Nephron

Clinical Practice: Mini-Review

Nephron
DOI: 10.1159/000536243

Received: October 13, 2023
Accepted: December 23, 2023
Published online: January 12, 2024

Glomerular Filtration Rate Estimation in Adults: Myths and Promises

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Keywords
Creatinine · Glomerular filtration rate · Cystatin C

Abstract
Background: In daily practice, glomerular filtration rate (GFR) is estimated with equations including renal biomarkers. Among these biomarkers, serum creatinine remains the most used. However, there are many limitations with serum creatinine, which we will discuss in the current review. We will also discuss how creatinine-based equations have been developed and what we can expect from them in terms of performance to estimate GFR. ***Summary:*** Different creatinine-based equations have been proposed. We will show the advantages of the recent European Kidney Function Consortium equation. This equation can be used in children and adults. This equation can also be used with some flexibility in different populations. ***Key Messages:*** GFR is estimated by creatinine-based equations, but the most important for nephrologists is probably to know the limitations of these equations.

What Glomerular Filtration Rate Estimation Is (and What It Is Not)

In daily practice and since the seventies, glomerular filtration rate (GFR) is estimated by equations where the main important variable is a renal biomarker [1]. In 2024, spanning nearly one century [2–5], serum creatinine remains the most commonly used biomarker in daily practice. The problems of serum creatinine as the biomarker of choice to estimate GFR are numerous and of different nature [6, 7]. First, we can describe a sort of "mathematical" problem which is due to the inverse relationship between serum creatinine and GFR (the association is thus not linear but hyperbolic). Indeed, the same change in serum creatinine will correspond to a large change in GFR at high GFR levels but to a very limited change of GFR in the low GFR range [8]. Second, there are "analytical" considerations to be made. Measuring serum creatinine in the plasma is easy and cheap, but it must be reminded that standardization of the assays to measure serum creatinine is crucial to produce comparable results between laboratories [9, 10]. The impact of a lack of standardization of estimated GFR (eGFR) is far from negligible [11, 12]. Also, there are still some possible

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interferences in the measurement [6]. Third, there are also "physiological" considerations. Indeed, serum creatinine concentration is not only dependent on GFR but can be influenced by other variables. It must be emphasized that serum creatinine is the catabolite of creatine, a muscular protein. It is thus not unexpected that serum creatinine concentration is influenced by muscle mass [13–15]. At the same creatinine concentration, the GFR in a bodybuilder or a patient with sarcopenia will be tremendously different. This example is however extreme. The role of muscular mass on serum creatinine is also important to explain that for the same level of GFR, serum creatinine will be different according to age, sex, weight, and (even if this is largely debated) race. Therefore, it is not a coincidence that these simple variables are included in most eGFR equations [16, 17]. At this point, it is of importance to keep in mind how GFR and serum creatinine are influenced by these variables, and the easiest way to illustrate this point is to consider healthy people. When indexed by body surface area (even if this indexation can also be considered as a myth [18]), GFR is obviously not different in men and women [19]. GFR seems also not different between American, European, and African populations (some data suggest that GFR could be slightly lower in Asian, but these data are limited) [20–22]. According to age, it is well known that after a maturation time of ~2 years during which GFR is increasing after birth [23], body surface area-indexed GFR becomes and remains constant in healthy people from 2 years to ~40 years [24, 25]. At this age, renal senescence is starting, and GFR is continuously decreasing by ~ 0.5–0.8 mL/min/1.73 m^2/year [26]. But how is serum creatinine affected by these same variables? The most obvious difference is between men and women. In healthy adult populations, serum creatinine is around 0.7 mg/dL in women and around 0.9–1.0 mg/dL in men, which is a big difference [27, 28]. This difference is usually explained by the difference in muscular mass between men and women [15, 29, 30]. Serum creatinine is also affected in a totally different way by age than GFR: serum creatinine linearly increases during childhood, not different in girls and boys until puberty, but with an acceleration in adolescent males compared to females, ending in a plateau value at around 25 years [28, 31, 32]. With further aging, serum creatinine is relatively stable, whereas GFR is decreasing from 40 years on [28]. Differences due to age and sex between GFR and serum creatinine are mostly explained by the muscular mass hypothesis: serum creatinine is increasing during childhood and puberty because of growing and muscular mass gain, and after 25 years, serum creatinine is stable because the decrease in GFR from age 40 is, at least partially, compensated by a decrease in muscular mass with aging [33–35]. The impact of "race" on serum creatinine is still more complex and the subject of an ongoing debate [36]. A semantic remark should be made first. Race is a word that can only be accepted in its societal meaning. Indeed, it is obvious that race has no biological meaning. The word "race" is used without restriction in the USA with this societal meaning, whereas, in Europe, the societal aspect is less charged, and, as a consequence, using the word "race" is considered as racism in itself [37]. Beyond this semantic difference between the USA and Europe, we really think that serum creatinine is not different between races in its societal meaning but between populations (see Table 1, median serum creatinine is the same in Black and White US healthy women). Here, the word "population" is vague on purpose and certainly not limited to race. Indeed, keeping the same strategy of focusing on healthy populations, the "normal" serum creatinine concentration is easy to determine in different populations, and some conclusions are simple and straightforward (Table 1). First, there are some differences, but these differences are particularly more relevant in men than in women. Indeed, the median normal serum creatinine is varying between 0.70 and 0.74 mg/dL (a difference of maximum 0.04 mg/dL) in Black and White women in Europe, the USA, or Africa, whereas the variation for men in the same populations will be between 0.90 and 1.03 mg/dL (a difference reaching 0.13 mg/dL, eventually close to the difference of 0.20 mg/dL observed between men and women) [38–40]. Keeping in mind that GFR is not different between men and women and between populations, this observation leads to three important conclusions: first, race, in its societal meaning, is not the explanation of the difference in serum creatinine concentration because otherwise the difference should be the same in men and women. It is also remarkable that, in men, the difference in normal serum creatinine is as large between White Europeans (0.90 mg/dL) and Black Africans (0.96 mg/dL) than between Black Africans and Black Europeans (1.02 mg/dL) or even Black US people (1.00 mg/dL). Once again, the assertion that race or ethnicity (or still worse skin color) is influencing serum creatinine is a scientific "oversimplification." Second, there are still variations in serum creatinine between populations, and ignoring these differences in eGFR equations can only lead to bias [38, 41, 42]. Third, if a correction should be applied to creatinine-based equations, it should definitively be at the creatinine level, not at the GFR level [43, 44]. If we have demonstrated that there are differences in serum creatinine concentration between populations, two unresolved issues remain. The first question is physiological: why do we observe such differences in serum creatinine between populations? The easy answer would be to evoke the differences in muscular mass, but this assumption is supported

Table 1. Q values determined in different adult populations

	Q value in women	Q value in men	Origin	Reference
White European	0.70	0.90	Big data from laboratories in Sweden and Belgium	[27, 28]
Black European	0.74	1.02	Living kidney donors in Paris	[38]
Black Africans (Central Africa)	0.72	0.96	Healthy people in Congo	[39]
White US population-specific	0.73	0.93	Big data from laboratories from University of Washington Medicine System	[51]
Black US population-specific	0.73	1.00	Big data from laboratories from University of Washington Medicine System	[51]
White US population-specific	0.70	0.94	National Health and Nutrition Examination Survey	[41]
Black US population-specific	0.72	1.03	National Health and Nutrition Examination Survey	[41]
US race-free	0.73	0.97	Big data from laboratories from University of Washington Medicine System	[51]
China	0.62	0.88	27,830 healthy people	[40]

All results are expressed in mg/dL. Q values correspond to the median serum creatinine value observed either in extensive, general, and sex-specific data from laboratories or in more limited but phenotypically healthy well-defined groups. These Q values are only applicable to adult populations. Specific Q values according to age are required for populations younger than 18 years.

by poor evidence in the USA [36, 42] (data are stronger in Europe [45, 46]). We must admit in 2024 that we don't know why such differences are observed. One could also evoke the difference of diet (notably the difference in meat consumption which is known to influence serum creatinine [47–50]), but this hypothesis is also purely speculative. The second question is about the definition of a "population." It would be very questionable to define a population only based on race or skin color. What about mixed populations? What about minorities with well-known different muscular mass and different serum creatinine concentration like transgender people? If a bias is unavoidable, is it possible to limit it? We will try to answer these important questions in the second part of the article.

We have largely commented on the problems with serum creatinine as a renal biomarker due to non-GFR determinants and the impact of diet [47–50]. However, there is one other important limitation we want to briefly comment on. Creatinine is secreted by the renal tubules, and this secretion tends to increase when GFR decreases, meaning that the relationship between GFR and serum creatinine is not the same in healthy and chronic kidney disease (CKD) populations [52–54], which is reflected by a different power coefficient (exponent) for creatinine according to creatinine level in the most recently published creatinine-based equations (namely, the equations from the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) [16, 55] and from the European Kidney Function Consortium (EKFC)).

With all these problems in mind, it could seem like a miracle that serum creatinine is still used to estimate GFR. It is a truism, but it remains important to keep in mind that an eGFR is an estimation.

An Estimation for Populations

What fundamentally constitutes an eGFR equation? This is a mathematical relationship obtained from a, ideally, large and representative population (in terms of age, sex, and GFR range) between measured GFR (mGFR) as the dependent variable and serum creatinine with other variables (as age, sex, etc.) as independent variables. The result of the analysis integrating these different variables will be an estimated result for the mGFR. In an ideal world, the mathematical expression will be able to estimate GFR in the population used for its development without any significant bias. This last metric (bias, defined as the mean or median difference between eGFR and mGFR) is by nature a metric useful to assess the performance of an equation at the

population level [56]. Most recent equations can reach this goal with the absence of significant bias in populations. This was, for example, the case for the CKD-EPI$_{2009}$ equation (at least for ages >30 years) [55]. The CKD-EPI$_{2021}$ equation specifically developed to be used without the variable race in the USA presents a bias both in Black and non-Black populations on purpose (the goal of this equation being that the absolute bias is equal between the two populations) [17]. Bias is once again a metric of particular importance at the population level. In the seminal article of the CKD-EPI$_{2021}$ equation, the bias in White populations moves from 0.5 to 3.9 mL/min/1.73 m^2 (the new equation overestimating mGFR) [17]. In a European epidemiological study, moving from the CKD-EPI$_{2009}$ to CKD-EPI$_{2021}$ has a tremendous impact with a decrease of 25% in the CKD prevalence (defined as eGFR<60 mL/min/1.73 m^2) [57]. The new EKFC equation has the great advantage to have a constant and minimal bias for the whole age range (from 2 years to old ages), with one unique equation [16]. At the population level, the challenge is not to develop an equation with a zero bias, but to have a population large and representative enough to be applicable in all other cohorts (= in external validation studies). Here, also, one can find some advantages for the EKFC equation which is not exclusively based on regression analyses but also considers the physiological change with age of both mGFR and the biomarker.

Caution for Individuals

Although the notion of bias is so important in epidemiological studies, most nephrologists are taking care of individuals, not populations. At the individual level, bias is not without interest, but it is not the main metrics of interest. Indeed, considering a well-known bias of 3 mL/min/1.73 m^2, it means that the result of the equation at 60 mL/min/1.73 m^2 could correspond to a mGFR value between 57 and of 63 mL/min/1.73 m^2, which could be considered as clinically negligible. But unfortunately, bias is only one part of the total error associated with estimating equations. Beyond the systematic error (= the bias), there is also the random error or imprecision. The imprecision is the illustration of the true performance of an equation. Mathematically speaking, imprecision can be estimated as the standard deviation (or interquartile range) representing the spread of the results around the bias [56]. It is (relatively) easy to obtain a bias close to zero when developing an equation; however, reaching zero imprecision is extremely difficult. All the limitations we have described about serum creatinine will necessarily impact on the precision of all serum creatinine-based equations. More importantly, mGFR has its own imprecision, affecting the imprecision of every equation developed to estimate GFR. In the same subject, mGFR, like any other biological variable, has also its own biological variability. For mGFR, this variability is between 5 and 10%, which, in other words, means that, in the same subject, a difference of mGFR of more than 10% must be reached to be considered as a significant difference [58–60]. We could also evoke the different markers and methodologies used to measure GFR which can also impact the precision of eGFR equations [61]. Accordingly, the fact that the CKD-EPI equation has been developed with iothalamate urinary clearance in the USA, whereas the EKFC equation has been mostly developed from iohexol plasma clearance in Europe could explain, at least in part, some discrepancies in the performance of these equations when they are studied in the USA or in Europe. Considering these observations with mGFR, it seems unrealistic to expect from an eGFR equation to be able to estimate mGFR with a precision of 10%. Most researchers in the field of eGFR accept to consider as a goal an accuracy within 30%. The accuracy within 30% is a parameter only used in the field of GFR. This metrics is a bit arbitrary and not free from criticism [62]. Accuracy is influenced both by bias and precision. Accuracy within 30% is the percentage of eGFR results within 30% of results obtained with mGFR. Once again, the value of 30% is used a bit arbitrary, but better goals (notably accuracy within 10%) seem illusionary because it is more or less corresponding to the variability of mGFR. As clinicians, we must be aware of the real meaning of the imprecision (and inaccuracy) of creatinine-based equations at the individual level. The traditional goal for an equation is to reach an accuracy within 30% of 90%. This goal is however not even attained by the best creatinine-based equations. The best results are more between 80 and 85% (result being better in high GFR ranges) [16, 17]. This means that 10–15% of an eGFR will be beyond 30% of mGFR. This also means that we are considering as acceptable an eGFR giving a result between plus or minus 30% of mGFR. To give simple examples, an equation is considered as "acceptable" if the estimated result is between 70 and 130 mL/min/1.73 m^2 for a mGFR of 100 mL/min/1.73 m^2 or between 21 and 39 mL/min/1.73 m^2 for a mGFR of 30 mL/min/1.73 m^2. We are really far from the values of 3 or 5 mL/min/1.73 m^2 considered if we would erroneously focus on the bias only!

The Best Equation? The Most Flexible

We have already underlined the strengths of the recent EKFC creatinine-based equation: the same equation can be used in children, adolescents, and adults with a perfect continuity during transition from pediatrics to adult nephrology care, and the EKFC equation has the same

mathematical form when other renal biomarkers are considered (like cystatin C) [16, 63]. However, in our opinion, one of the most important strengths of the EKFC equation is the flexibility of the Q value, which is the median normal serum creatinine concentration in a given population [28, 43]. This flexibility in Q value has the potential to make the equation unbiased for specific populations. Up to now, Q values have been developed and proposed for White Europeans [16], Black Europeans [38], Black Africans [39], White US [41, 51], Black US [41, 51], and Chinese populations [40], making the EKFC equation applicable in these different populations (Table 1). In mixed population groups, a specific mixed Q value can be easily developed. In the USA, when societal considerations restrict the use of the race variable, a completely race-free Q value can be applied [64]. In some specific populations, like transgender populations, one can easily imagine applying the EKFC equation with specific Q values, which are actually available in the literature [65, 66]. As already said, we proposed to develop Q values specific to populations. But the term "population" can be very flexible: it can reflect a continent or a country, a specific social group, a minority or, at the opposite, a mixed population group [64]. A Q value can also be easily developed by each laboratory and then applied by this laboratory, assuming that this locally derived Q value will be adapted to the population served by the laboratory. One disadvantage of this sort of geographically derived Q value is when patients will move, for example, from one continent to another one. However, here also, the impact at the individual level should not be exaggerated. As an example, each change in Q value of 0.01 (for a male person with Q of 0.90 mg/dL), a corresponding change in eGFR of 0.75 mL/min/1.73 m^2 is expected (around the threshold of 60 mL/min/1.73 m^2). Changing from one Q value to another one for an individual will thus have minimal consequences in comparison to the error associated with the estimation itself (within 30%).

Cystatin C as a Conclusion

In the current opinion paper, we have focused on creatinine-based equations because they remain the most used equations in clinical practice. We tried to show that if these equations are very relevant at the population level and/or in epidemiological studies, their performances are more questionable at the individual level. To end this article, we will briefly comment on the new renal biomarker, cystatin C. This biomarker has several advantages compared to creatinine: its concentration is not influenced by race, and much less influenced by sex (a race- and sex-free cystatin C-based EKFC equation has been recently proposed with a minimal loss of performance) [63]. This makes the equations based on this biomarker interesting in mixed populations and in some specific groups. Cystatin C is also better associated with cardiovascular outcomes and mortality than serum creatinine. It is beyond the scope of the present review to discuss the mechanisms by which cystatin C has this better prediction and/or how to manage patients with discrepant results between creatinine and cystatin C, but several explanations have been advanced in the literature like the shrunken pore syndrome [67]. However, *sensu stricto*, and in the context of eGFR, cystatin C is not better than creatinine to estimate GFR, as the cystatin C-based equations are not performing better than creatinine-based equations [17, 63]. *Ad absurdum*, this absence of any added value for cystatin C to estimate GFR is the proof that non-GFR biomarkers are also influencing cystatin C concentrations. Having said that, this observation in general populations or general CKD cohorts does not mean that cystatin C could not be effectively better than creatinine in very specific populations (like populations with very abnormal muscular mass). Furthermore, the majority of studies indicate that equations incorporating both biomarkers indeed provide added value in terms of performance to estimate GFR [17, 63]. Today, there are still some limitations to the implementation of cystatin C (notably the fact that some assays are not well standardized), and the most important limitation is certainly the cost and overall availability of the assays. The cost for cystatin C remains abnormally high, for example, compared to other turbidimetric assays like C-reactive protein. One can imagine (and hope) that current costs for cystatin C will decrease in the future when this biomarker will be more widely used [68]. The question of the cost of such a biomarker is crucial, notably, but not only, in countries which are financially less advantaged.

Conflict of Interest Statement

Pierre Delanaye and Etienne Cavalier are consultants for Nephrolyx.

Funding Sources

This study was not supported by any sponsor or funder.

Author Contributions

Pierre Delanaye wrote the first draft. Etienne Cavalier, Thomas Stehlé, and Hans Pottel reviewed it critically for important intellectual content and approved the final version to be published.

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