za različite dobi i spol (9), budući da je razlika između muškaraca i žena statistički značajna i budući da postoji obrnuta povezanost između dobi i GFR kod oba spola. Međutim, ne postoje informacije o mogućem utjecaju varijacija dobi i spola na GFR izračunatu jednadžbom MDRD. Iako je nedavno postavljena hipoteza da bi izračun GFR novom jednadžbom mogao biti točniji (6), rezultati ove epidemiološke analize potvrdili su da niti jednadžba MCQE ne može nadoknaditi varijacije dobi i spola, jer zahtijeva uporabu različitih korektivnih parametara. Osobito valja naglasiti da bi statističke razlike između spola i dobnih razreda od po deset godina mogle biti rezultatom činjenice da manja tjelesna veličina ima niže metaboličke zahtjeve te da je, prema tome, nižim osobama potrebna manja funkcija bubrega. Kao logična posljedica slijedi da nedostatak referentnih raspona prilagođenih dobi i spolu kod procjena objema jednadžbama (MDRD i MCQE) ukazuje na to da bi mnogim bolesnicima sa srednjim do teškim bubrežnim oštećenjem mogla biti pogrešno postavljena dijagnoza.

Svjesni smo da bi rezultati ovoga istraživanja mogli imati neka ograničenja. Retrospektivna revizija zapravo predstavlja samo populaciju obrađenu u našem laboratoriju, stoga nam nedostaju klinički podaci s uputnicama i analiza kontrolnih pregleda. Stoga je, kako bi se potvrdili preliminarni rezultati, potrebno provesti daljnja prospektivna istraživanja po mogućnosti na heterogenijoj populaciji. Štoviše, GFR nismo mogli procijeniti pomoću zlatnog standarda. Važno je naglasiti da se izračunom GFR sadašnjim referentnim pristupom, koji uključuje klirens egzogenih biljega filtracije, ne može procijeniti filtracija kod zdravih ispitanika. Upotreba jednadžba u koje je uključena koncentracija cistatina C samo je kod djece mlađe od 14 godina bolja od procjene temeljene na koncentraciji kreatinina (2).

of age and gender variations on the MCQE derived GFR. Although it has recently been hypothesized that GFR estimation by this newly developed formula might be a more accurate approach (6), the results of this epidemiological analysis confirm that even the MCQE equation might fail to compensate for age and gender variations, requiring implementation of different corrective actions. This is of particular concern, in that the difference between genders and age decades may be due to the fact that smaller body size has lower metabolic demands and shorter individuals require less renal function. As a logical consequence, the lack of age- and gender-adjusted reference ranges for both MDRD and MCQE estimates implies that many patients with moderate to severe renal failure might go misdiagnosed.

We are aware that the outcome of this investigation might have some limitations. In fact, the retrospective audit is only representative of the population served by our laboratory, and we lack clinical information on request forms and one-point follow up analysis. It will therefore require further prospective investigations to confirm these preliminary findings, preferably in more heterogeneous population settings. Moreover, we could not assess GFR by the gold standard approach. However, it is to mention that GFR calculation by the current reference approach that employs the clearance of exogenous filtration markers is discouraged in populations of healthy subjects, and the use of cystatin C-derived equations is superior to creatinine-based prediction equations only in children aged < 14 years (2).

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