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Demystifying ethnic/sex differences in kidney function: Is the difference in (estimating) glomerular filtration rate or in serum creatinine concentration?

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ABSTRACT

Background: The recent evaluation of the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation for estimating the glomerular filtration rate (GFR) in multiple ethnicities has raised the question on how well this equation performs for African-American and Asian subjects. There is no doubt that serum creatinine (Scr) concentration differs between ethnicities and sexes. We show that creatinine-based equations for white populations may be inaccurate for estimating GFR in other ethnic/gender groups, especially in populations from Asia.
Methods: This study presents a mathematical analysis of the CKD-EPI-equation complemented with a literature review of median and reference values for IDMS-standardized Scr-concentrations for multiple ethnicities.
Results: The study shows that at equal eGFR-CKD-EPI-values, the ratio of Scr between females and males equals 0.79 and between other ethnicities/sexes and white males is constant too. From this information, it is possible to calculate mean Scr-values that correspond very well with literature values directly obtained from Scr-distributions in healthy white males and females and in black males, but the discrepancy is larger for other populations.
Conclusions: Our results confirm the criticism that has been raised for using the CKD-EPI-equation for these ethnicities. An alternative eGFR-model is proposed based on a population-normalized Scr that needs further validation.

1. Introduction

The evaluation of the Chronic Kidney Disease Epidemiology Collaboration equation for estimating the glomerular filtration rate in multiple ethnicities [1] resulted in small adaptations in the coefficients of the previously published two-level CKD-EPI equation. All equations are still of the mathematical form

$$eGFR = A'x(0.993)^{Age}x(Scr/\kappa)^{B'}$$

where A′ depends on sex and ethnicity, B' depends on sex and Scr-level and $\kappa = 0.7$ for females and 0.9 for males. According to Stevens [1], each ethnic population therefore has 4 equations, depending on sex and Scr-level. All GFR and eGFR values in this study are corrected for body surface area (BSA) and expressed in mL/min/1.73 m^2.

The ideal all-purpose GFR prediction equation probably does not exist, as GFR changes during life and the major determining factor in all eGFR-equations, serum creatinine, changes also during life, but in a completely different way (see Fig. 1). With particular reference to children, the normal level of GFR varies with age, and consequently with body size, and increases with maturation from infancy, approaching adult mean values at approximately 2 years of age. It remains constant during growth from child to adult and then gradually starts to decline with age, as part of the normal biological process of senescence. Serum creatinine, reflects the maternal serum creatinine level at birth, rapidly decreasing during the first month of life to about 0.25 mg/dL and then gradually increasing with age until adolescence, where further growth and development of muscle mass results in different constant values for men and women. Finally, at older ages, serum creatinine slightly goes up again.

It is now widely accepted that GFR in adults declines with age. Whether GFR depends on sex or race is not that clear. The most important physiological determinant of most common eGFR equations is Scr. When the GFR is considered at a fixed and equal Scr-concentration,

Abbreviations: CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; GFR, Glomerular Filtration Rate; Scr, serum creatinine; Scr_F, serum creatinine of females; Scr_M, serum creatinine males; WM, white males; BM, Black males; BF, Black females; AM, Asian males; AF, Asian females; HM, Hispanic males; HF, Hispanic females; IDMS, isotope dilution mass spectrometry; WF, white females; CKD, chronic kidney disease.

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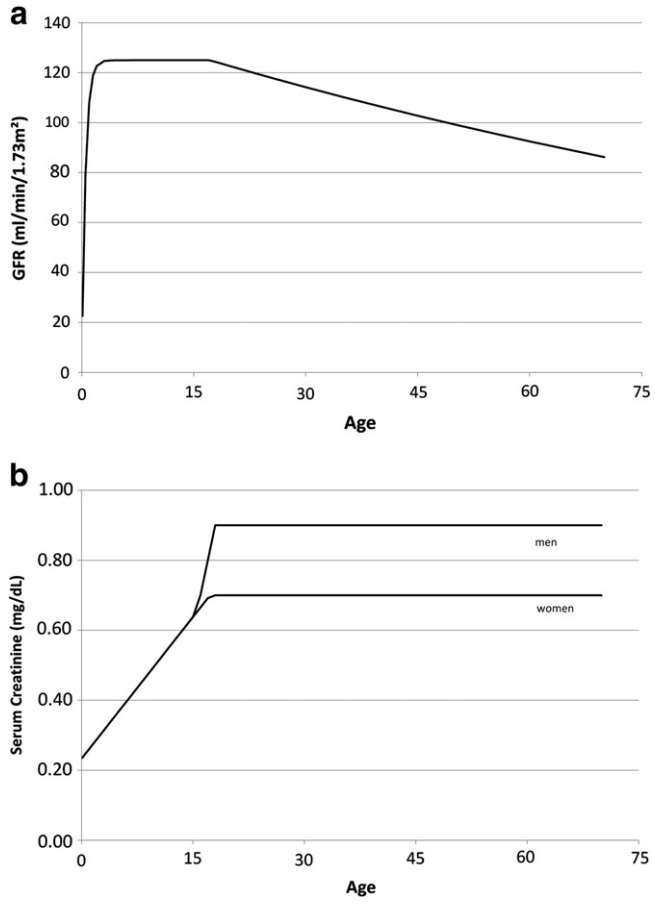

Fig. 1. Expected time-evolution of GFR (a) and serum creatinine concentration (b) in healthy Caucasians.

there will be differences between men and women and between races. However, when GFR is compared at equal physiological Scr-values, then the differences in GFR are not obvious. Equal physiological values are the median Scr-values for a specific healthy population (Q). It has been shown previously that Q = 0.70 mg/dL and Q = 0.90 mg/dL are the median Scr-levels for the healthy Caucasian female and male population respectively [2,3] and therefore these values are at equal physiological levels for healthy men and women. Note that Scr/0.90 and Scr/0.70 also appear in the CKD-EPI equation. Scr/Q equals '1' for the average healthy person of a specific population (as Scr = Q) and consequently Scr/Q has an intuitive appeal as it quantifies how far from expected is the individual Scr of a possibly impaired kidney function. Note also that Scr/Q is independent of gender. In other words, Scr/Q with Q = 0.90 mg/dL for white males and 0.70 mg/dL for white females becomes equal to '1' when the average healthy person of that population is considered. Moreover, it can be shown that Scr/Q varies between the same lower (±0.67) and upper reference values (±1.33) for healthy people, independent of sex and age [4].

The same reasoning can be applied for race. African-American men have higher Scr-values, on average, than Caucasian males, mainly because they have more muscle mass. The mean Scr for black males is Q = 1.03 mg/dL [3]. When comparing eGFR-CKD-EPI for white men with black men at 0.90 mg/dL and 1.03 mg/dL respectively, we find 123–124 mL/min/1.73 m^2 at the age of 18 years and 88–89 at the age of 65 years. This demonstrates that the effect of race is at the Scr-level, not at the GFR-level. As we believe that this is also true for other races, it makes sense to transform the CKD-EPI four-level equation into an equation that depends on Scr/Q, with Q the median Scr-level for a specific healthy population. We have previously shown how to do this and one global form of the CKD-EPI equation can be obtained, namely

$$eGFR = A(Scr/Q)^{B}C^{Age}$$

with A = 142,
B = −1.232 for Scr/Q≥1 (or −0.405, for Scr/Q<1) and
C = 0.993,

and with different values for Q, depending on race and sex [4]. Differences in GFR due to race and sex are limited when GFR is compared at equivalent Scr-levels. The dependency of Scr on race and sex and age, disappears when Scr is normalized with Q, where Q is a specific population-dependent constant corresponding with the median Scr-level of the healthy population.

To further strengthen our reasoning that GFR is independent of race and sex, we searched the literature for 'true' GFR data for different races and sexes but could not find direct GFR results that clearly demonstrate clinically significant differences between men and women or between races [5–8]. The CKD-EPI eGFR-equation predicts estimated GFR-values of 123 mL/min/1.73 m^2 for men at the age of 20 years and an average Scr-level of 0.90 mg/dL (average healthy man) and 125 mL/min/1.73 m^2 for women at the age of 20 and an average Scr-level of 0.70 mg/dL (average healthy woman). Normal eGFR-values have been published by van den Brand [9] and are clearly declining with age. Stevens [5] mentions normal values of *approximately* 130 mL/min/1.73 m^2 in young men and 120 mL/min/1.73 m^2 in young women. Poggio [7] mentions a statistically significant difference between men (106.1 mL/min/1.73 m^2) and women (108.7 mL/min/1.73 m^2) in potential living kidney donors, a difference that we do not consider clinically important (and in the opposite direction of the results mentioned by Stevens et al.). Poggio did not find an association between donor race and measured GFR [7]. Ma [8] found lower measured GFR values in apparently healthy young Chinese men (104 mL/min/1.73 m^2) and women (110.1 mL/min/1.73 m^2), compared with Western populations (reported values of 109–125 mL/min/1.73 m^2), but similar age-associated decreases. Ma suggested that this discrepancy might be caused by variations in dietary intake among racial groups living in distinct regions, differences in age and sex distributions in different studies, and, varying methods for GFR measurements. In conclusion, there is a clear lack of evidence of differences in GFR between sexes and races, but there is overall agreement on the GFR-decline with age. Therefore, we here assume equal GFR at physiologically equal Scr-levels and at the same age.

2. Results

2.1. The general form of the alternative CKD-EPI equation

We previously proposed to rewrite the CKD-EPI equation as

$$eGFR = Ax(Scr/Q)^{B}xC^{Age}.$$

The mathematical background on how to arrive at this equation and how to derive the constants is described in length in Pottel [4]. We here only give the final result

$$eGFR = 142x(0.993)^{Age}x(Scr/Q)^{-1.232} \quad \text{for } Scr/Q > 1$$

$$eGFR = 142x(0.993)^{Age}x(Scr/Q)^{-0.405} \quad \text{for } Scr/Q \leq 1.$$

The more general equation also proposes to switch from B-coefficient at Scr = Q, which is different for each population.

We further showed in Pottel [4] that our alternative CKD-EPI equation is very similar in form, but also in prediction results as the CKD-EPI equation, e.g. deviations between the original CKD-EPI equation