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Editorial Comment

EDITORIAL COMMENT

A step forward for estimating GFR in young adults

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INTRODUCTION

Glomerular filtration rate (GFR) normalized to a standard body surface area of 1.73 m^2 remains essential for assessing kidney function [1]. For a long time, serum creatinine was the only endogenous biomarker to estimate GFR, which was flawed and had numerous problems; for instance, muscle mass may be indirectly accelerated during puberty in boys, diet, differences in tubular handling, and methodological problems. The problems with various methodologies for its measurement were ameliorated with the calibration of creatinine against isotope dilution mass spectrometry (IDMS). This happened in the early 2000s and resulted in much activity to update the formulae for estimating GFR. In the pediatric age range, with constantly changing body size, creatinine is indexed to height [1]. Age is the most important factor in adults due to the natural attrition of nephrons with time [2]. Young adults have been understudied. Growing evidence shows that it is better to continue using pediatric concepts for young adults ages 25 [3], 30 [4], or even 40 [5]. There is currently no consensus on which approach is best for young adults.

The best approach for estimating GFR in adults and pediatrics is a combination of cystatin C and creatinine; however, cystatin C availability is limited. Therefore, creatinine-only formulae remain the mainstay for estimating GFR.

The study 'Estimating glomerular function in young people' by Pierre Delanaye *et al.*

In this volume of *Clinical Kidney Journal*, Pierre Delanaye *et al.* [6] published a study of 2366 young adults aged 18–25 in whom reference (such as inulin, ^{51}chromium ethylenediamine tetraacetic acid, iohexol, and others) methods clearance studies with simultaneous determination of IDMS traceable creatinine were performed. The authors tested three commonly used formulae: the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) [7], the Lund-Malmö Revised (LMR) [8], and the European Kidney Function Consortium (EKFC) equations [9]. They found that the diagnostic performance of CKD-EPI was inferior to the LMR and EKFC equations. The study's strengths include the fact that different regions of the world were included, such as the CKD-EPI approach, although Africa and Asia were missing. The European cohort comprised 1892, and the US cohort included 474 participants.

Interestingly, they found that LMR and EKFC performed better than CKD-EPI in the non-black US population, and bias was similar for the Black population. In contrast, LMR and EKFC performed better throughout the European population. The group of Black participants was underpowered. CKD-EPI systematically overestimated measured GFR (mGFR). These findings were confirmed in subgroup populations, except for patients with a high GFR in whom CKD-EPI had a lower bias. In the European cohort, creatinine was directly measured with an IDMS traceable assay, whereas serum creatinine results were mostly indirectly recalibrated in US cohorts. The authors used only the race-free versions. Another strength was the analysis of body mass index. They also performed an analysis by sex, which upheld the observed difference. Figure 1 in the paper by Delanaye *et al.* also adds value as it shows that the agreement between the three formulae improves as patients approach age 30, in keeping with recent literature suggesting that people under 30 are not well served with CKD-EPI.

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The study groups had significantly different mGFRs [mean 89.5 ml/min/1.73 m^2 in the European and 61.5 ml/min/1.73 m^2 in the US cohort ($P < .0001$, unpaired *t*-test with Welch's correction)] and differed in the number of participants. It is essential to acknowledge that because each formula performs best in the range where the data were generated [1]. In addition, different exogenous markers used for the different equations may also affect differences in performance due to many factors such as plasma protein binding [1]. [1] Overall, the mGFR in the CKD-EPI study, which was based on 8254 measurements, was 67.6 ± 39.6 ml/min/1.73 m^2 [7]. The LMR study included only 37 participants between 18 and 29 years. The mGFR in the LMR study had a median of 55 ml/min/1.73 m^2 [8]. For the EKFC study, which was based on 972 participants aged 18–40, the mGFR of the development cohort was 76.9 ± 33.1 ml/min/1.73 m^2, closer to the overall cohort in this study [9]. It is, therefore, not surprising that this formula performed well.

The authors state that the EKFC formula has been recognized as 'validated' in the most recent KDIGO guidelines and advocate for using that formula rather than the CKD-EPI formula for young adults [6]. Indeed, the median bias of 2.28 ml/min/1.73 m^2 for the Europeans, 0.37 ml/min/1.73 m^2 for the US non-Black, and -0.78 ml/min/1.73 m^2 for Black Americans is convincing. However, within 30%, only 84.4% for Europe and 79.3 for the USA means that between 15.6% and 20.7% of values are not even within 30%. Substantial work remains to be done to reduce the variability, but the results are in keeping with the consensus of what is acceptable in GFR estimation.

Where do we go from here?

While the approach proposed by Delanaye *et al*. forms a step forward and does suggest that switching from CKD-EPI to the EKFC formula improves GFR estimation, we need precision medicine. Identifying patients who have abnormal GFR is especially important. As the authors state, adding cystatin C may help improve performance. Our group found that combining the modified Schwartz formula for creatinine and the Filler formula for cystatin C has a higher accuracy than the CKD-EPI formula and the Pierce U25 formula based on cystatin C and creatinine combined [2]. There is strong evidence that combining different eGFR biomarkers improves accuracy [1]. Cystatin C would be the second most widely available biomarker, although globally, the availability needs to be better. Other GFR biomarkers, such as beta-2-microglobulin and beta-trace protein, may offer improved performance in females, but their availability is very limited [1]. We also need race-free equations because race is a social construct, not a biological variable. For precision medicine, we must think outside the box and evaluate all aspects, even the so-called gold-standard GFR. As shown in the latest version of our Assessment of Kidney function in children, adolescents, and young adults, the 'gold-standard method' is often not gold-standard [1]. Two compartmental, non-linear models must be used to measure GFR within sufficient time for the equilibration between the intravascular and extravascular compartments for the exogenous GFR marker. Two-point measurements with Brøchner Mortenson correction and without a scan of the injection site for extravasation are inaccurate. Most Canadian centers do not utilize three-point measurement.

Furthermore, we need to move past single-center studies, as the authors of this paper did. Ideally, all continents should be included, and various gold-standard methods should be included to develop accurate eGFR formulae. We also need additional biomarkers.

Even without new biomarkers, we need to tackle several questions. First, there needs to be clarification if we can use the actual weight of a patient when we normalize the mGFR to the body surface area. The kidneys clear the extracellular volume of fluid and not the fat mass [1]. We have recently shown that the scatter of the mGFR versus the biomarker-derived eGFR can be reduced substantially if the ideal body weight is used and not the absolute body weight [10]. Using the actual body weight leads to underestimation in obese and overestimation of the mGFR in thin individuals [10]. A body mass index z-score of +4 may be as much as 20 ml/min/1.73 m^2 underestimation of the GFR [10]. Using ideal rather than actual weight to normalize the body surface area can substantially reduce the scatter in the GFR range >75 ml/min/1.73 m^2 [2]. This approach should be carefully tested and, potentially, all mGFRs should be recalculated for the formula generation. Moreover, we must overcome some limitations in large individuals because the formulae for the body surface area, such as the Dubois and Dubois or Mosteller formulae, are outdated [1]. Because of the acceleration of height occurring mainly in the legs, which comprise a large proportion of the body surface area, we may be substantially underestimating the body surface area [1]. We urgently need new ways to estimate body surface area in large and tall individuals. Ideally, we also need formulae across the entire age spectrum to avoid implausible improvements of GFR on transition from pediatrics to adult medicine, as we witnessed when switching from the pediatric U25 formula to CKD-EPI [2].

The finding that hyperfiltration patients may work with CKD-EPI is interesting. It is well known that creatinine has significant limitations in patients with a high mGFR [1]. This subgroup requires further study. However, we must find a way to monitor the GFR of patients with kidney disease longitudinally and across the entire spectrum of mGFR. The implausible increase of GFR when switching from pediatric to adult formula forms a problem [2]. The EKFC and LMR equations are used throughout all age ranges and therefore warrant further investigation into whether these equations may lessen the sudden increase in eGFR when that occurs during the transition to adult-focused care. Also, the definition of impaired GFR in a pediatric patient is <90 ml/min/1.73 m^2, whereas it is 60 ml/min/1.73 m^2 in an adult. It is implausible to assume that a GFR of 75 ml/min/1.73 m^2 in a 25 year-old is normal.

SUMMARY

Despite the need for more work to establish accurate precision medicine eGFR tools, we congratulate Delanaye *et al*. for collating this large cohort study from two continents and analyzing which currently available formulae are best for estimating young adults. Implementing their suggestion will lead to a more accurate estimation of GFR in young adults. The impact of switching from pediatric to adult formula is yet to be evaluated.

CONFLICT OF INTEREST STATEMENT

None declared.

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