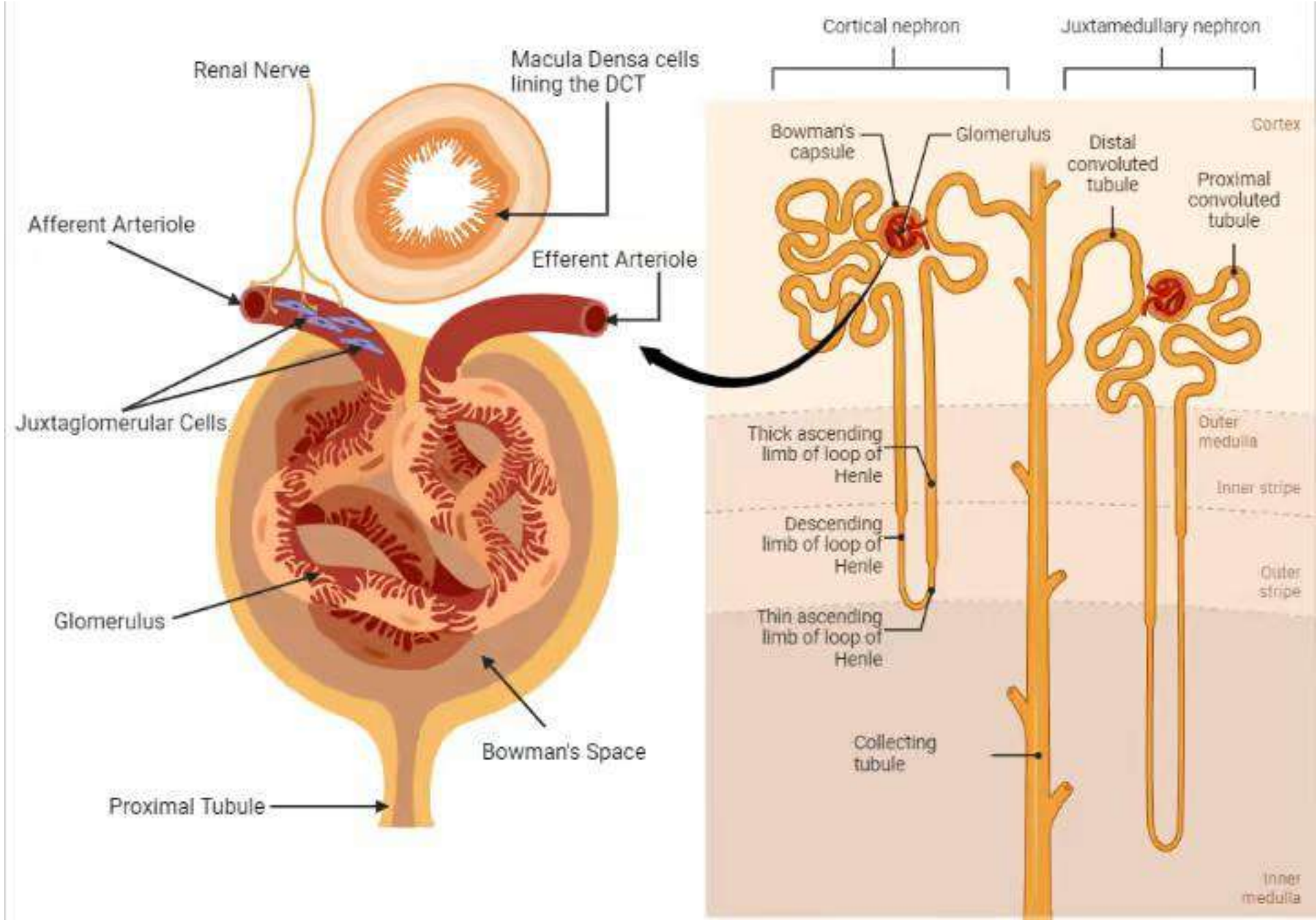
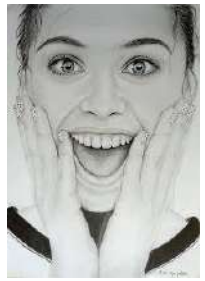
GFR meghatározási módszerek

Karvaly Gellért Balázs

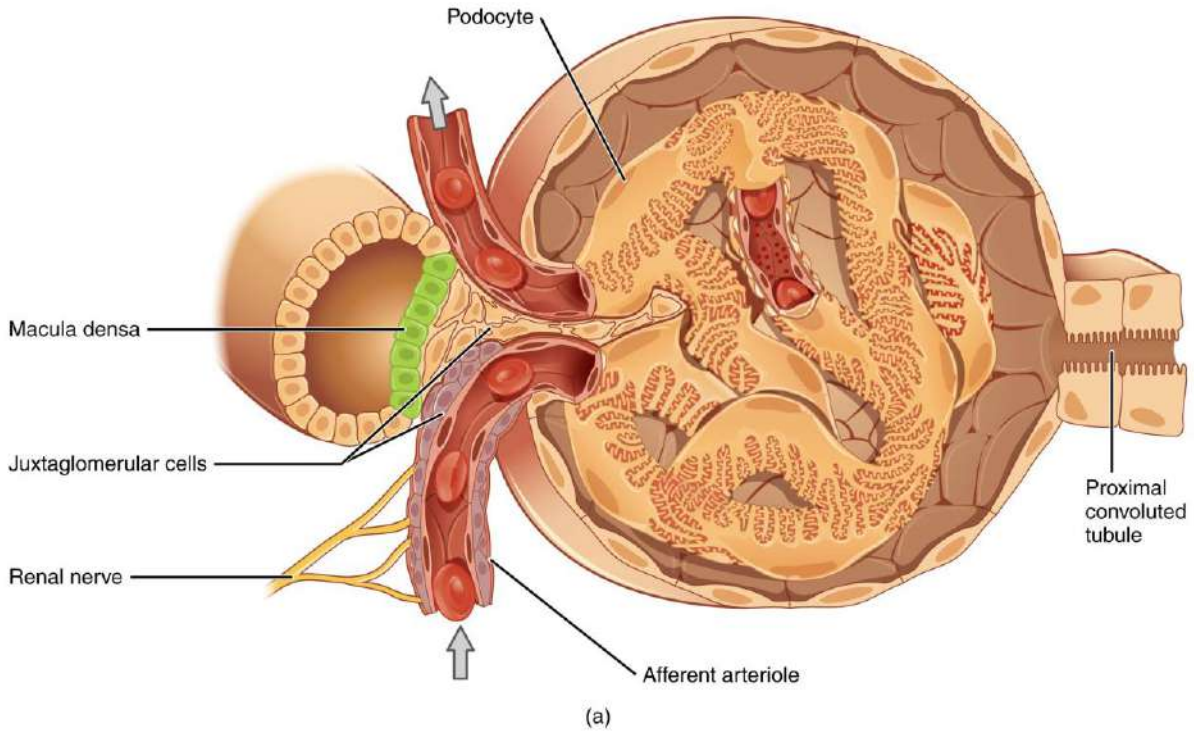

Renal Nerve
Macula Densa cells lining the DCT
Afferent Arteriole
Efferent Arteriole
Juxtaglomerular Cells
Glomerulus
Bowman's Space
Proximal Tubule
Cortical nephron
Juxtamedullary nephron
Bowman's capsule
Glomerulus
Distal convoluted tubule
Proximal convoluted tubule
Cortex
Thick ascending limb of loop of Henle
Descending limb of loop of Henle
Thin ascending limb of loop of Henle
Collecting tubule
Outer medulla
Inner stripe
Outer stripe
Inner medulla

- Glomeruláris filtrációs ráta:
  - 130-145 l/nap (90-100 ml/min)



  - 165-180 l/nap (115-125 ml/min)

- Nefronok száma felnőttekben: kb. 860 000 ± 370 000 / vese
- A nefronok száma születés után nem nő
- A szklerotizált nefronok nem regenerálódnak
- A GFR a működő veseszövet tömeg mutatója



Rétegek:

1. Fenesztrált glomeruláris endothel
2. Glomerulus bazális membrán
3. Podocyta nyúlványok

- 30 kDa-nál kisebb molekulatömegű anyagok szabadon filtrálódnak
- A 30-50 kDa közötti molekulatömegű anyagok filtrációja korlátozott
- 100 kDa-nál nagyobb molekulatömegű anyagok lényegében nem ürülnek
- Az endothel, a bazális membrán és a podociták érintkező felszíne negatív töltésű → semleges és pozitív töltésű anyagok hatékonyabban filtrálódnak

$$GFR = Lp\ x\ S\ x\ (P_{gc} - P_{bs}) - s\ x\ (\Pi_p - \Pi_{bs})$$

Lp: a kapillárisfal egységnyi permeabilitása
S: a filtrációhoz elérhető felület
P_{gc}: hidrosztatikus nyomás a glomerulus kapillárisban (kb. 55 Hgmm)
P_{bs}: hidrosztatikus nyomás a Bowmann-tokban (kb. 15 Hgmm)
s: fehérje impermeabilitási tényező (0-1)
Π_p: onkotikus nyomás a glomerulus kapillárisban
Π_{bs}: onkotikus nyomás a Bowmann-tokban (kb. 0 Hgmm)

$$GFR = Lp\ x\ S\ x(P_{gc} - P_{bs}) - \Pi_p$$

- Veseclearance: az a plazmatérfogat, amelyből az adott anyag kiürül időegység alatt a vesén keresztül

$$CL = \frac{U \times V}{P}$$

CL: veseclearance (ml/min)
U: Vizsgált anyag koncentrációja a vizeletben (pl. µmol/l)
V: Időegység alatt ürített vizelet térfogata (ml/min)
P: Vizsgált anyag koncentrációja a plazmában (pl. µmol/l)

$$CL = \frac{U \times V}{P \times T} \times \frac{1{,}73}{BSA}$$

T: gyűjtési idő (min)
BSA: testfelszín (m^2)

Clearance tesztek

- Clearance-t befolyásoló tényezők:
  - Véráramlás sebessége
  - A vizsgált anyag glomelurális filtrációja, tubuláris szekréciója és tubuláris reabszorpciója
  - A veseműködés állapota

- GFR meghatározására való alkalmasság kritériumai:
  - Állandó plazmaszint
  - Exkréció kizárólag glomeruláris filtrációval történjen
  - Ne legyen tubuláris szekréció és/vagy reabszorpció

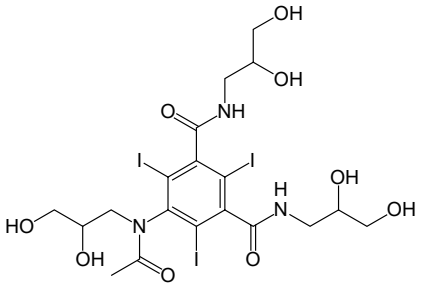
- Exogén vegyületek bejuttatásával végzett vizsgálatok: mGFR meghatározás
- Endogén vegyületek mérésével végzett vizsgálatok: eGFR meghatározás

Exogén vegyületekkel végzett clearance tesztek

- Bejuttatás: iv bolus, folyamatos iv infúzió

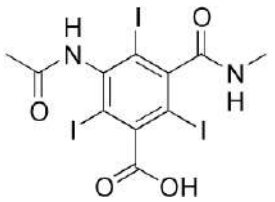
- Nem izotóppal jelölt anyagok:
  - Inulin
    - Fruktopoliszacharid (molekulatömeg: 5200 Da)
    - GFR meghatározás referencia módszere
    - Nem szívódik fel gasztrointesztinálisan → intravénásan kell bejuttatni
    - Nem lép ki az érpályákból, nincs metabolizmus
    - Exkréció kizárólag a glomerulusokban történik, nincs tubuláris szekréció vagy reabszorpció
    - Klinikai gyakorlatban nem tudjuk használni a körülményes kivitelezés és a magas költség miatt
    - Vizsgálat: kolorimetria, HPLC-UV

  - Iohexol
    - Kismolekula: 821 Da
    - Közel 100%-ban glomeruláris filtrációval ürül
    - Alkalmazása teljesen biztonságos
    - Nemionos vegyület



Exogén vegyületekkel végzett clearance tesztek

- Nem izotóppal jelölt anyagok:
  - Iothalamate
    - Kismolekula: 614 Da
    - Alkalmazásakor a hiperszenzitivitási reakció gyakoribb volt, mint az iohexol esetében



- Izotóppal jelölt anyagok:
  - ^{125}I-iothalamate
  - ^{125}I-diatrizoate
  - ^{51}Cr-EDTA
  - ^{99}Tc-DTPA

- GFR számítás:

$$Clearance = \frac{Dózis}{Plazma\ koncentráció - idő\ görbe\ alatti\ terület}$$

Endogén vegyületekkel végzett clearance tesztek

- Vizsgálat menete:
  - 24 órás vizeletgyűjtés – U, V meghatározása
  - 12 óránál plazmaszint meghatározása

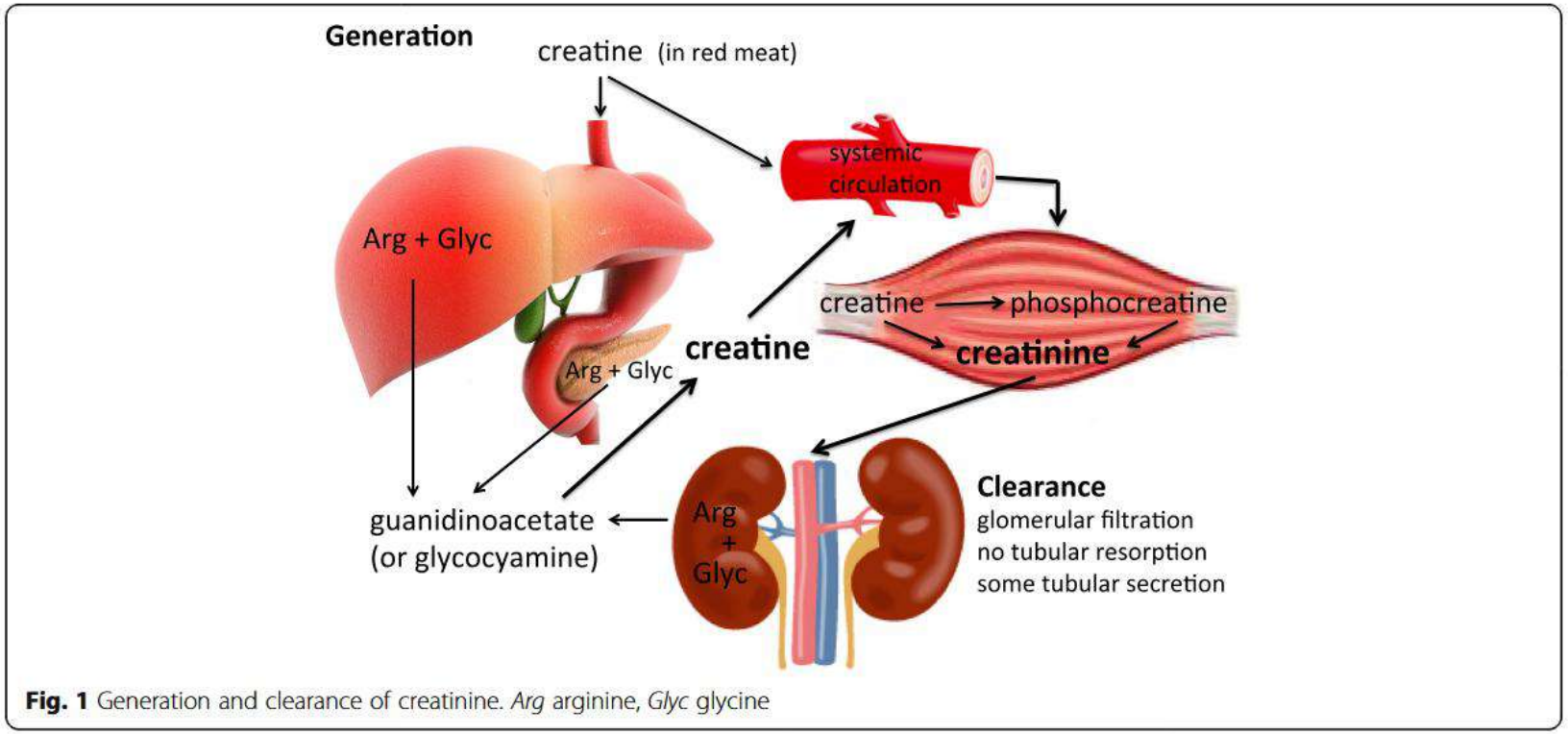


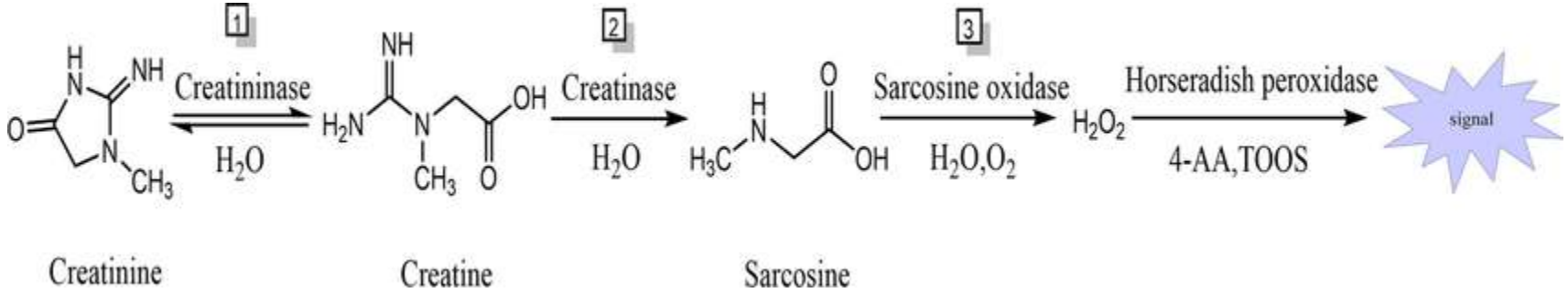
Fig. 1 Generation and clearance of creatinine. *Arg* arginine, *Glyc* glycine

A kreatinin néhány jellemzője

- Vese nem termeli, nem reabszorbeálódik, nem metabolizálódik
- Proximális tubulus szekréció (10-20%)
- Izomtömeg és étrend befolyásolja a szérum kreatinin szintet
- GFR beszűkülésekor a tubuláris szekréció kompenzál, akár a vizelet kreatinin szint kb. 35%-a ebből származhat
- A vesefunkció beszűkülését a szérum kreatinin szint változása kb. 24 órás késéssel követi
- Vizeletben a baktériumok felhalmozódása a kreatinin kreatinné alakulását eredményezi (pH változás miatt, esetleg kreatininnáz-katalizált reakcióban)

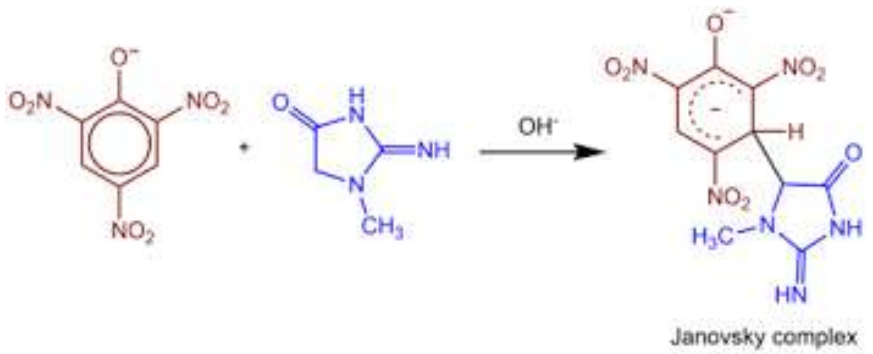
Kreatinin vizsgálati módszerek

- Enzimatikus reakció:



4-AA: 4-amino-antipirin
TOOS: (N-ethyl-N-(2-hydroxy-3-sulfopropyl)-3-methylaniline

- Kinetikus Jaffé-reakció:



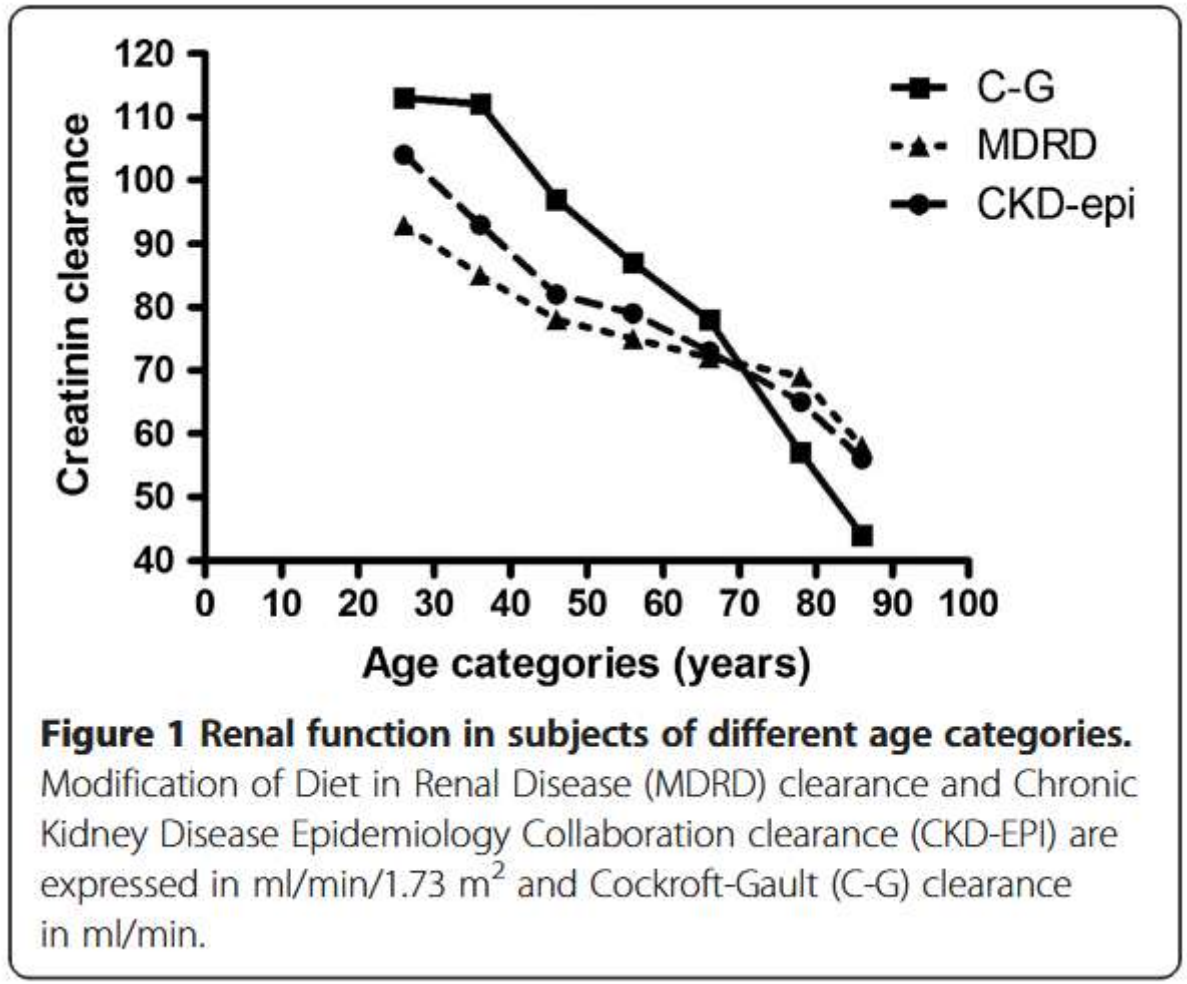


Figure 1 Renal function in subjects of different age categories. Modification of Diet in Renal Disease (MDRD) clearance and Chronic Kidney Disease Epidemiology Collaboration clearance (CKD-EPI) are expressed in ml/min/1.73 m^2 and Cockroft-Gault (C-G) clearance in ml/min.

Willems JM et al. BMC Geriatrics 2013;13:113.

A cystatin C néhány jellemzője

- Fehérje (13 000 Da)
- Cisztein proteáz inhibitor
- Minden maggal rendelkező sejt termeli
- Glomerulusokban szabadon filtrálódik
- A szérum cystatin C szint nem függ az életkortól, nemtől, izomtömegtől

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New Creatinine- and Cystatin C–Based Equations to Estimate GFR without Race

L.A. Inker, N.D. Eneanya, J. Coresh, H. Tighiouart, D. Wang, Y. Sang, D.C. Crews, A. Doria, M.M. Estrella, M. Froissart, M.E. Grams, T. Greene, A. Grubb, V. Gudnason, O.M. Gutiérrez, R. Kalil, A.B. Karger, M. Mauer, G. Navis, R.G. Nelson, E.D. Poggio, R. Rodby, P. Rossing, A.D. Rule, E. Selvin, J.C. Seegmiller, M.G. Shlipak, V.E. Torres, W. Yang, S.H. Ballew, S.J. Couture, N.R. Powe, and A.S. Levey, for the Chronic Kidney Disease Epidemiology Collaboration*

ticipants than in non-Black participants.[5-7] Although not yet widely used, the serum cystatin C level is recommended for confirmatory testing of eGFR.[8] The current equation for eGFR that uses

Inclusion of race in GFR estimating equations, along with other algorithms in medicine, is facing increasing scrutiny because race is a social and not a biologic construct; its inclusion

METHODS

We developed new eGFR equations without race using data from two development data sets: 10 studies (8254 participants, 31.5% Black) for serum creatinine and 13 studies (5352 participants, 39.7% Black) for both serum creatinine and cystatin C. In a validation data set of 12 studies (4050 participants, 14.3% Black), we compared the accuracy of new eGFR equations to measured GFR. We projected the prevalence of chronic kidney disease (CKD) and GFR stages in a sample of U.S. adults, using current and new equations.

The studies involved only ambulatory adult populations without serious coexisting conditions; thus, our results may not apply to patients in acute care settings.

Table 2. Current and New Equations to Estimate GFR.*

Model; Name of Equation†	Intercept μ (95% CI)	Coefficients for Creatinine (95% CI)‡		Coefficients for Cystatin C (95% CI)§		Coefficient c for Age (95% CI)	Coefficient d for Female Sex (95% CI)	Coefficient e for Black Race (95% CI)
		a_1	a_2	b_1	b_2			
2021 CKD-EPI creatinine–cystatin C (2012 CKD-EPI creatinine–cystatin C fit without race); eGFRcr-cys(AS), new	135 (132 to 137)	F: –0.219 (–0.336 to –0.101); M: –0.144 (–0.245 to –0.042)	–0.544 (–0.572 to –0.515)	–0.323 (–0.426 to –0.220)	–0.778 (–0.809 to –0.746)	0.9961 (0.9957 to 0.9965)	0.963 (0.952 to 0.974)	—

$$eGFR = 135 \cdot A1^{\alpha} \cdot A2^{-0,544} \cdot B1^{-0,323} \cdot B2^{-0,778} \cdot 0,9961^{\text{Életkor(év)}} \cdot A3 \quad \text{[ml/min/1,73 m}^2\text{]}$$

A1: mért szérum kreatinin szint (mg/dl) / A4, ha a hányados kisebb, mint 1; egyébként 1
A2: mért szérum kreatinin szint (mg/dl) / A4, ha a hányados nagyobb, mint 1; egyébként 1
A3: Ha a beteg férfi, értéke 1. Ha a beteg nő, értéke 0,963
A4: Ha a beteg férfi, értéke 0,9. Ha a beteg nő, értéke 0,7
B1: mért szérum cystatin C szint (mg/l) / 0,8, ha a hányados kisebb, mint 1; egyébként 1
B2: mért szérum cystatin C szint (mg/l) / 0,8, ha a hányados nagyobb, mint 1; egyébként 1
α: Ha a beteg férfi, értéke -0,144. Ha a beteg nő, értéke -0,219.

https://www.kidney.org/professionals/gfr_calculator

$$eGFR = 142 \cdot A1^{\alpha} \cdot A2^{-1,200} \cdot 0{,}9938^{\text{Életkor(év)}} \cdot A3 \qquad \text{[ml/min/1,73 m}^2\text{]}$$

A1: mért szérum kreatinin szint (mg/dl) / A4, ha a hányados kisebb, mint 1; egyébként 1
A2: mért szérum kreatinin szint (mg/dl) / A4, ha a hányados nagyobb, mint 1; egyébként 1
A3: Ha a beteg férfi, értéke 1. Ha a beteg nő, értéke 1,012
A4: Ha a beteg férfi, értéke 0,9. Ha a beteg nő, értéke 0,7
α: Ha a beteg férfi, értéke -0,302. Ha a beteg nő, értéke -0,241.

2021 CKD-EPI creatinine (2009 CKD-EPI creatinine fit without race); eGFRcr(AS), new	142 (139 to 144)	F: –0.241 (–0.344 to –0.138); M: –0.302 (–0.403 to –0.202)	–1.200 (–1.211 to –1.189)	—	—	0.9938 (0.9935 to 0.9942)	1.012 (1.000 to 1.023)	—

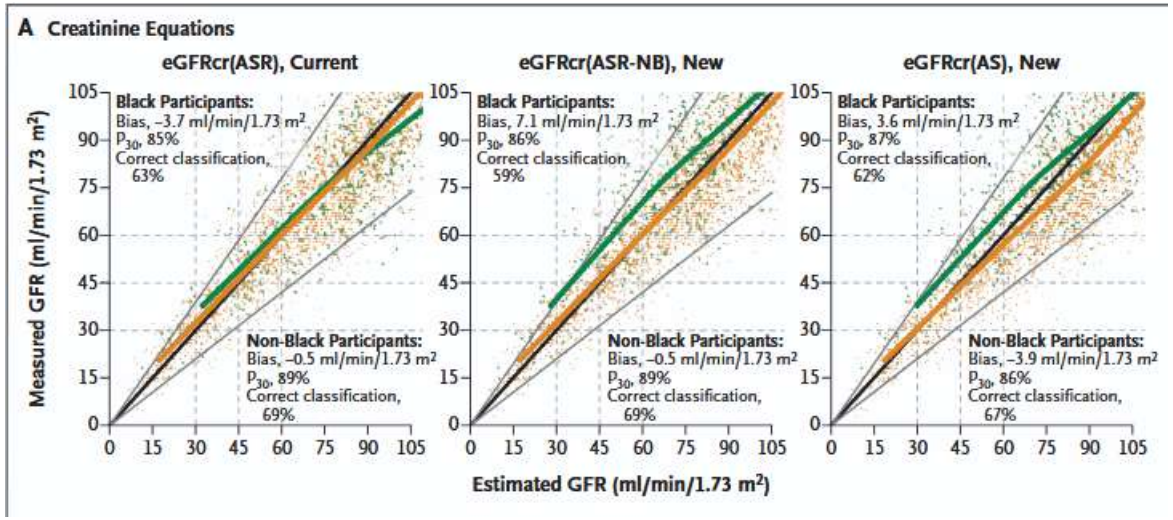
https://www.kidney.org/professionals/gfr_calculator

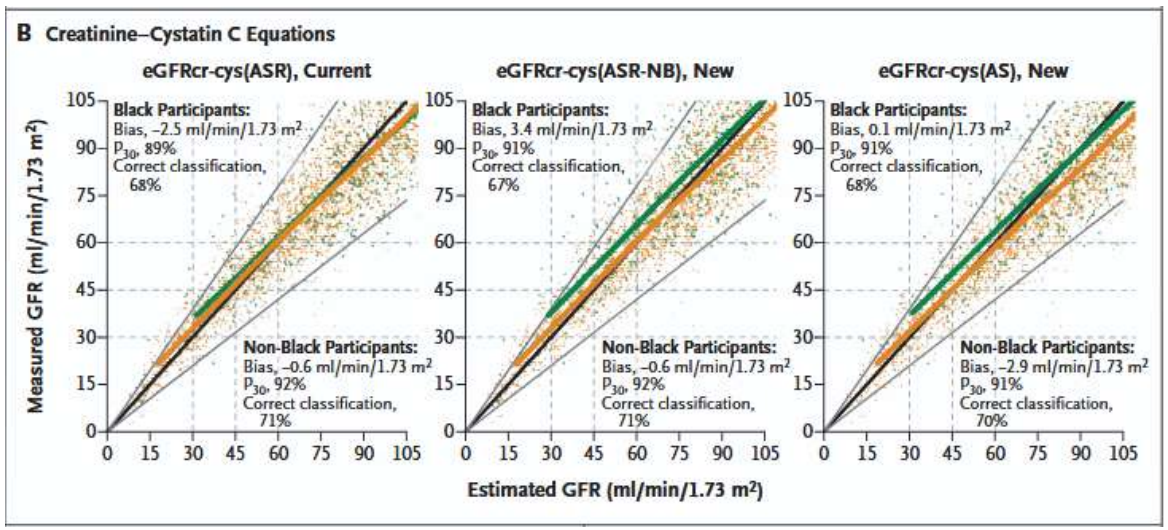
$$eGFR = 133 \cdot B1^{-0,499} \cdot B2^{-1,328} \cdot 0,9962^{\text{Életkor(év)}} \cdot A3$$ [ml/min/1,73 m^2]

A3: Ha a beteg férfi, értéke 1. Ha a beteg nő, értéke 0,932
B1: mért szérum cystatin C szint (mg/l) / 0,8, ha a hányados kisebb, mint 1; egyébként 1
B2: mért szérum cystatin C szint (mg/l) / 0,8, ha a hányados nagyobb, mint 1; egyébként 1

2012 CKD-EPI cystatin C[9]; eGFRcys (AS), current	133 (130 to 136)	—	—	–0.499 (–0.610 to –0.388)	–1.328 (–1.344 to –1.312)	0.9962 (0.9957 to 0.9966)	0.932 (0.921 to 0.944)	—

https://www.kidney.org/professionals/gfr_calculator





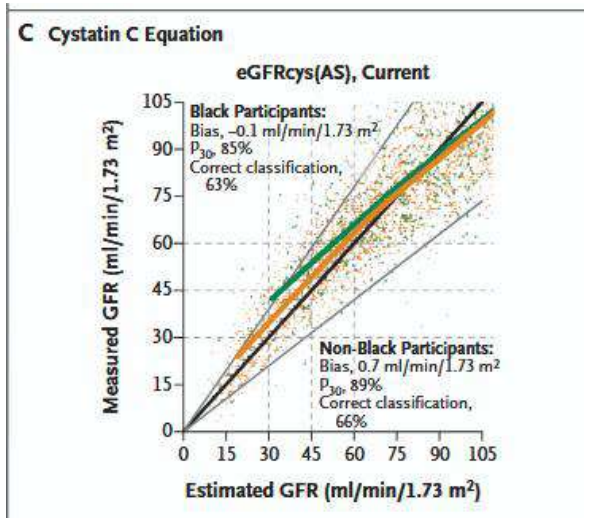
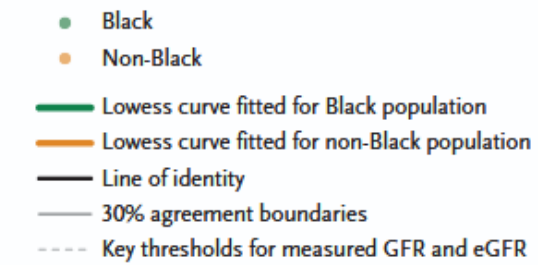


Figure 1 (facing page). Comparison of Measured GFR and Estimated GFR (eGFR) According to Race Group across Alternative GFR Estimating Equations.

The equations are referred to by the filtration marker or markers (creatinine [eGFRcr], cystatin C [eGFRcys], or creatinine–cystatin C [eGFRcr-cys]) and the demographic factors (age, sex, and race [ASR] or age and sex [AS]) that were used in their development. Non-Black (NB) refers to equations in which the Black race coefficient was omitted in computation of the eGFR value. Data from the validation data set are shown. Data from the development data set are shown in Figure S4 in the Supplementary Appendix. Bias is defined as the median difference between measured GFR and eGFR. A positive sign indicates underestimation of measured GFR, and a negative sign indicates overestimation of measured GFR. P_{30} is the proportion of eGFR within 30% of measured GFR. Correct classification refers to agreement between measured GFR and eGFR categories of more than 90, 60 to 89, 45 to 59, 30 to 44, 15 to 29, and less than 15 ml per minute per 1.73 m².



Nem részletezzük:

- 2009-es CKD-EPI képlet
- MDRD képlet
- Jelliffe-képletek (Jelliffe 1973, módosított Jelliffe 2002)
- Cystatin C képletek (Grubb, Larsson)

Laboratóriumi vizsgálati módszerek

the purposes of these analyses. Measurement of creatinine, cystatin C, and GFR followed previously reported methods.[5,9,21,22]

Table S2: Assays and Quality Control for Creatinine, Cystatin C, B2M and BTP

Analyte	Assay	Manufacturer	Instrument	Assay CV (Low and High Concentration)
B2M	Immunoturbidimetric, standardized against the WHO standard	Roche	Roche Cobas 6000 analyzer	1.5% at 2.31 mg/L; 1.4% at 5.22 mg/L
BTP	Immunonephelometric	Siemens	ProSpec	5.7% at 0.594 mg/L; 4.0% at 1.769 mg/L
Creatinine	Enzymatic, standardized against IDMS	Roche	Roche Cobas analyzer	3.0% at 0.83 mg/dL; 1.1% at 3.82 mg/dL
Cystatin C	Immunoturbidimetric, standardized against international calibrator standard ERM-DA47/IFCC	Gentian	Roche Cobas 6000 analyzer	5.6% at 0.76 mg/L; 3.8% at 3.22 mg/L

Inker LA et al. Am J Kidney Dis 2021;77:673-683.e1
(ref. 21)

B2M: béta-2-mikroglobulin
BTP: béta-trace fehérje

Krónikus vesekárosodás diagnózisa

CURRENT CHRONIC KIDNEY DISEASE (CKD) NOMENCLATURE USED BY KDIGO

CKD is defined as abnormalities of kidney structure or function, present for a minimum of 3 months, with implications for health. CKD is classified based on Cause, Glomerular filtration rate (GFR) category (G1–G5), and Albuminuria category (A1–A3), abbreviated as CGA.

KDIGO: Prognosis of CKD by GFR and albuminuria categories

GFR categories (ml/min/1.73 m²) Description and range				Persistent albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30–300 mg/g 3–30 mg/mmol	>300 mg/g >30 mg/mmol
	G1	Normal or high	≥90			
	G2	Mildly decreased	60–89			
	G3a	Mildly to moderately decreased	45–59			
	G3b	Moderately to severely decreased	30–44			
	G4	Severely decreased	15–29			
	G5	Kidney failure	<15			

Green: low risk (if no other markers of kidney disease, no CKD); Yellow: moderately increased risk; Orange: high risk; Red: very high risk. GFR, glomerular filtration rate.

https://kdigo.org/wp-content/uploads/2024/03/KDIGO-2024-CKD-Guideline.pdf

eGFR meghatározás 1-17 éves kor között (Schwartz-képletek)

$$eGFR = 0{,}413 \cdot \frac{Testmagasság\ (cm)}{Szérum\ kreatinin\ (\frac{mg}{dl})} \qquad [ml/min/1{,}73\ m^2]$$

$$eGFR = 70{,}69 \cdot (Szérum\ Cystatin\ C^{-0{,}931}) \qquad [ml/min/1{,}73\ m^2]$$

$$eGFR = 39{,}8 \cdot (\frac{Testmagasság\ (m)}{Szérum\ kreatinin\ (\frac{mg}{dl})})^{0{,}456} \cdot (\frac{1{,}8}{Szérum\ Cystatin\ C\ (\frac{mg}{dl})})^{0{,}418} \cdot (\frac{30}{Szérum\ karbamid\ (\frac{mg}{dl})})^{0{,}079} \cdot (1{,}076^{Sex} \cdot \frac{Testmagasság\ (m)}{1{,}4})^{0{,}179}$$

Sex: ha a beteg fiú, értéke 1. Ha a beteg lány, értéke 0

48% were within 10%.[33,39] The equation is valid in the range of 15-75 mL/min/1.73 m^2 and uses a standardized creatinine measurement and nephelometric assay for cystatin C (Siemens Dade Behring).[33] The cystatin C values have not been referenced to an IFCC

Mian AN, Schwartz GJ. Adv Chronic Kidney Dis 2017;24:348-356.

Kitérő: a testfelszín számítása

DuBois-képlet:

$$BSA = 0{,}007184 \cdot Testsúly^{0{,}425} \cdot Testmagasság^{0{,}725}$$

DuBois-képlet
logaritmizált formában:

$$\lg BSA = -2{,}144 + 0{,}425 \cdot \lg Testsúly + 0{,}725 \cdot \lg Testmagasság$$

Mosteller-képlet:

$$BSA = \sqrt{\frac{Testmagasság \cdot Testsúly}{3600}}$$

Testfelszín: m^2
Testmagasság: cm
Testsúly: kg

Eur J Appl Physiol (2000) 82: 250–254

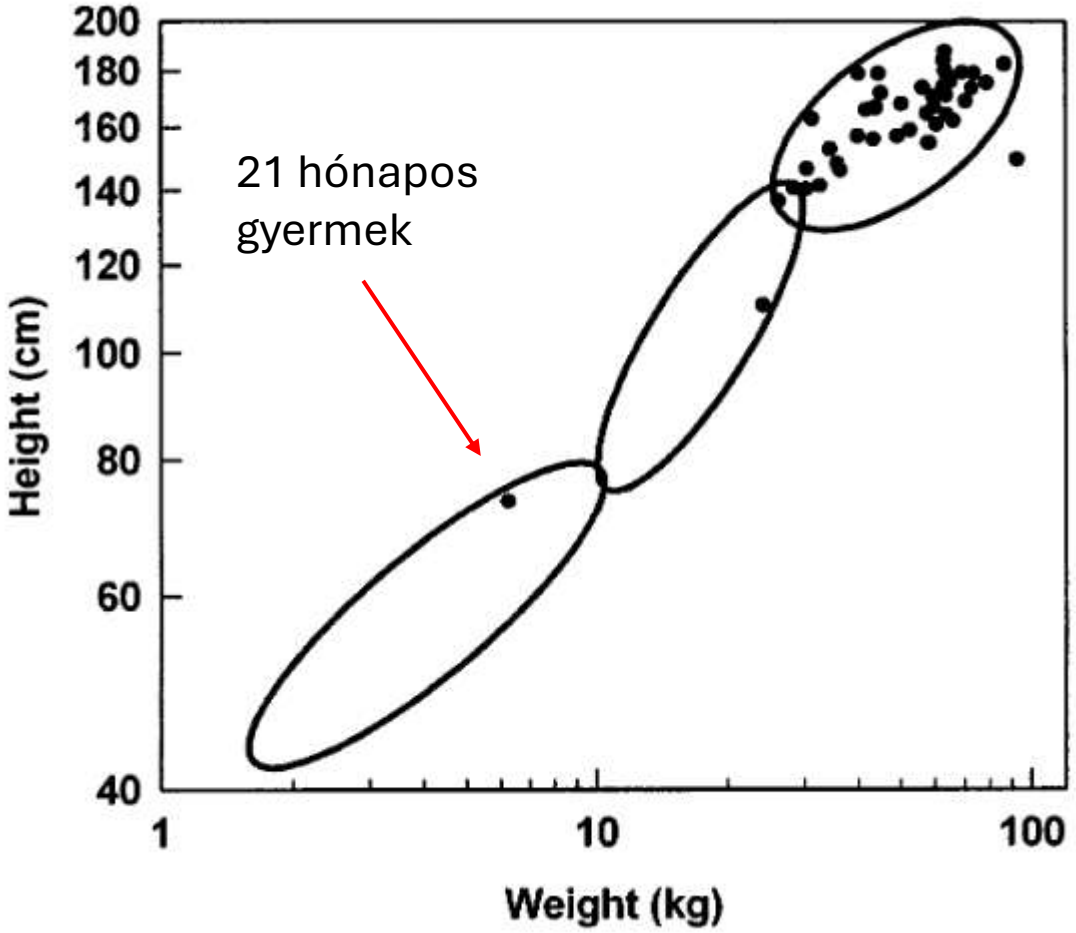
ORIGINAL ARTICLE

Borys Shuter · Alireza Aslani

Body surface area: Du Bois and Du Bois revisited

$= 94.9 \times [\text{weight (kg)}^{0.441}] \times [\text{height (cm)}^{0.655}]\}$. Although the original equation obtained by Du Bois and Du Bois was found to be adequate in adults, we recommend that it should not be used in daily practice, owing to the low number of subjects used in its derivation. The work presented here has placed the original area. Note that there was an error in the statement of Eq. 2 by Du Bois and Du Bois; a × symbol was shown in place of the correct + symbol. Several authors who have published since Du Bois and Du

The widespread utilisation of the formula of Du Bois and Du Bois (1916) has conferred on it the status of a medical icon. However, it does not appear to be widely appreciated that the Du Bois and Du Bois formula was derived from measurements obtained on only nine subjects (Gurney 1996; Lentner 1984; Reilly and Workman 1993). Such a low number would not warrant an application to the general community. However, the



DuBois és DuBois a 42 vizsgált alany közül 32 adatait nem vett figyelembe, a 33. alanyét a 10 alanyon végzett számítást követően elvetette

constant $A = 0.425$ and constant $B = 0.725$. Du Bois and Du Bois used the constraint:

$$3/A + 1/B = 2 \qquad (2)$$

Javasolt egyenlet:

These values ought to be considered as those Du Bois and Du Bois would have derived if they had access to modern techniques. We recommend the set $A = 0.441$, $B = 0.655$, $C = 94.9$, for which the constraint of Eq. 2 does not hold exactly, but is very close to 2 (1.978).

$$BSA = 0{,}00949 \cdot Testsúly^{0{,}441} \cdot Testmagasság^{0{,}655}$$

$$\frac{3}{A} + \frac{1}{B} = 1{,}978$$

A Shuter és Aslani által javasolt számítási módszerekkel, illetve a Mosteller-képlettel kapott testfelszín eredmények eltérése a DuBois-képlettel kapott eredményektől

Sorszám	Testmagasság (cm)	Testsúly (kg)	Shuter és Aslani (m^2)	Haycock (m^2)	Mosteller (m^2)
1	170	70	-1.3%	0.8%	0.5%
2	160	90	-0.5%	5.8%	3.8%
3	190	80	-1.9%	-1.4%	-1.0%
4	150	50	-1.0%	1.1%	0.8%

DuBois	$BSA = 0{,}007184 \cdot Testsúly^{0{,}425} \cdot Testmagasság^{0{,}725}$
Shuter és Aslani	$BSA = 0{,}00949 \cdot Testsúly^{0{,}441} \cdot Testmagasság^{0{,}655}$
Haycock	$BSA = 0{,}02427 \cdot Testsúly^{0{,}538} \cdot Testmagasság^{0{,}396}$
Mosteller	$BSA = \sqrt{\frac{Testmagasság \cdot Testsúly}{3600}}$

JAMA Internal Medicine

Article

CLINICAL CALORIMETRY
TENTH PAPER A FORMULA TO ESTIMATE THE APPROXIMATE SURFACE AREA IF HEIGHT AND WEIGHT BE KNOWN

DELAFIELD Du BOIS, B.S.; EUGENE F. Du BOIS, M.D.

Arch Intern Med (Chic)
Published Online: June 1916
1916;XVII;(6_2):863-871. doi:10.1001/archinte.1916.00080130010002

Összefoglalás – GFR meghatározás

- A pontos GFR meghatározás exogén anyagok bejuttatásával, a vizelet és a szérum szintek együttes meghatározásával lehetséges
- Az eGFR a krónikus vesekárosodást jelző EGYIK marker, értékelése a vizelet albumin-kreatinin aránnyal együtt ad klinikailag releváns információt
- Az eGFR legpontosabb meghatározása a kreatinin és a cystatin C együttes vizsgálatával lehetséges
- A kreatinin mérést LC-MS/MS-sel kapott eredményekre standardizált enzimatikus módszerrel kell végezni

Kreatinin-clearance meghatározás egyéb módszerei

Cockroft-Gault képlet:

$$Kreatinin\ clearance = \frac{\left(140 - \text{Életkor}\right) \cdot Testsúly(kg)}{72 \cdot Szérum\ kreatinin\ szint\ (\frac{mg}{dl})} \cdot Sex$$

Sex: értéke 1, ha a beteg férfi; értéke 0,85, ha a beteg nő.

Jelliffe-képlet
(változó veseműködés):

$$Kreatinin\ clearance = \frac{100 \cdot \{[(V_d \cdot (SeCr1 - SeCr2)] + P\}}{1440 \cdot (\frac{(SeCr1 + SeCr2)}{2})}$$

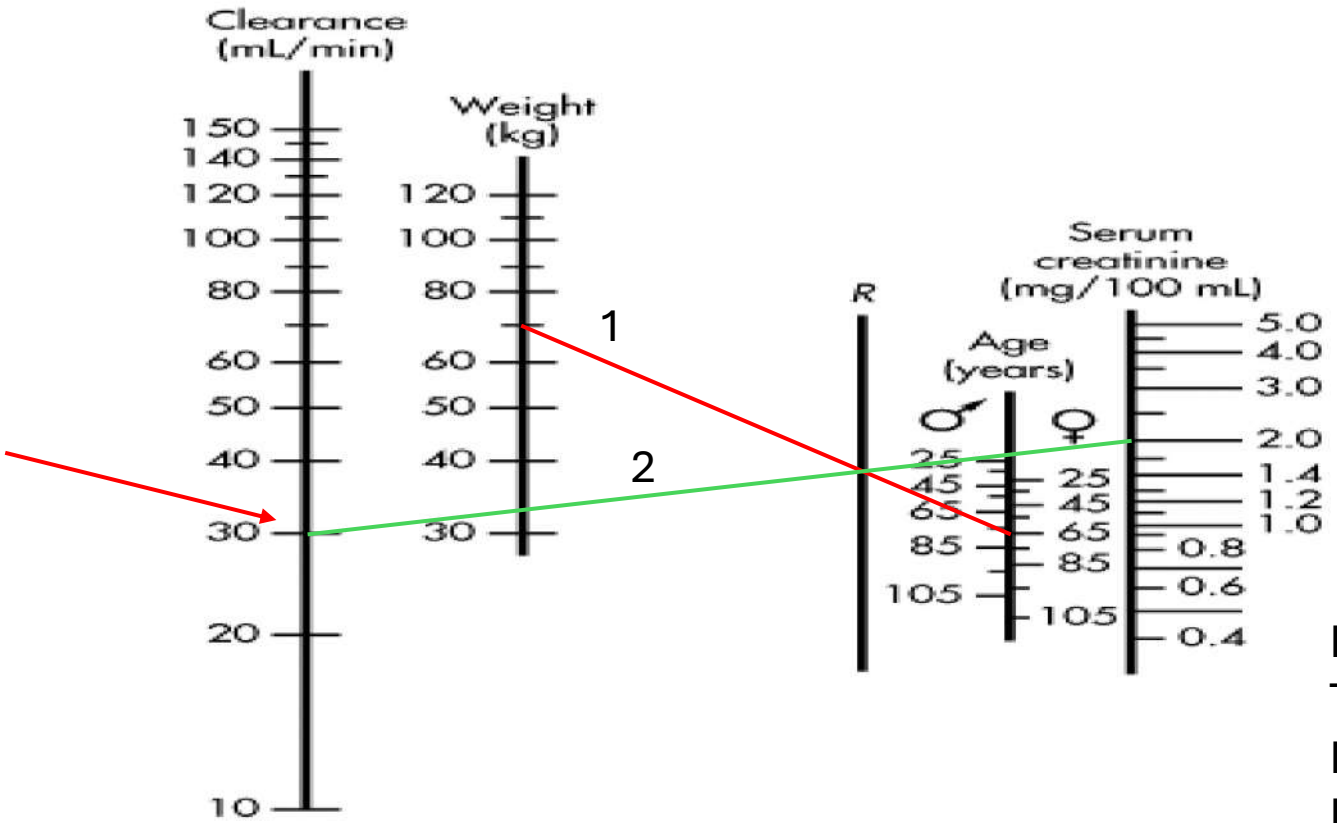
$$P = \left[29{,}305 - \left(0{,}203 \cdot \text{Életkor}\right)\right] \cdot [1{,}037 - (0{,}0338 \cdot \frac{(SeCr1 + SeCr2)}{2}) \cdot Sex$$

Sex: értéke 0,85, ha a beteg férfi; értéke 0,765, ha a beteg nő.

Egy kis időutazás: a Siersbæk-Nielsen nomogram

The nomogram method of *Siersback-Nielsen* et al (1971):

- estimates CrCl based on age, weight, and SCr conc.



Eredmény:
CrCL= 30 ml/min

Bemeneti adatok:
Testsúly
Nem
Életkor
Szérum kreatinin szint (mg/dl)

A Cockroft-Gault képlet (1976)

- A nomogram módszer alternatívájaként dolgozták ki (első számítógépek megjelentek!)
  - elsőként vizsgáltak nagyszámú beteget (n=534)
  - a kreatinin szint méréshez automatát használtak (N-11B autoanalizátor módszer, Technicon Instruments Corp.)
  - a betegek 96%-a férfi volt
  - a nőkre vonatkoztatott szorzó hipotetikus
- Elsősorban farmakokinetikai modellezés során használják → nem klinikai mutató, hanem matematikai tényező!

Cockroft DW, Gault MH. Nephron 1976;16:31-41.

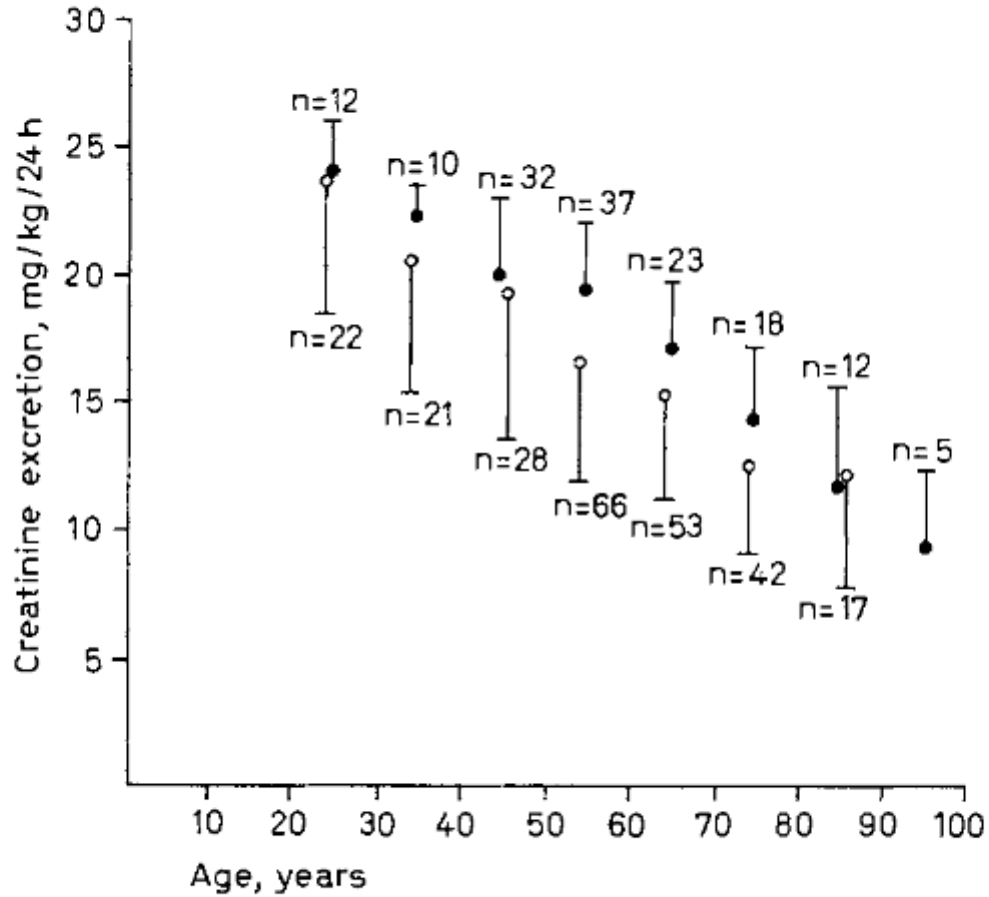


Fig. 1. Creatinine excretion. ● = SIERSBÆK-NIELSEN *et al.* [5], 149 males, age 20–99 years; ○ = present study, 249 males, age 18–92 years.

Table 1 Salient features of various methods that could be employed to measure GFR in ICU setup

Sl no	Methods	Merits	Demerits
1	CG formula	Easily computable	Highly inaccurate in the critical care setup. Considerable degree of GFR overestimation
2	4-variable MDRD	More accurate than CG. May offer value close to 6-variable MDRD in healthier patients with preserved BUN/Cr ratio	Dependency on creatinine. May not be accurate when BUN/Cr ratio is increased. Does not take into account blood urea nitrogen and albumin. Overestimation of GFR when baseline GFR is high
3	6-variable MDRD	BUN and serum albumin are taken into account. More accurate when BUN/CR ratio is increased. Better concordance correlation coefficient when compared with CG and 4-variable MDRD	Dependency on creatinine. Ongoing creatinine production and its fluid balance variations are not taken into account. Less accurate when compared with cystatin C and novel methods
4	CKD-EPI formula	Greater precision and reliability when compared with MDRD. More accurate when GFR >60 ml/min/1.73 m^2	Not validated extensively in hospitalized and sick individuals. Dependency on serum creatinine
5	24-h creatinine clearance	More accurate when compared to CG and MDRD formulae	Collection of urine is an issue. Cannot provide immediate results. Becomes a problem when rapid administration of drugs is essential
6	Jelliffe's equation	Ongoing creatinine production and fluctuations in creatinine concentration over time are taken into account	Does not take into account the variations in creatinine concentration with respect to fluid balance
7	Modified Jelliffe's equation	Fluid balance variations of creatinine are also taken into account	Still less accurate when compared with cystatin C and fiberoptic radiometric methods
8	Serum cystatin C	Less affected by non-renal factors. Sensitive to changes in so-called creatinine blind GFR(40–70 ml/min); preferred agent in liver disease patients	Expensive and unreliable in the presence of thyroid dysfunction, may be affected in patients taking high dose steroids with renal dysfunction
9	Aminoglycoside clearance	May serve as an easy method for GFR estimation in patients already on aminoglycosides. May be better than 24-h creatinine clearance	Giving aminoglycoside for renal function estimation alone may not be wise or practically possible
10	Fiberoptic ratiometric fluorescent analyzer method	Most accurate way of all. Rapid, inexpensive, reproducible, and safe method	Still experimental. Requirement of technical expertise. Scarce studies in humans

Sunder S et al. J Intensive Care 2014;2:31.

Sunder *et al. Journal of Intensive Care* 2014, **2**:31
http://www.jintensivecare.com/content/2/1/31

JOURNAL OF INTENSIVE CARE

REVIEW Open Access

Estimation of renal function in the intensive care unit: the covert concepts brought to light

Sham Sunder, Rajesh Jayaraman*, Himanshu Sekhar Mahapatra, Satyanand Sathi, Venkata Ramanan, Prabhu Kanchi, Anurag Gupta, Sunil Kumar Daksh and Pranit Ram

Conclusions

The concept of estimating renal function in critically ill patients had always remained elusive. The issue of ARC should be considered to avoid improper dosing of drugs. CG and 4-variable MDRD equations should better be avoided in ICU setup. Cystatin C, modified Jelliffe's, Jelliffe's, and 6-variable MDRD equations could be employed in that order to estimate renal function and to provide instant and accurate results. While aminoglycoside clearance could be used in patients in whom they are therapeutically used, optic ratiometric method provides the most accurate and instant estimation of renal function in critically ill patients, although large-scale studies in humans are required to validate it.

Akut vesekárosodás markerei

Table 1 KDIGO definition and classification of AKI [6]

Diagnostic criteria for AKI:

AKI is defined as any of the following:

- Increase in serum creatinine by ≥0.3 mg/dl (≥26.5 μmol/l) within 48 h; or
- Increase in serum creatinine to ≥1.5 times baseline, which is known or presumed to have occurred within the prior 7 days; or
- Urine volume <0.5 ml/kg/h for 6 h.

AKI staging system:

AKI stage	Serum creatinine criteria	Urine output criteria
AKI stage I	Increase of serum creatinine by ≥0.3 mg/dl (≥26.4 μmol/L) or increase to 1.5–1.9 times from baseline	Urine output <0.5 ml/kg/h for 6–12 h
AKI stage II	Increase of serum creatinine to 2.0–2.9 times from baseline	Urine output <0.5 ml/kg/h for ≥12 h
AKI stage III	Increase of serum creatinine ≥3.0 times from baseline or serum creatinine ≥4.0 mg/dl (≥354 μmol/L) or treatment with RRT or in patients <18 years, decrease in estimated GFR to <35 ml/min per 1.73 m^2	Urine output <0.3 ml/kg/h for ≥24 h or anuria for ≥12 h

AKI **acute kidney injury,** ***GFR*** **glomerular filtration rate,** ***KDIGO*** **Kidney Disease Improving Global Outcomes,** ***RRT*** **renal replacement therapy**

Ostermann M, Joannidis M. Crit Care 2016;20:299.

Table 2 Potential pitfalls of AKI diagnosis based on creatinine and urine criteria

Clinical scenario	Consequence
Administration of drugs which interfere with tubular secretion of creatinine (i.e. cimetidine, trimethoprim)	Misdiagnosis of AKI (rise in serum creatinine without change in renal function)
Reduced production of creatinine (i.e. muscle wasting, liver disease, sepsis)	Delayed or missed diagnosis of AKI
Ingestion of substances which lead to increased generation of creatinine independent of renal function (i.e. creatin, cooked meat)	Misdiagnosis of AKI
Obesity	Overdiagnosis of AKI if using actual weight when applying urine output criteria
Conditions associated with physiologically increased GFR (i.e. pregnancy)	Delayed diagnosis of AKI
Interference with analytical measurement of creatinine (i.e. 5-fluorocytosine, cefoxitin, bilirubin)	Misdiagnosis and delayed diagnosis of AKI (depending on the substance)
Fluid resuscitation and overload	Delayed diagnosis of AKI (dilution of serum creatinine concentration)
Progressive CKD with gradual rise in serum creatinine	Misdiagnosis of AKI
Extrinsic creatinine administration as a buffer in medications (i.e. in dexamethasone, azasetron)	Pseudo-AKI
Oliguria due to acute temporary release of ADH (i.e. post-operatively, nausea, pain) enhanced by maximal sodium reabsorption in the setting of volume/salt depletion	Misdiagnosis of AKI

ADH **anti-diuretic hormone,** ***AKI*** **acute kidney injury,** ***CKD*** **chronic kidney disease,** ***GFR*** **glomerular filtration rate**

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Table 3 New diagnostic biomarkers of AKI evaluated in human studies

AKI biomarker	Description	Handling by the kidney	Factors affecting biomarker levels
Alanine aminopeptidase (AAP) Alkaline phosphatase (ALP) γ-Glutamyl transpeptidase (γ-GT)	Enzymes located on the brush border villi of the proximal tubular cells	Released from tubular brush border after damage to proximal tubular cells	
Angiopoietin-1 Angiopoietin-2	57 kDa endothelial growth factor secreted by endothelial cells, including renal endothelial cells	Upregulated in glomerular disease and sepsis	Systemic inflammation Diabetes Malignancy
Calprotectin	Cytosolic calcium-binding complex of two proteins of the S100 group (S100A8/S100A9); derived from neutrophils and monocytes; activator of innate immune system	Detectable in urine following intrinsic AKI	Inflammatory bowel disease Urinary tract infection CKD
Chitinase 3-like protein 1	39 kDa soluble intracellular protein of glycoside hydrolase family 18 expressed by chrondrocytes, macrophages, endothelial cells, neutrophils, smooth muscle, and cancer cells;	Glomerular filtration of serum concentrations; in addition: some secretion by macrophages within the kidneys upon renal stress or damage	Inflammatory diseases Malignancy COPD Liver cirrhosis Connective tissue disease Cardiovascular disease
Cystatin C	13 kDa cysteine protease inhibitor produced by all nucleated human cells and released into the plasma at a constant rate	Freely filtered in glomeruli and completely absorbed and catabolized by proximal tubular cells; no tubular resorption or secretion	Systemic inflammation Malignancy Thyroid disorders Glucocorticoid disorder Cigarette smoking Hyperbilirubinaemia Hypertriglyceridaemia HIV disease

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α Glutathione S-transferase (α GST)	47–51 kDa cytoplasmic enzyme in proximal tubule	Released into urine following tubular injury	
π Glutathione S-transferase (π GST)	47–51 kDa cytoplasmic enzyme in distal tubules	Released into urine following tubular injury	
Hepatocyte growth factor (HGF)	Antifibrotic cytokine produced by mesenchymal cells and involved in tubular cell regeneration after AKI	Released into urine following tubular injury	Advanced heart failure Hypertension Bowel inflammation
Hepcidin	2.78 kDa peptide hormone predominantly produced in hepatocytes but also in kidney, brain, and heart; regulator of iron metabolism	Freely filtered followed by tubular uptake and catabolism	Systemic inflammation Iron overload
Insulin-like growth factor binding protein-7 (IGFBP-7), tissue metalloproteinase-2 (TIMP-2)	Metalloproteinases involved in cell cycle arrest	Released into urine after tubular cell stress	
Interleukin-18 (IL-18)	18 kDa pro-inflammatory cytokine	Released into urine by proximal tubular cells following tubular injury	Inflammation Sepsis Heart failure
Kidney Injury Molecule-1 (KIM-1)	Transmembrane glycoprotein produced by proximal tubular cells after ischaemic or nephrotoxic injury	Released into urine following ischaemic or nephrotoxic tubular damage	Renal cell carcinoma Chronic proteinuria CKD Sickle cell nephropathy

Liver-type fatty acid-binding protein (L-FABP)	14 kDa intracellular lipid chaperone produced in proximal tubular cells and hepatocytes	Freely filtered in glomeruli and reabsorbed in proximal tubular cells; increased urinary excretion after tubular cell damage	CKD Polycystic kidney disease Liver disease Sepsis
α_1 Microglobulin	Low molecular weight protein produced in liver	Freely filtered by glomeruli; reabsorbed and catabolised by proximal tubular cells; urinary excretion after tubular dysfunction	Sepsis
β_2 Microglobulin	12 kDa light chain of major histocompatibility class I expressed on cell surface of every nucleated cell	Freely filtered by glomeruli; reabsorbed and catabolised by proximal tubular cells; urinary excretion after tubular dysfunction	
MicroRNA	Endogenous single-stranded molecules of non-coding nucleotides	Upregulated following tubular injury and detectable in plasma and urine	Sepsis
Monocyte chemoattractant peptide-1 (MCP-1)	Peptide expressed in renal mesangial cells and podocytes	Released into urine	Variety of primary renal diseases
N-acetyl-β-D-glucosaminidase (NAG)	>130 kDa lysosomal enzyme; produced in proximal and distal tubular cells and non-renal cells	Too large to undergo glomerular filtration; released into urine after tubular damage	Diabetic nephropathy
Neutrophil gelatinase-associated lipocalin (NGAL)	At least three different types: • Monomeric 25 kDa glycoprotein produced by neutrophils and epithelial tissues, including renal tubular cells • Homodimeric 45 kDa protein produced by neutrophils • Heterodimeric 135 kDa protein produced by renal tubular cells	25 kDa and 45 kDa NGAL undergo glomerular filtration and reabsorption in healthy tubular cells 25 kDa and 135 kDa NGAL are released into urine following tubular damage	Sepsis Malignancy CKD Urinary tract infection Pancreatitis COPD Endometrial hyperplasia
Netrin-1	50–75 kDa laminin-related molecule, minimally expressed in proximal tubular epithelial cells of normal kidneys	Highly expressed in injured proximal tubules and released into urine	

Proenkephalin	Endogenous polypeptide hormone in adrenal medulla, nervous system, immune system and renal tissue	Cleared by glomerular filtration	Systemic inflammation Pain
Retinol binding protein (RBP)	21 kDa single-chain glycoprotein; synthesized by liver	Totally filtered by the glomeruli and reabsorbed but not secreted by proximal tubules; released into urine following tubular injury	Diabetes Obesity Acute critical illness
Soluble triggering receptor expressed on myeloid cells-1 (sTREM-1)	Member of the immunoglobulin superfamily of receptors expressed on granulocytes and monocytes, also possibly produced by endothelial cells and tubular epithelial cells	Detectable in urine following glomerular filtration and possibly local production	Sepsis Systemic inflammation

AKI **acute kidney injury,** ***CKD*** **chronic kidney disease,** ***COPD*** **chronic obstructive pulmonary disease,** ***GFR*** **glomerular filtration rate,** ***HIV*** **human immunodeficiency virus**

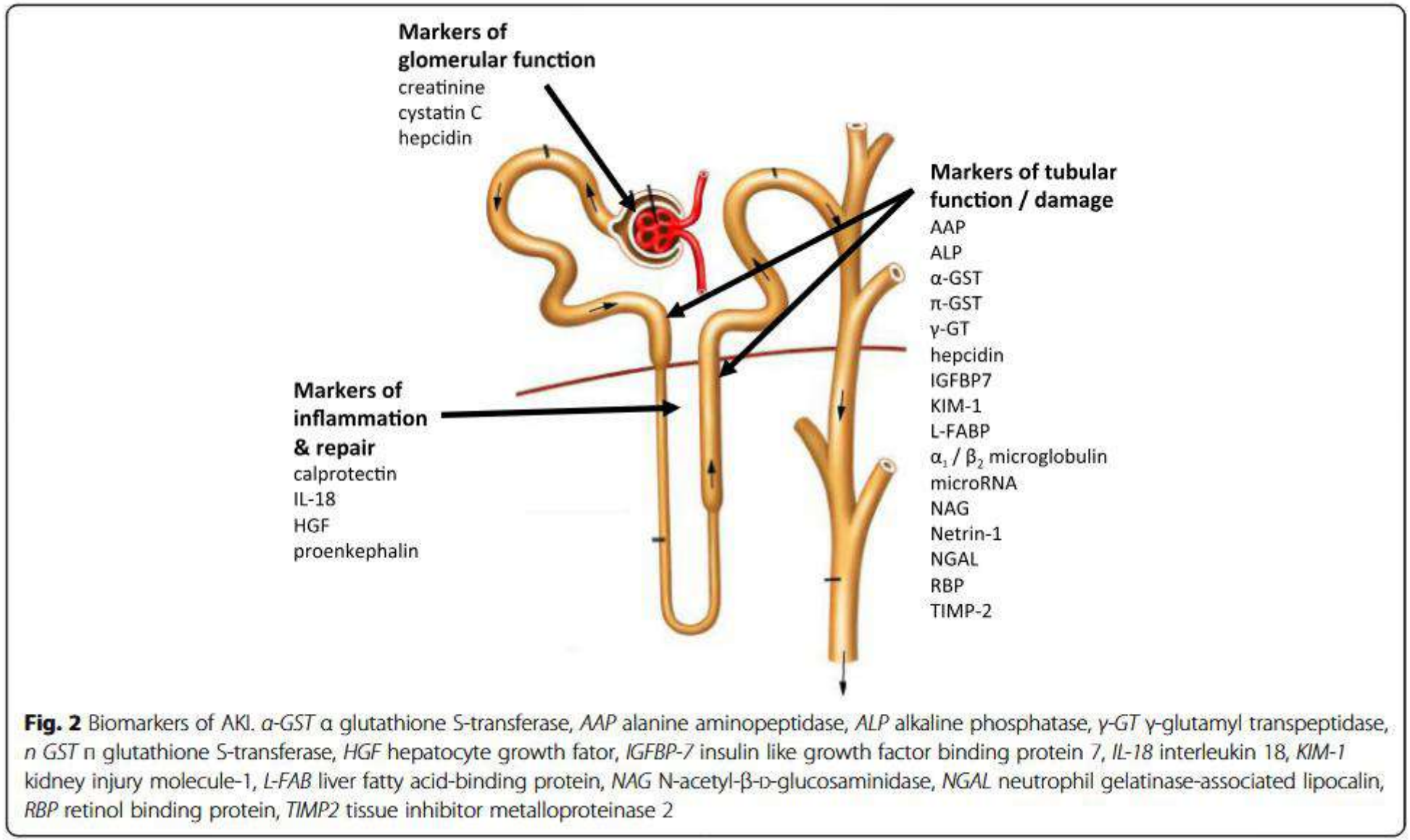

Fig. 2 Biomarkers of AKI. *α-GST* α glutathione S-transferase, *AAP* alanine aminopeptidase, *ALP* alkaline phosphatase, *γ-GT* γ-glutamyl transpeptidase, *π GST* π glutathione S-transferase, *HGF* hepatocyte growth fator, *IGFBP-7* insulin like growth factor binding protein 7, *IL-18* interleukin 18, *KIM-1* kidney injury molecule-1, *L-FAB* liver fatty acid-binding protein, *NAG* N-acetyl-β-D-glucosaminidase, *NGAL* neutrophil gelatinase-associated lipocalin, *RBP* retinol binding protein, *TIMP2* tissue inhibitor metalloproteinase 2

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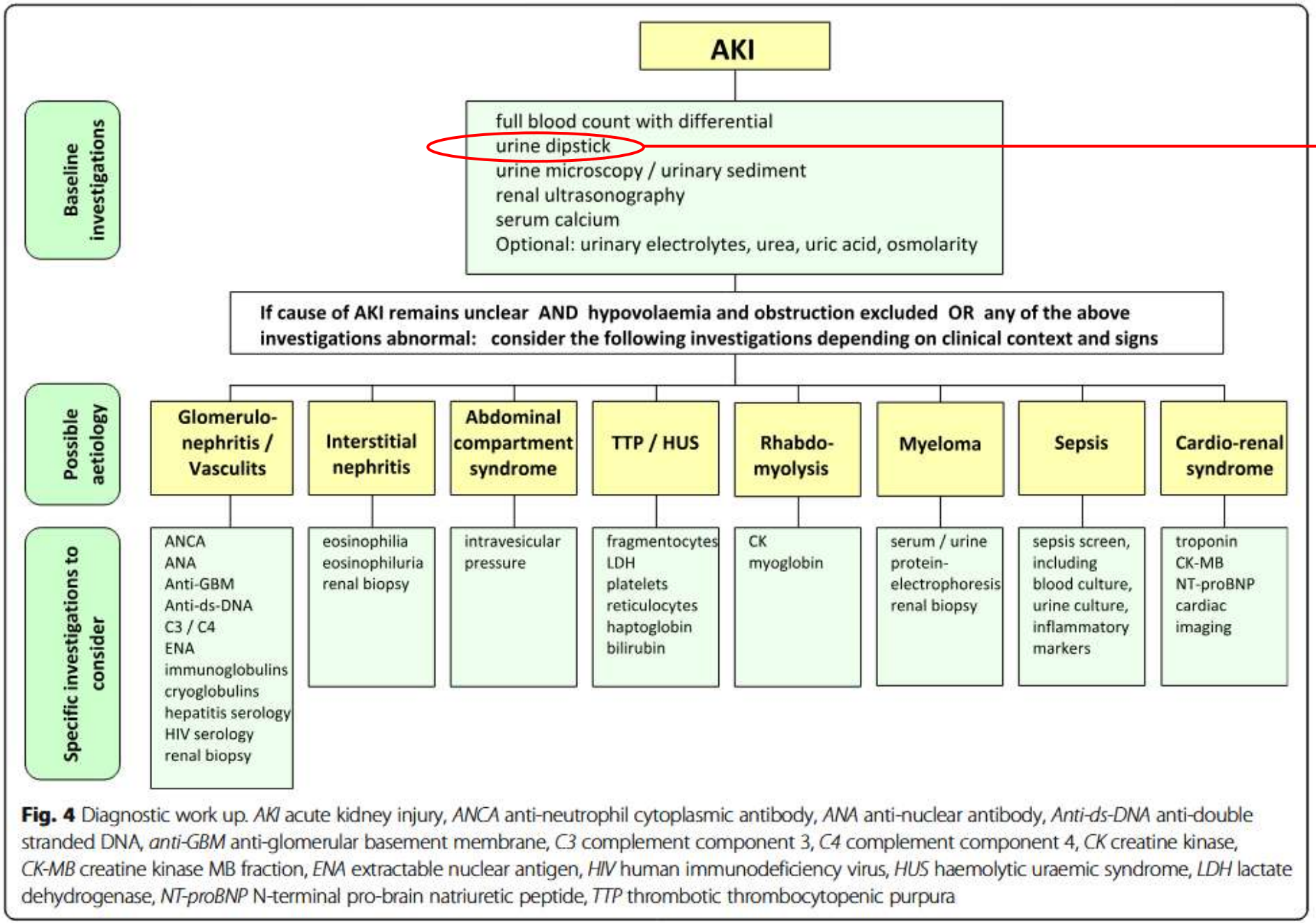

Fig. 4 Diagnostic work up. *AKI* acute kidney injury, *ANCA* anti-neutrophil cytoplasmic antibody, *ANA* anti-nuclear antibody, *Anti-ds-DNA* anti-double stranded DNA, *anti-GBM* anti-glomerular basement membrane, *C3* complement component 3, *C4* complement component 4, *CK* creatine kinase, *CK-MB* creatine kinase MB fraction, *ENA* extractable nuclear antigen, *HIV* human immunodeficiency virus, *HUS* haemolytic uraemic syndrome, *LDH* lactate dehydrogenase, *NT-proBNP* N-terminal pro-brain natriuretic peptide, *TTP* thrombotic thrombocytopenic purpura

Vér
Fehérje
FVS
Nitrit
Glukóz

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THANK GOD TODAY IS OVER