Automatizirani laboratorijski nalazi određivanja brzine glomerularne filtracije: jesu li dobri za zdravlje bolesnika i njihove liječnike?
Automated laboratory reporting of estimated glomerular filtration rate: is it good for the health of patients and their doctors?

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Sažetak

Koncentracija kreatinina u serumu je nepouzdan i neosjetljiv biljeg kronične bolesti bubrega (engl. *chronic kidney disease*, CKD). Kako bi poboljšali otkrivanje CKD mnogi europski i sjevernoamerički laboratoriji te svi australoazijski laboratoriji izračunavaju i u nalazu ispisuju procijenjenu brzinu glomerularne filtracije (engl. *estimated glomerular filtration rate*, eGFR) primjenjujući formulu MDRD (engl. *Modification of Diet in Renal Disease*, MDRD) kod svakog zahtjeva za određivanje koncentracije kreatinina u serumu. Cilj ovog rada je pružanje pravovremene informacije kliničkim kemičarima o snazi, slabostima te dostupnim dokazima o ulozi automatiziranih laboratorijskih nalaza eGFR u otkrivanju CKD. Točnost i preciznost eGFR su prihvatljivi za većinu odraslih osoba kod kojih su izračunane vrijednosti < 60 mL/min/1,73 m2. Međutim, u određenim okolnostima eGFR treba tumačiti s oprezom (osobito kod bolesnika s eGFR > 60 mL/min/1,73 m2 te kod djece). U ovom se radu također raspravlja o odlukama koje su povezane eGFR, a tiču se kliničkih postupaka, indikacija za upućivanje nefrologu, važnosti standardizacije određivanja kreatinina, te uloge eGFR u odluci o doziranju lijeka. Zaključno, automatizirani laboratorijski nalazi eGFR povećati će rano otkrivanje CKD te omogućiti pravovremeno određivanje odgovarajućih renalno- i kardioprotektivnih terapija, kao i pružiti bolje informacije kod odlučivanja o propisivanju lijekova koji se izlučuju bubregom.

Ključne riječi: kronična bubrežna bolest, Cockcroft-Gaultova jednadžba, brzina glomerularne filtracije, jednadžbe za procjenu brzine glomerularne filtracije, jednadžba za modifikaciju prehrane kod bubrežne bolesti, kreatinin u serumu

Abstract

Serum creatinine concentration is an unreliable and insensitive marker of chronic kidney disease (CKD). To improve CKD detection, many European and North American laboratories and all Australasian laboratories calculate and report an estimated glomerular filtration rate (eGFR) using the Modification of Diet in Renal Disease (MDRD) formula with every request for serum creatinine concentration. The aim of this paper is to provide timely information to Clinical Chemists about the strengths, weaknesses and available evidence for the role of automated laboratory reporting of eGFR in CKD detection. The accuracy and precision of eGFRs is reasonable in most adults in whom calculated values are < 60 mL/min/1.73 m^2. However, eGFRs should be interpreted with caution in some settings, (particularly patients with eGFRs > 60 mL/min/1.73 m^2 and children). This paper also discusses eGFR-related decision points for clinical actions, the indications for nephrologist referral, the importance of creatinine assay standardisation and the role of eGFR in drug dose decision-making. In conclusion, automatic laboratory reporting of eGFR will enhance early detection of CKD, allow the timely institution of appropriate reno- and cardioprotective therapies, and better inform decisions regarding the prescription of renally excreted medications.

Keywords: chronic kidney disease, Cockcroft-Gault equation, glomerular filtration rate, glomerular filtration rate estimating equations, modification of diet in renal disease equation, serum creatinine

Pristiglo: 21. veljače 2007. *Received: February 6, 2007*
Prihvaćeno: 2. travnja 2007. *Accepted: April 2, 2007*

Kronična bubrežna bolest postaje sve više javnozdravstveni problem koji se često ne otkrije

Kronična bubrežna bolest (CKD) je znatan globalni javnozdravstveni problem. Na temelju studije *Ausdiab* (1) procjenjuje se da će jedna od sedam odraslih osoba oboljeti od CKD, uključujući i jednog od 10 pojedinaca s barem umjerenim zatajenjem bubrega (definiranim kao brzina glomerularne filtracije [GFR] < 60 mL/min/1,73 m^2). O sličnim je podatcima također izviješteno u Sjevernoj Americi (2) i Europi (3). Štoviše, u 1% odraslih osoba svake će se godine razviti nova CKD. Tijekom proteklih 25 godina stanovništvo je u svijetu raslo približno 1,5% godišnje, a broj pojedinaca koji su liječeni dijalizom i presađivanjem bubrega povećao se za više od 8% godišnje (4). Često CKD nije povezana sa značajnim simptomima i ne prepoznaje se u 80-90% slučajeva (1,5,6). Prisutnost te bolesti je vrlo jak čimbenik rizika za kardiovaskularnu bolest, toliki da osobe s CKD imaju 10 do 20 puta veći rizik za smrt od srčane bolesti nego kontrolni ispitanici iste dobi i spola bez CKD (7,8). Tako, primjerice, 25-godišnja žena s uznapredovalom CKD ima približno isti rizik za smrt of kardiovaskularnog oboljenja kao i 75-godišnji muškarac bez bubrežne bolesti (7). Nadalje, za bolesnike s CKD je barem 20 puta vjerojatnije da će umrijeti od kardiovaskularne bolesti nego preživjeti do toga da trebaju dijalizu ili presađivanje bubrega. Rana identifikacija i obrada CKD je visoko isplativa i može smanjiti rizik napredovanja kardiovaskularne bolesti i zatajenja bubrega za 20-50% (9).

Nedavno je automatiziran laboratorijski nalaz procijenjenog GFR (engl. *estimated GFR*, eGFR) predložen kao jednostavna i učinkovita strategija za pojačano otkrivanje CKD, a time i lakše i pravovremeno određivanje terapija za koje je dokazano da usporavaju ili sprječavaju napredovanje zatajenja bubrega, za poboljšanje adekvatne procjene i modifikacije kardiovaskularnog rizika, te osiguranje informacija vezanih za propisivanje lijekova koji se izlučuju bubregom (10). Ciljevi ovog članka su pregled snage i slabosti te dostupnih dokaza o ulozi automatiziranih laboratorijskih nalaza eGFR u otkrivanju CKD.

Procjena bubrežne funkcije: uloga procijenjene brzine glomerularne filtracije

Najčešće primjenjivano mjerenje ukupne bubrežne funkcije u kliničkoj praksi je određivanje koncentracije kreatinina u serumu. Na žalost, na to mjerenje utječu mnogi čimbenici osim razine bubrežne funkcije i ono značajno varira ovisno o dobi, spolu i mišićnoj masi. Štoviše, postoje i značajni kalibracijski problemi povezani s mjerenjem kreatinina u serumu koji rezultiraju međulaboratorijskom varijacijom do 20% (11). Za koncentraciju kreatinina u serumu je poznato da je neosjetljiva za otkrivanje blagoga do

Chronic kidney disease is an increasingly common health problem that is often undetected

Chronic kidney disease (CKD) is a major global public health problem. Based on data from the Ausdiab study (1), it is estimated that one in every 7 adults will have CKD, including one in 10 individuals with at least moderate kidney failure (defined as a glomerular filtration rate [GFR] < 60 mL/min/1.73m^2). Similar findings have also been reported in North America (2) and Europe (3). Moreover, 1% of adults each year will develop new-onset CKD. Over the last 25 years, while the world's population has grown by approximately 1.5% per annum, the number of individuals being treated with dialysis or kidney transplantation has increased more than 8% per annum (4). CKD is often not associated with significant symptoms and is unrecognized in 80-90% of cases (1,5,6). Its presence is a very strong risk factor for cardiovascular disease, such that individuals with CKD have up to a 10- to 20-fold greater risk of cardiac death than age- and sex-matched controls without CKD (7,8). For example, a 25 year old woman with advanced CKD has approximately the same risk of cardiovascular death as a 75 year old male without kidney disease (7). Furthermore, patients with CKD are at least 20 times more likely to die from cardiovascular disease than survive to the point of needing dialysis or kidney transplantation. Early identification and management of CKD is highly cost-effective and can reduce the risk of kidney failure progression and cardiovascular disease by 20% - 50% (9).

Recently, automated laboratory reporting of estimated GFR (eGFR) has been suggested as a simple, effective strategy for enhancing detection of CKD, thereby facilitating the timely institution of therapies proven to slow or prevent kidney failure progression, enhancing the appropriate assessment and modification of cardiovascular risk, and informing decisions regarding the prescription of drugs excreted by the kidneys (10). The aims of this article are to review the strengths, weaknesses and available evidence for the role of automated laboratory reporting of eGFR in CKD detection.

Assessment of kidney function: Role of estimated glomerular filtration rate

The most commonly used measure of overall kidney function in clinical practice is serum creatinine concentration. Unfortunately, this measurement is affected by many factors other than the level of kidney function and varies markedly with age, gender and muscle mass. Moreover, there are significant calibration issues associated with the measurement of serum creatinine that lead to inter-laboratory variation of up to 20% (11). Serum creatinine concentration is notoriously insensitive for detecting

umjerenog zatajenja bubrega, tako da kod bolesnika treba biti isključeno 50% ili više funkcije bubrega prije nego što vrijednost kreatinina bude više od gornje granice normalnih vrijednosti (12). Takva situacija, u kojoj "normalan" kreatinin prikriva značajno slabljenje bubrežne funkcije, osobito je važna kod starijih bolesnika kod kojih se slabljenje bubrežne funkcije povezano s dobi ne odražava povišenom koncentracijom kreatinina u serumu zbog istodobnog smanjenja mišićne mase.

Nekoliko je proteina u serumu s niskom molekularnom težinom, uključujući β_2-mikroglobulin, retinol-vežući protein, te cistatin C, predloženo prikladnim alternativnim biljezima endogene filtracije (13-15). Od navedenih je, s obzirom na objavljenu literaturu, cistatin C privukao najviše pozornosti i čini se da je bolji biljeg od kreatinina u serumu za otkrivanje smanjene bubrežne funkcije, posebice u ranim stadijima (16). Međutim, prednost cistatina C u serumu pred serumskim kreatininom za otkrivanje zatajenja bubrega nije više očigledna kada se mjerenja prilagode ili stratificiraju prema dobi, spolu i težini. Povrh toga, na koncentracije cistatina u serumu znatno utječe nekoliko čimbenika uz GFR, uključujući dob, spol, tjelesnu veličinu, trenutno pušenje cigareta, koncentraciju C-reaktivnog proteina u serumu, liječenje kortikosteroidima, ciklosporin A, tiroidnu disfunkciju, fizičku aktivnost, određene maligne bolesti, te trudnoću. Postoji također značajna zabrinutost koja se odnosi na isplativost određivanja cistatina C u serumu radi otkrivanja CKD.

Mjerenje GFR je široko prihvaćeno kao najbolji ukupni pokazatelj bubrežne funkcije (17,18). Najčešća metoda za procjenu GFR u prošlosti bilo je provođenje pravovremenog prikupljanja mokraće radi određivanja klirensa kreatinina. Ta je pretraga, međutim, neprikladna i često netočna kao rezultat neadekvatnog prikupljanja te precjenjivanja GFR zbog tubularnog lučenja kreatinina u bubregu (18). Općenito je za mjerenja klirensa kreatinina zaista pokazano da pružaju manje pouzdane procjene GFR od jednadžbi za predviđanje GFR (19). Uobičajeno korišteni egzogeni biljezi filtracije (iotalamat, DTPA, EDTA, ioheksol) predstavljaju prihvatljive alternativne mjere brzine glomerularne filtracije (GFR), premda trošak te intenzivan rad vezan za te biljege ograničava njihovu kliničku iskoristivost kao pomagala u probiranju na CKD.

Odnedavno se ističe izračun procijenjenog GFR (eGFR) uz primjenu empirijske matematičke formule kao jednostavan, brz i pouzdan način procjene bubrežne funkcije (6,20-22). U većini slučajeva eGFR je barem jednako točan kao i određivanje klirensa kreatinina (17). Trenutno postoji ne manje od 47 različitih jednadžbi za predviđanje eGFR, iako su dvije najčešće korištene jednadžbe Cockroft-Gaultova (23) te skraćena formula MDRD (engl. *Modification of Diet in Renal Disease*, MDRD) (20) (Tablica 1).

Cockroft-Gaultova formula je izvorno dobivena na 249 uzastopno hospitaliziranih bolesnika (96% muških, raspon dobi 18-92 godine) u *Queen Mary Veterans' Hospital*

mild-to-moderate kidney failure, such that patients must lose 50% or more of their kidney function before the serum creatinine value rises above the upper limit of normal (12). This situation of a "normal" creatinine masking a significant decline in kidney function is especially important in elderly patients, in whom the age-related decline in kidney function is not reflected by an increase in serum creatinine level because of a concomitant decrease in muscle mass.

A number of low molecular weight serum proteins, including β_2-microglobulin, retinol-binding protein and cystatin C, have been proposed as suitable alternative endogenous filtration markers (13-15). Of these, cystatin C has received the most interest in the published literature and appears to be superior to serum creatinine for detecting reduced kidney function, particularly in the early stages (16). However, the advantage of serum cystatin C compared with serum creatinine for the detection of kidney failure is no longer apparent when measurements are adjusted or stratified for age, gender and weight. Moreover, serum cystatin concentrations are significantly influenced by a number of factors other than GFR, including age, gender, body size, current cigarette smoking, serum C-reactive protein levels, corticosteroid treatment, cyclosporine A, thyroid dysfunction, physical activity, certain malignancies and pregnancy. There are also significant concerns pertaining to the cost-effectiveness of serum cystatin C for CKD detection.

Measuring GFR is widely accepted as the best overall index of kidney function (17,18). The most common method for assessing GFR in the past was performing a timed urine collection for evaluation of creatinine clearance. However, this test was inconvenient and frequently inaccurate as a result of improper collection and overestimation of GFR due to kidney tubular secretion of creatinine (18). Indeed, creatinine clearance measurements have generally been shown to provide less reliable estimates of GFR than GFR prediction equations (19). Commonly used exogenous filtration markers (iothalamate, DTPA, EDTA, iohexol) provide acceptable alternative measures of glomerular filtration rate (GFR), although their cost and labour-intensiveness limit their clinical utility as a screening tool for CKD.

More recently, calculation of estimated GFR (eGFR) using an empirical mathematical formula has been encouraged as a simple, rapid and reliable means of assessing kidney function (6,20-22). In most cases, eGFR is at least as accurate as measuring creatinine clearance (17). There are no fewer than 47 different prediction equations currently available, although the 2 most common in use are the Cockcroft-Gault (23) and the abbreviated Modification of Diet in Renal Disease (MDRD) formulae (20) (Table 1).

The Cockcroft-Gault formula was originally derived in 249 consecutive hospitalised patients (96% male, age range 18–92 years) at the Queen Mary Veterans' Hospital in

Tablica 1. Jednadžbe za procijenjenu brzinu glomerularne filtracije (eGFR) u odraslih osoba na temelju koncentracije kreatinina u serumu*.

Table 1. Equations for estimated glomerular filtration rate (eGFR) in adults based on serum creatinine concentration*.

Cockcroft-Gault equation
CrCl(mL/min) = (140 – age) x weight x 1.228 ÷ S_{Cr} x (0.85 if female)

Abbreviated MDRD equation
GFR (mL/min/1.73 m^2) = 186 x (S_{Cr} ÷ 88.4)$^{-1.154}$ x (age)$^{-0.203}$ x (0.742 if female) x (1.212 if Afro-American)

Re-expressed Abbreviated MDRD equation (for use with a standardised serum creatinine assay)
GFR (mL/min/1.73 m^2) = 175 x (Standardised S_{Cr} ÷ 88.4)$^{-1.154}$ x (age)$^{-0.203}$ x (0.742 if female) x (1.212 if Afro-American)

SCr = serum creatinine concentration
* For each equation, SCr is in μmol/L, age is in years and weight is in kilograms.
eGFR derived by the Cockcroft-Gault formula should subsequently be corrected for body surface area (multiply by 1.73 then divide by calculated body surface area).

u Kanadi na temelju srednjih vrijednosti dva 24-satna klirensa kreatinina (23). Koncentracije kreatinina u serumu bile su određene Jafféovom reakcijom na autoanalizatoru (N-11B, Technicon Instruments Corp, NY). Dobivena je formula zatim korištena za predviđanje klirensa kreatinina u drugoj validacijskoj kohorti koja se sastojala od 236 bolesnika (206 muškaraca, srednja vrijednost klirensa kreatinina 72,7 ± 36,6 mL/min). Prednosti Cockroft-Gaultove jednadžbe su da je široko poznata, lakša za pamćenje i opsežnije validirana nego formula MDRD. Iako je jednadžba razvijena na hospitaliziranoj bjelačkoj muškoj populaciji, od kojih mnogi nisu imali CKD, kasnije je opsežno validirana i utvrđeno je da pokazuje zadovoljavajuću preciznost i netočnost (engl. *bias*) u različitim populacijama uključujući žene i različite etničke skupine, te kroz širok raspon GFR. Glavni nedostatci Cockroft-Gaultove formule su zahtjev za mjerenjem težine i visine (visina se traži radi ispravka izračuna površine tijela), procjena klirensa kreatinina, a ne GFR, te nemogućnost da se kliničke laboratorijske analize kreatinina kalibriraju prema laboratoriju koji je proveo analize na uzorcima korištenima za dobivanje Cockroft-Gaultove jednadžbe.

Nasuprot tome, jednadžba MDRD je razvijena na 1628 bolesnika s CKD uvrštenih u osnovno razdoblje studije Modifikacije prehrane u bubrežnoj bolesti (engl. *Modification of Diet in Renal Disease*, MDRD), od kojih je 1070 odabrano nasumce kao izvedeni uzorak, a preostalih 558 bolesnika činilo je uzorak za validaciju (20). Primjenom analize višestruke regresije početno je razvijena jednadžba sa 6 varijabli koja je uključivala varijable kreatinina u serumu, dobi, spola, etničke pripradnosti (Afroamerikanci ili dr.), te ureju i albumin u serumu. Jednadžba je validirana prema GFR ispravljenom za površinu tijela (engl. *body surface area*, BSA) tako da je, za razliku od Cockroft-Gaultove formule, predviđeni GFR izražen kao mL/min/1,73 m^2 i ne iziskuje naknadnu normalizaciju BSA. Kasnije je radi po-

Canada, based on the means of two 24-hour creatinine clearances (23). Serum creatinine concentrations were determined by Jaffé reaction using an autoanalyzer (N-11B, Technicon Instruments Corp, NY). The derived formula was then used to predict creatinine clearance in a second validation cohort consisting of 236 patients (206 males, mean creatinine clearance 72.7 ± 36.6 mL/min). The Cockcroft-Gault equation has the advantages of being more widely known, easier to remember and more extensively validated than the MDRD formula. Although the equation was developed in hospitalised, white men, many of whom did not have CKD, it has subsequently been extensively validated and found to exhibit satisfactory precision and bias in diverse populations including women and various ethnic groups, and across a broad range of GFRs. The principal disadvantages of the Cockcroft-Gault formula are the requirement to measure weight and height (the latter is required for the purposes of body surface area correction), its estimation of creatinine clearance rather than GFR, and the inability of clinical laboratory creatinine assays to be calibrated to the laboratory that performed the assays on samples used to derive the Cockcroft-Gault equation.

In contrast, the MDRD equation was developed in 1628 CKD patients enrolled in the baseline period of the Modification of Diet in Renal Disease (MDRD) study, of whom 1070 were randomly selected as the derivation sample and the remaining 558 patients constituted the validation sample (20). Using multiple regression analysis, a 6-variable equation was initially developed, which included the variables of serum creatinine, age, gender, ethnicity (African-American or other), serum urea and serum albumin. The equation was validated against GFR corrected for body surface area (BSA) and so, unlike the Cockcroft-Gault formula, the predicted GFR is expressed as mL/min/1.73 m^2 and does not require subsequent BSA norma-

jednostavljenja kliničke uporabe predložena razmjerno točna jednadžba MDRD s 4 varijable koja uključivala kreatinin u serumu, dob, spol i etničku pripadnost (24). Ta je jednadžba ponovno izražena 2005. godine za primjenu u standardiziranoj analizi kreatinina u serumu koja daje 5% niže vrijednosti koncentracije serumskog kreatinina (25). Prednosti formule MDRD su u tome što ne traži poznavanje bolesnikove težine (što je čini daleko pogodnijom za automatizirane laboratorijske nalaze), ne treba ispravke za površinu tijela (pa stoga ne iziskuje podatke o bolesnikovoj visini), te je za nju općenito dokazano da je preciznija i točnija od Cockroft-Gaultove jednadžbe kad je GFR niži od 60 mL/min/1,73 m^2 (validirano u preko 10.000 ispitanika) (pregled u 20). Međutim, obje jednadžbe za predviđanje GFR, tj. i MDRD i Cockroft-Gaultova, daju loše rezultate kod bolesnika s normalnom i gotovo normalnom bubrežnom funkcijom, uključujući i zdrave darovatelje bubrega (26-28) te dijabetičare u ranom stadiju bolesti (29,30).

Međunarodne smjernice za automatizirane laboratorijske nalaze eGFR

Smjernice Inicijative za kvalitetu ishoda bubrežnih bolesti i dijalize (engl. *Kidney and Dialysis Outcomes Quality Initiative*, K/DOQI) Nacionalne fondacije za bubreg u Sjevernoj Americi preporučuju da je sama koncentracija kreatinina u serumu suboptimalna za procjenu razine bubrežne funkcije te da bi laboratoriji trebali istodobno izvještavati i o eGFR određenome pomoću jednadžbe za predviđanje kao što je formula MDRD (17). I druge su organizacije sastavile slične preporuke, uključujući Britansku renalnu udrugu (31) te smjernice za Globalno poboljšanje ishoda bubrežnih bolesti (engl. *Kidney Disease Improving Global Outcomes*, KDIGO) (32). Te se preporuke temelje na zapažanjima da laboratorijski nalazi eGFR značajno povećavaju otkrivanje CKD (21) te da pravodobna intervencija može smanjiti rizik progresivnog zatajenja bubrega i kardiovaskularne bolesti u bolesnika s CKD (9).

U kolovozu 2005. godine australoazijska Radna skupina za eGFR, u kojoj su okupljeni predstavnici Australoazijske udruge kliničkih biokemičara (engl. *Australoasian Association of Clinical Biochemists*, AACB), Australskog i novozelandskog nefrološkog društva (engl. *Australian and New Zealand Society of Nephrology*, ANZSN), Australske udruge za zdravlje bubrega (engl. *Kidney Health Australia*, KHA), te Kraljevskog australoazijskog zbora patologa (engl. *Royal Australoasian College of Pathologists*, RCPA) jednoglasno je prihvatila i objavila preporuke prema kojima laboratoriji trebaju izračunati i izvještavati o eGFR primjenom formule MDRD uz svaki zahtjev za koncentracijom kreatinina u serumu (33):

- eGFR se automatski izračunava prema skraćenoj formuli MDRD za svaki zahtjev za određivanje koncentracije kreatinina u serumu u osoba starijih od 18 godina;

lisation. Subsequently, a comparably accurate 4-variable MDRD equation consisting of serum creatinine, age, gender and ethnicity was proposed to simplify clinical use (24). The equation was re-expressed in 2005 for use with a standardised serum creatinine assay, which yields 5% lower values for serum creatinine concentration (25). The advantages of the MDRD formula are that it does not require knowledge of the patient's weight (making it far more suitable for automated laboratory reporting), does not need correction for body surface area (and therefore does not require knowledge of the patient's height) and has been generally shown to be more precise and accurate than the Cockcroft-Gault equation when the GFR is below 60 mL/min/1.73 m^2 (validated in over 10,000 subjects) (reviewed in (22)). Both the MDRD and Cockcroft-Gault prediction formulae perform poorly in patients with normal or near-normal renal function, including healthy kidney donors (26-28) and early diabetics (29-30).

International guidelines for automated laboratory reporting of eGFR

In North America, the National Kidney Foundation Kidney and Dialysis Outcomes Quality Initiative (K/DOQI) guidelines have recommended that serum creatinine concentration alone is sub-optimal for assessing the level of kidney function and that pathology laboratories should concomitantly report eGFR, as determined by a prediction equation, such as the MDRD formula (17). Similar recommendations have been made by other organizations, including the British Renal Association (31) and the Kidney Disease Improving Global Outcomes (KDIGO) guidelines (32). These recommendations are based on observations that laboratory reporting of eGFR significantly enhances CKD detection (21) and that timely intervention can reduce the risk of progressive kidney failure and cardiovascular disease in CKD patients (9).

In August 2005, an Australasian eGFR Working Group convened by representatives of the Australasian Association of Clinical Biochemists (AACB), Australian and New Zealand Society of Nephrology (ANZSN), Kidney Health Australia (KHA) and Royal Australasian College of Pathologists (RCPA) unanimously endorsed and published recommendations that laboratories calculate and report an eGFR using the MDRD formula with every request for serum creatinine concentration (33):

- An eGFR using the abbreviated MDRD formula shall be automatically calculated for every request for serum creatinine concentration in individuals aged ≥ 18 years.
- GFR values that calculate to be in excess of 60 mL/min/1.73m2 should be reported as ">60mL/min/1.73m2" and not as a precise figure.
- Automatic reporting of eGFR may include age-related reference intervals for individuals aged ≥ 65 years.

- O vrijednostima GFR koje su prema izračunu više od 60 mL/min/1,73 m^2 treba izvijestiti u obliku "> 60mL/min/1.73 m^2", a ne točnom znamenkom.
- Automatski nalaz eGFR može uključivati dobne referentne intervale za osobe starije od 65 godina.
- Provođenje automatskog izdavanja nalaza eGFR iziskuje pravovremeni edukacijski program kojime se osigurava dostupnost informacija zdravstvenim stručnjacima radi pomoći u tumačenju vrijednosti eGFR.

Stoga svi australski i novozelandski laboratoriji za patologiju danas automatski izdaju nalaze eGFR za svaku odraslu osobu sa zahtjevom za određivanje kreatinina u serumu.

Važnost standardizacije analiza kreatinina

Nepostojanje kalibracije analiza kreatinina u serumu može predstavljati izvor značajne pogreške u procjeni GFR pomoću empirijske formule. Kalibracija mjerenja kreatinina u serumu nije standardizirana, što dovodi do znatnih varijacija unutar i između laboratorija. Od 11 uobičajenih biokemijskih pretraga koje se vrednuju u 700 laboratorija Američkog zbora patologa (engl. *College of American Pathologists*), razlike u kalibraciji analiza kreatinina u serumu (približno 18 µmol/L među laboratorijima) uzrokovale su 85% razlika između laboratorija i bile su veće nego za bilo koji drugi od ostalih 10 ispitanih analita (34). Koncentracija kreatinina u serumu bila je previsoko procijenjena za prosječnih 13,3% u usporedbi s referentnom metodom. Čini se da je netočnost kod kalibracije bilo osobito važna kod nižih koncentracija kreatinina u serumu. Slični su rezultati utvrđeni i među 102 laboratorija koji su sudjelovali u Nordijskom projektu o referentnim intervalima (engl. *Nordic Reference Interval Project*, NORIP) (35). Još skorije vrednovanje sudionika u Kemijskom pregledu Američkoga zbora patologa pokazalo je da je srednja vrijednost netočnosti za instrumentalnu metodu u ravnopravnim skupinama varirala od -0,06 do 0,31 mg/dL (–5,3 do 27,4 µmol/L), uz značajnu netočnost (P < 0,001) u 30 (60%) od 50 skupina (36). Promjenljivost netočnosti bila je povezana prije s proizvođačem instrumenta nego vrstom metode, uz značajnu netočnost kod 24 (63%) od 38 metoda s alkalnom pikričnom kiselinom te kod 6 (50%) od 12 enzimskih metoda.

Murthy i sur. (37) nedavno su izračunali pogreške u procjenama GFR na temelju raspona razlika u kalibraciji u pregledu Američkog zbora patologa iz 1994. godina korištenjem eGFR prema MDRD. Nije bilo iznenađujuće da su pogreške bile veće kod više razine eGFR (i nižih koncentracija kreatinina u serumu) te postale klinički važne kod vrijednosti eGFR od 60 mL/min/1,73 m^2; u toj je točci 95%-tni interval pouzdanosti za srednju vrijednost kalibracijske razlike bio povezan s maksimalnim rasponom pogrešaka u procjenama GFR, tj. od +4,6 do -18,1 mL/min/1,73 m^2 (+7,6 do

- The implementation of automatic eGFR reporting will require a timely educational program that ensures information is available to health professionals to aid in interpretation of eGFR values.

All Australian and New Zealand pathology laboratories now automatically report eGFR in any adult with a request for serum creatinine determination.

Importance of standardisation of creatinine assays

Lack of calibration of serum creatinine assays can represent a source of significant error in the estimation of GFR by empiric formulae. Calibration of serum creatinine measurements is not standardised, thereby leading to substantial variation within and between laboratories. Of 11 common biochemical tests evaluated across 700 laboratories by the College of American Pathologists, differences in calibration of serum creatinine assays (approximately 18 µmol/L between labs) accounted for 85% of the difference between laboratories and were greater than for any of the other 10 analytes examined (34). Serum creatinine concentration was over-estimated by an average of 13.3% compared with a reference method. Calibration biases appear to be particularly important at lower serum creatinine levels. Similar results were found among the 102 laboratories participating in the Nordic Reference Interval Project (NORIP) (35). A more recent evaluation of participants in the College of American Pathologists Chemistry Survey demonstrated that the mean bias for 50 instrument-method peer groups varied from -0.06 to 0.31 mg/dL (-5.3 to 27.4 µmol/L), with 30 (60%) of 50 peer groups having significant bias (P < 0.001) (36). The bias variability was related to instrument manufacturer rather than method type, with 24 (63%) of 38 alkaline picric acid methods and with 6 (50%) of 12 enzymatic methods having significant biases.

Murthy et al (37) recently computed errors in GFR estimates based on the range of calibration differences from the 1994 College of American Pathologists survey using MDRD eGFR. Not surprisingly, errors were higher at higher level of eGFR (and lower levels of serum creatinine) and became clinically important at an eGFR value of 60 mL/min/1.73 m^2, at which point the 95% confidence interval for the mean calibration difference was associated with a maximal range of error in GFR estimates from +4.6 to -18.1 mL/min/1.73 m^2 (+7.6 to -30.2%). Based on these results, the K/DOQI (32) and Australasian (33) guidelines both recommend that clinical laboratories report a specific value for GFR estimates only when the estimated GFR is less than 60 mL/min/1.73m^2 and as "≥60 mL/min/1.73m^2" for higher values. The National Kidney Disease Education Program (NKDEP) has launched the Creatinine Standardization Program to address inter-laboratory variation in creatinine assay calibration and provide more accura-

-30,2%). Na temelju tih rezultata australoazijske smjernice (33) te smjernice K/DOQI (32) preporučuju da klinički laboratoriji izdaju nalaz sa specifičnom vrijednošću procjena GFR samo kad je procijenjeni GFR niži od 60 mL/min/1,73 m^2, te u obliku "≥ 60 mL/min/1,73 m^2" kod viših vrijednosti. Nacionalni program edukacije o bubrežnim bolestima (engl. *National Kidney Disease Education Program*, NKDEP) je pokrenuo Program standardizacije kreatinina kako bi se riješila međulaboratorijska varijacija u kalibraciji analize kreatinina i pružile točnije procjene GFR. Sličan se proces već odvija u Australoaziji gdje je većina analiza kreatinina općenito usklađena s masenom spektrometrijom s razrjeđenjem izotopa (engl. *isotope dilution mass spectrometry*, IDMS). Zbog toga je australoazijska Radna skupina za eGFR preporučila uporabu ponovno izražene ("175") formule MDRD za automatizirano laboratorijsko izdavanje nalaza. Radna skupina za standardizaciju procjene brzine glomerularne filtracije Međunarodnog saveza za kliničku kemiju i laboratorijsku medicinu (engl. *International Federation of Clinical Chemistry and Laboratory Medicine Working Group on Standardisation of Glomerular Filtration Rate Assessment*, IFCC:WG-GFRA) trenutačno razmatra prijedloge za osnivanje referentne laboratorijske mreže za kreatinin kako bi pomogla proizvođačima kod validacije sljedivosti njihovih metoda, te uvela smjernice za globalnu procjenu eGFR primjenom revidirane skraćene jednadžbe MDRD.

Ograničenja automatiziranih nalaza eGFR

Postoji nekoliko ograničenja vezanih za eGFR:

- brze promjene bubrežne funkcije (npr. akutno zatajenje bubrega);
- bolesnici ovisni o dijalizi;
- izuzetni unos prehranom (npr. vegetarijanska prehrana, visokoproteinska dijeta, nadopune kreatina);
- ekstremne tjelesne veličine;
- bolesti skeletnih mišića, paraplegija, osobe s velikom mišićnom masom i osobe s amputacijama;
- teška bolest jetre;
- djeca (mlađa od 18 godina);
- vrijednosti eGFR iznad 60 mL/min/1,73 m^2;
- Aboridžini i narod s Torres Strait otoka;
- Azijske populacije (uključujući Japance, Kineze i Vijetnamce);
- Maori i narodi otočja u Tihom oceanu.

Ta ograničenja uključuju pogreške koje se odnose na mjerenje kreatinina u serumu, kao što su nasumične pogreške, kratkotrajne varijacije bubrežne funkcije, varijacije u tubularnom lučenju kreatinina, varijacije u izvanbubrežnom (u crijevu) izlučivanju kreatinina, te varijacije u stvaranju kreatinina u mišiću ili unosom kroz prehranu. Štoviše, formule za predviđanje eGFR slabo su validirane za djecu (38) tako da se njihova uporaba trenutačno preporučuje samo kod odraslih (≥ 18 godina). Nakon dobi od 30 godi-

te estimates of GFR. A similar process has already taken place in Australasia, such that most creatinine assays are generally aligned with isotope-dilution mass spectrometry (IDMS). Consequently, the Australasian eGFR Working Group has recommended using the re-expressed ("175") MDRD formula for automated laboratory reporting. The International Federation of Clinical Chemistry and Laboratory Medicine Working Group on Standardisation of Glomerular Filtration Rate Assessment (IFCC:WG-GFRA) is currently considering proposals to establish a reference laboratory network for creatinine to assist manufacturers in validating traceability of their methods and to introduce guidelines for global introduction of eGFR applying the revised abbreviated MDRD equation.

Limitations of automated eGFR reports

There are a number of limitations associated with eGFR:

- rapidly changing kidney function (eg acute kidney failure);
- dialysis-dependent patients;
- exceptional dietary intake (eg vegetarian diet, high protein diet, creatine supplements);
- extremes of body size;
- diseases of skeletal muscle, paraplegia, those with high muscle mass and amputees;
- severe liver disease;
- children (under 18 years);
- eGFR values above 60 mL/min/1.73 m^2;
- Aboriginal and Torres Strait Islander peoples;
- Asian populations (including Japanese, Chinese and Vietnamese);
- Maori and Pacific Islander peoples.

These limitations include errors related to serum creatinine measurement, such as random errors, short-term variations in renal function, variations in tubular creatinine secretion, variations in extra-renal (gut) creatinine excretion and variations in creatinine generation by muscle or dietary intake. Moreover, prediction formulae for eGFR have been poorly validated in children (38) and so their use is currently only recommended in adults (≥ 18 years). After the age of 30 years, GFR progressively declines at an average rate of 8 mL/min per decade (39). Based on North American data (39), it is estimated that 25% of the population over the age of 70 years will have an eGFR below 60 mL/min/1.73 m^2. While most studies show that GFR declines with age, accepting this as normal runs the risk of "normalising" a pathological state caused by age-related diseases rather than age itself. A fall in GFR is not an inevitable consequence of ageing with the Baltimore Longitudinal Study on Ageing showing that the decline in GFR with age was largely accountable for by hypertension (40). Moreover, a reduced GFR remains a strong predictor

na, GFR progresivno opada u prosjeku 8 mL/min po desetljeću (39). Na temelju sjevernoameričkih podataka (39), procjenjuje se da 25% populacije starije od 70 godina ima eGFR ispod 60 mL/min/1,73 m^2. Dok većina studija ukazuje da GFR opada s dobi, prihvaćanjem da je to normalno postoji opasnost da se "normaliziraju" patološka stanja uzrokovana bolestima povezanima s dobi, a ne samom starošću. Pad vrijednosti GFR nije neizbježna posljedica starenja, a Baltimorska uzdužna studija starenja je pokazala da je smanjenje vrijednosti GFR s dobi bilo uvelike prouzročeno hipertenzijom (40). Štoviše, sniženi GFR ostaje jakim pretkazateljem kardiovaskularne smrtnosti te smrtnosti od različitih uzroka čak i u starijoj populaciji (41-43). Zaista se čini da je učinak sniženog GFR uvelike neovisan o dobi, iako je jedna opsežna studija smrtnosti pokazala slabiju povezanost smrtnosti u starijih osoba nego u mlađim skupinama (44). Australoazijska Radna skupina za eGFR je predložila da automatizirano laboratorijsko izdavanje nalaza eGFR može uključivati referentne intervale povezane s dobi za pojedince starije od 65 godina. Međutim, definicija CKD nije modificirana prema dobi i takav je scenarij zapravo sličan onome za hipertenziju. Naime, iako vrijednosti krvnoga tlaka rastu s dobi i prevalencija im je velika u starijih osoba u razvijenom svijetu, prag za dijagnozu hipertenzije na temelju vrijednosti krvnog tlaka nije promijenjen za starije osobe jer je hipertenzija u toj starosnoj skupini snažno povezana s nepovoljnim ishodima. Slično tome, jako snižene vrijednosti eGFR u starijih bolesnika ispod 60 mL/min/1,73 m^2 treba smatrati značajnima. Australoazijska Radna skupina za eGFR nedavno je ponovno razmatrala to pitanje u prosincu 2006. godine i zaključila da je za sada prerano preporučiti dobno definirane točke za odlučivanje o eGFR no da je liječnike primjereno savjetovati da se u osoba starih 70 godina i starijih eGFR od 45 do 59 mL/min/1,73 m^2, - ako je postojan dulje vrijeme i nije praćen drugim dokazima oštećenja bubrega, - može protumačiti kao tipičan eGFR za tu dob te da nije vjerojatno da je povezan s komplikacijama CKD. Važno je da se ovo često utvrđeno umjereno sniženje eGFR kod starijih osoba treba uvijek razmatrati kad se donose odluke o dozama lijekova koji se izlučuju bubregom.

Osim krajnjih vrijednosti dobi, postoji nekoliko drugih kliničkih situacija kod kojih se izdani rezultati eGFR trebaju tumačiti s oprezom bilo zbog pomanjkanja odgovarajuće validacije ili dokazanog nedostatka preciznosti ili točnosti (npr. kod vrijednosti eGFR iznad 60 ml/min/1,73 m^2). Smjernice CARI (19) trenutačno preporučuju da bi se izravno mjerenje GFR (npr. klirensom kreatinina ili jednom od referentnih metoda za GFR) moglo zatražiti u situacijama u kojima bi eGFR mogao biti nepouzdan, ili u kojima se zahtijeva visok stupanj točnosti procjene GFR (kao što je slučaj prije doziranja lijekova koji se izlučuju bubregom, a koji su visoko toksični, ili kod vrednovanja bubrežne funkcije u potencijalnih živih darovatelja bubrega).

of all-cause and cardiovascular mortality, even in elderly populations (41-43). Indeed, the impact of reduced GFR appears largely independent of age, although one large mortality study has demonstrated a weaker association of mortality in the elderly than in the younger groups (44). The Australasian eGFR Working Group has suggested that automatic laboratory reporting of eGFR may include age-related reference intervals for individuals aged ≥ 65 years. However, the definition of CKD is not modified according to age. This scenario is analogous to that for hypertension. Even though blood pressure levels rise with age and are highly prevalent in the elderly in the developed world, the threshold for diagnosing hypertension based on blood pressure level is not altered in older individuals because hypertension in this age group is still strongly associated with adverse outcomes. Similarly, severely reduced eGFR values in elderly patients below 60 mL/min/1.73 m^2 should be considered significant. The Australasian eGFR Working Group recently revisited this issue in December 2006 and concluded that at this time it was premature to recommend age-related decision points for eGFR but that it was appropriate to advise practitioners that, in those of 70 years and older, an eGFR from 45 to 59 mL/min/1.73m^2, when stable over time and unaccompanied by other evidence of kidney damage, may be interpreted as consistent with a typical eGFR for this age and unlikely to be associated with CKD complications. Importantly, this commonly found moderate reduction in eGFR in the elderly should always be considered when drug dosing decisions are being made about renally excreted drugs.

In addition to extremes of age, there are a number of other clinical situations where reported eGFR results should be interpreted with caution due either to lack of appropriate validation or to demonstrated lack of precision or accuracy (eg with eGFR values above 60 mL/min/1.73 m^2). The CARI Guidelines (19) currently recommend that direct measurement of GFR (e.g. by creatinine clearance or one of the GFR reference methods) may be required in situations in which eGFR may be unreliable or in which a high degree of accuracy in GFR estimation is required (such as prior dosing with renally-excreted medications that have high toxicity or evaluation of renal function in potential live kidney donors).

Interpretation of eGFR values on pathology reports

The normal GFR in young adults is around 120 mL/min/1.73 m^2. eGFR values below 60 mL/min/1.73 m^2 are abnormal and generally indicate the presence of CKD if present for more than 3 months. In individuals with an eGFR value > 60 mL/min/1.73 m^2, CKD considered to be present if there is concomitant evidence of kidney damage (including microalbuminuria, macroalbuminuria, persiste-

Tumačenje vrijednosti eGFR u patološkim nalazima

Normalan GFR u mladih odraslih osoba je oko 120 mL/min/1,73 m^2. Vrijednosti eGFR ispod 60 mL/min/1,73 m^2 su patološke i općenito ukazuju na prisutnost CKD ako se nalaze tijekom više od 3 mjeseca. U osoba s vrijednošću eGFR > 60 mL/min/1,73 m^2 smatra se da je CKD prisutna ako istovremeno postoje dokazi bubrežnog oštećenja (uključujući mikroalbuminuriju, makroalbuminuriju, tvrdokornu glomerularnu hematuriju ili radiološke abnormalnosti bubrega). Smjernice K/DOQI i CARI podijelile su CKD u pet različitih stadija na temelju vrijednosti GFR (17,45); ti su stadiji navedeni u tablici 2 zajedno s planom kliničkog djelovanja utemeljenom na vrijednosti eGFR.

Bolesnici sa značajnim sniženjem eGFR (<60 mL/min/1,73 m^2) imaju znatno povišeni rizik kardiovaskularne bolesti i napredovanja bubrežnog zatajenja. Takve bi bolesnike trebalo minimalno ispitati primjenom omjera proteina i kreatinina u mokraći, mjerenjem krvnoga tlaka, te ultrazvukom bubrega. Glavni ciljevi obrade CKD su:

a) smanjenje kardiovaskularnog i bubrežnog rizika (promjena načina življenja, antiproteinurijski agensi, kontrola krvnoga tlaka te kolesterola, glikemijska kontrola, smanjenje tjelesne težine, prestanak pušenja, rješavanje djelomične anemije);

nt glomerular haematuria or radiological renal abnormalities). The K/DOQI and CARI guidelines have classified five different stages of CKD based on the level of GFR (17,45). These are listed in Table 2, together with a clinical action plan based on eGFR level.

Patients with a significant reduction in eGFR (<60 mL/min/1.73 m^2) are at significantly increased risk of cardiovascular disease and renal failure progression. At a minimum, such patients should be investigated with an urinary protein:creatinine ratio, blood pressure measurement and renal ultrasongraphy. The principal goals of CKD management are:

a) reduction of cardiovascular and renal risk (lifestyle modification, antiproteinuric agents, blood pressure control, cholesterol control, glycaemic control, weight reduction, smoking cessation, partial anaemia correction);
b) early detection and management of CKD complications (such as hypertension, secondary hyperparathyroidism, renal osteodystrophy, anaemia, sleep apnoea, restless legs, cardiovascular disease, and malnutrition);
c) avoidance of nephrotoxic medications and evaluation of prescribed medications to ensure that dosages are appropriate for the level of kidney function; and,

Tablica 2. Klasifikacija stadija CKD

Table 2. Classification of CKD stage

CKD Stage	GFR (mL/min)	Comments
1	≥ 90	Diagnosis requires evidence of kidney damage (eg scarring on renal ultrasound, proteinuria, etc)
2	60 – 89	Diagnosis requires evidence of kidney damage (eg scarring on renal ultrasound, proteinuria, etc)
3	30 – 59	Moderate kidney failure Treat kidney and cardiac risk factors (esp. blood pressure, cholesterol, blood sugar, smoking, obesity) Antiproteinuric drugs (angiotensin converting enzyme inhibitors &/or angiotensin receptor blockers) if appropriate Avoid nephrotoxic drugs Correct anaemia, acidosis and hyperparathyroidism Ensure drug dosages are appropriate for the level of kidney function Consider referral to nephrologist (mostly not required)
4	15 – 29	Severe kidney failure As above + Refer to nephrologist Prepare for dialysis or transplantation if appropriate
5	< 15	End-stage kidney failure As above + Refer to nephrologist Institute dialysis or transplantation if appropriate

b) rano otkrivanje i obrada komplikacija CKD (kao što je hipertenzija, sekundarni hiperparatiroidizam, bubrežna osteodistrofija, anemija, apneja u snu, simptom nemirnih nogu, kardiovaskularna bolest, pothranjenost);
c) izbjegavanje nefrotoksičnih lijekova i procjena propisanih lijekova kako bi se osiguralo da su doziranja primjerena razini bubrežne funkcije, te,
d) pravovremeno upućivanje bolesnika s CKD nefrologu u ograničenim okolnostima, kad je to primjereno (u Tablici 3. je popis trenutačnih indikacija za upućivanje nefrologu prema preporuci australske Radne skupine za pregled bubrega).

Primjena eGFR kod doziranja lijekova

Adekvatno propisivanje mnogih lijekova ovisi o poznavanju bubrežne funkcije bolesnika. Postoji opća suglasnost da je o odlučivanje o prilagodbi doze lijeka kod osoba s CKD pojačano procjenom bubrežne funkcije utemeljene na GFR, a ne na samoj koncentraciji kreatinina u serumu. Iako formula MDRD osigurava pouzdaniju procjenu GFR od Cockroft-Gaultove, ova druga se trenutačno smatra optimalnom za doziranje lijekova jer se većina preporuka o doziranju lijekova za bubrege zasniva na Cockroft-Gaultovom klirensu kreatinina, te zato jer se doziranje lijeka treba temeljiti na stvarnom GFR (mL/min), a ne na GFR normaliziranom prema površini tijela (mL/min/1,73 m^2) (46). S druge strane, postoji zabrinutost u vezi s varijabilnošću preporučene uporabe Cockroft-Gaultove formule s obzirom na primjenu procijenjene idealne ili stvarne tjelesne težine te na primjenu zastarjele formule koja nije izmijenjena da bi obrazložila promjene u restandardizaciji analize kreatinina u serumu. Rezultat primjene Cockroft-Gaultove kao i jednadžbe MDRD uglavnom su sukladne preporuke za propisivanje lijekova, no nedavna je studija ukazala na potencijalno klinički važne razlike u kliničkom

d) timely referral of CKD patients to a nephrologist in the limited circumstances where this is appropriate (Table 3 lists the current indications for nephrologist referral, as recommended by the Kidney Check Australia Taskforce).

Use of eGFR for drug dosing

The appropriate prescribing of many drugs depends on knowledge of the patient's renal function. There is wide agreement that decision making in drug dose adjustment in people with CKD is enhanced by an assessment of kidney function based on GFR rather than a serum creatinine concentration alone. Although the MDRD formula provides a more reliable estimate of GFR than that of Cockcroft-Gault, the latter is currently considered optimal for drug dosing because most of the renal dosing recommendations are based on Cockcroft-Gault creatinine clearance and because drug dosing should be based on actual GFR (mL/min) rather than GFR normalised to body surface area (mL/min/1.73 m2) (46). On the other hand, there are concerns about the variability in the recommended use of the C-G formula with regard to use of estimated ideal or actual body weight and the use of an outdated formula which has not been revised to account for changes in serum creatinine assay re-standardisation. Use of both the Cockcroft-Gault and MDRD equations mostly results in concordant prescribing recommendations, but a recent study suggested that potentially clinically important differences in clinical decision-making occurred in 21-37% of patients (47). It is not yet known whether the use of the Cockcroft-Gault or the MDRD eGFR for drug dosing results in superior clinical outcomes. Most guideline groups cautiously recommend using the Cockcroft-Gault creatinine clearance for drug dosing until more clinical studies with the MDRD formula are performed, although the Australasian eGFR Working Party recommends that it appears

Tablica 3. Indikacije za upućivanje bolesnika s CKD nefrologu

Table 3. Indications for referral of CKD patients to a nephrologist.

eGFR <30mL/min1.73m²
Unexplained decline in kidney function (> 15% drop in GFR over 3 months)
Proteinuria > 1g/24hrs
Glomerular haematuria (particularly if proteinuria present)
CKD and hypertension that is hard to get to target
Diabetes with eGFR < 60mL/min/1.73m²
Unexplained anaemia with eGFR < 60mL/min/1.73m²

odlučivanju koje su zabilježene kod 21-37% bolesnika (47). Još uvijek nije poznato je li uporaba eGFR prema Cockroft-Gaultu ili prema MDRD kod doziranja lijeka rezultira boljima kliničkim ishodima. Većina skupina smjernica oprezno preporučuje korištenje Cockroft-Gaultovog klirensa kreatinina kod doziranja lijeka sve dok se ne provede više kliničkih studija s formulom MDRD, premda australoazijska Radna skupina za eGFR preporučuje kao prihvatljivo i zapravo pogodnije, - a u odsutnosti bilo koje druge mjere za bubrežnu funkciju, - primjenu eGFR prema MDRD (uz prihvaćanje njenih ograničenja) kao pokazatelja kod propisivanja, posebice kod doza lijekova koji nisu kritični u općoj praksi. U najmanju ruku eGFR prema MDRD upozorava liječnike na mogućnost smanjene bubrežne funkcije te po želji i na primjenu drugih procjena.

Učinak automatiziranog laboratorijskog izdavanja nalaza eGFR na otkrivanje CKD

Za automatizirane nalaze eGFR je pokazano da rezultiraju povećanim otkrivanjem CKD u zajednici te poboljšanim upućivanjem bolesnika s CKD nefrolozima. Akbari i sur. (2004.) su proveli studiju stanja prije i poslije ispitivanja u 324 bolesnika starih ≥ 65 godina u ambulanti obiteljske medicine. Intervencija u studiji uključivala je automatizirani laboratorijski nalaz Cockroft-Gaultovog klirensa kreatinina te edukacijsku intervenciju usmjerenu na liječnike opće prakse. Prepoznavanje CKD (GFR < 60 mL/min) od strane liječnika opće prakse bilo je primarna ciljana mjera i bilo je značajno povišeno nakon intervencije, s porastom od 24,4% do 85,1% bolesnika s CKD. Povećano prepoznavanje CKD dovodi do povišenih postotaka upućivanja uglavnom odgovarajućih bolesnika, što je važno u koncentriranju ograničenih sredstava. Revizijom provedenom 2006. godine u Australiji pregledane su uputnice za tercijarnu bolnicu, pokrajinsku bolnicu te ordinaciju privatne prakse prije i poslije uvođenja automatiziranih nalaza eGFR. Ukupni postotci upućivanja porasli su samo u tercijarnoj bolnici za približno 53%, dok je kvaliteta, prosuđena prema smjernica KCAT za upućivanje, ostala nepromijenjena kod dvije trećine adekvatnih uputnica.
Potrebno je tek odrediti hoće li rutinsko izdavanje nalaza eGFR poboljšati ishode CKD u zajednici, iako je već sad u Kanadi u tijeku randomizirano kontrolirano ispitivanje. Ipak, u nerandomiziranom kontroliranom ispitivanju 52 bolesnika s šećernom bolesti u kojima je CKD otkrivana u primarnoj praksi na temelju patoloških rezultata eGFR i/ili proteinurije, Martinez-Ramirez i sur. (48) su dokazali da su bolesnici koji su bili upućeni nefrologu manifestirali bolje očuvanje bubrežne funkcije od bolesnika koji su ostali na liječenju samo kod obiteljskog liječnika. Druge su studije također ukazale da su rano otkrivanje CKD i pravovremena intervencija s renoprotektivnim terapijama povezani s 20-50%-tnim smanjenjem kardiovaskularnog i bubrežnog rizika (9).

reasonable and indeed preferable, in the absence of any other measure of kidney function, to use the MDRD eGFR (recognising its limitations) as a guide to prescribing particularly with non-critical dose drugs in general practice. At the very least, the MDRD eGFR alerts treating doctors to the possibility of reduced renal function to allow the use of other estimates, if desired.

The impact of automatic laboratory eGFR reporting on CKD detection

Automatic eGFR reporting has been shown to result in enhanced detection of CKD in the community and improved referral of CKD patients to nephrologists. Akbari et al (2004) conducted a before-and-after study of 324 patients aged ≥ 65 years at an outpatient family medicine practice. The intervention consisted of automatic laboratory reporting of Cockcroft-Gault creatinine clearance together with an educational intervention directed at primary care physicians. Recognition of CKD (GFR < 60 mL/min) by the primary care physician was the primary outcome measure and was significantly increased by the intervention increasing from 22.4% to 85.1% of patients with CKD. Increased recognition of CKD leads to increased referral rates of mostly appropriate patients, important in concentrating limited resources. An audit in 2006 in Australia looked at referrals to a tertiary hospital, a provincial hospital and a private practice pre and post introduction of automated eGFR reporting. Overall the referral rates only increased in the tertiary hospital by approximately 53% and the quality, as adjudicated by the KCAT guidelines for referral, remained unchanged with two thirds appropriately referred.
It remains to be determined whether routine reporting of eGFR will improve CKD outcomes in the community, although a randomised controlled trial is currently underway in Canada. Nevertheless, in a non-randomised controlled trial of 52 diabetic patients in whom CKD was detected in primary practice on the basis of an abnormal eGFR report and/or proteinuria, Martinez-Ramirez et al (48) demonstrated that patients who were subsequently referred to a nephrologist exhibited better preservation of renal function than those who remained treated by only their family doctors. Other studies have also suggested that early detection of CKD and timely intervention with renoprotective therapies is associated with a 20%-50% reduction in cardiovascular and renal risk (9).

Conclusions

Automatic laboratory reporting of eGFR on each occasion a serum creatinine concentration is ordered will significantly increase the likelihood of early detection of CKD, allow the institution of appropriate management strategies to

Zaključci

Automatizirano laboratorijsko izdavanje nalaza eGFR kod svakog zahtjeva za određivanjem koncentracije kreatinina u serumu značajno će povećati vjerojatnost ranog otkrivanja CKD, omogućiti ustanovi adekvatne strategije obrade radi smanjenja rizika za progresiju zatajenja bubrega i kardiovaskularne smrti u zajednici, te osigurati informacije kod odluka povezanih s propisivanjem lijekova koji se izlučuju bubregom. Klinički kemičari trebaju biti svjesni potrebe za postizanjem bolje standardizacije mjerenje kreatinina u serumu te sljedivosti svih mjerenja kako bi povećali točnost i kliničku iskoristivost automatiziranih nalaza eGFR (osobito kod nižih vrijednosti kreatinina u serumu).

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reduce the risks of kidney failure progression and cardiovascular death in the community, and inform decisions regarding the prescription of renally excreted medications. Clinical chemists need to be aware of the need to achieve better standardisation of serum creatinine measurements and traceability of all measurements to enhance the diagnostic accuracy of automated eGFR reports (especially at lower serum creatinine values).

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