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EDITORIAL COMMENTARY

Still trouble with serum creatinine measurements

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Introduction

Utilizing serum creatinine to calculate the estimated glomerular filtration rate (eGFR) is a vital tool in classifying chronic kidney disease (CKD) stages and demands correct measurement. The study in this issue of *Pediatric Nephrology*, titled "Large Inter-assay Difference of Serum Creatinine in the Pediatric Population: a Threat to Accurate Staging of Chronic Kidney Disease," addresses an important concern regarding limitations of precise creatinine measurement in a pediatric sample from Beaumont Health, Royal Oak, MI, USA. In pediatric populations, there are multiple factors which contribute to lower serum creatinine levels, including lower muscle mass overall and increased levels of non-creatinine chromogens, such as bilirubin [1]. Calibration procedures, which are traceable to isotope dilution mass spectroscopy (IDMS), allow standardization of serum creatinine levels [2]. The creation of reference materials is valuable and efforts to create standardized tools should be applauded. Unfortunately, there remains a paucity of reference materials that incorporate the much lower creatinine concentrations commonly seen in children.

The study by Lao et al.

In this context, we are delighted to see the study by Lao et al. in this issue [3]. The authors of this study address the lack of reference materials for creatinine measurements near the lower detection limit. Kriselle Lao and her research team impressively identified an increase in creatinine and eGFR results in pediatric patients following an instrumentation change between the Siemens Jaffe to Abbott Jaffe assay in their single center [3]. This prompted the authors to ask the important question of how our laboratory techniques can impact the clinical decisions that we make. In this context, we agree that addressing this concern is important to classify CKD stages in children, adolescents, and young adults correctly and are pleased to read Lao's study assessing inter-assay variability of creatinine [3].

Lao's team included 1971 serum creatinine results of <0.8 mg/dL (70.74 µmol/L) by the Abbott Jaffe method. These specimens were collected from patients under 19 years of age, from July to December 2019, and divided into the following cohorts: prepubertal females (<11 years; n = 540), pubertal females (11–<19 years; n = 556), prepubertal males (<12 years; n = 639), and pubertal males (12–<19 years; n = 236). Specimens were analyzed using the six most common creatinine assays including the following: Roche Jaffe and enzymatic assays, Siemens Jaffe, Beckman Jaffe, in addition to Abbott Jaffe and enzymatic assays. Their results confirmed large inter-assay variability proportional for each subgroup and how it decreased as creatinine concentrations increased. The greatest difference was noted between the Abbott enzymatic method compared to the Abbott Jaffe method, showing an average difference (enzymatic-Jaffe) of −0.18 mg/dL (15.92 µmol/L) in prepubertal females. Of note, the Jaffe methods remain more widely used worldwide due to lower cost. Additionally, IDMS traceable serum creatinine samples were obtained at values of 0.273 mg/dL

Editorial on "Large Inter-assay Difference of Serum Creatinine in Pediatric Population: a Threat to Accurate Staging of Chronic Kidney Disease" for *Pediatric Nephrology*

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(24.14 µmol/L), 0.440 mg/dL (38.90 µmol/L), 0.594 mg/dL (52.52 µmol/L), and 0.634 mg/dL (56.06 µmol/L). These were analyzed by the various assays mentioned above, and the largest bias was observed in the sample with the lowest creatinine [3]. In summary, Lao and team demonstrated in a large number of pediatric creatinine measurements that greater inter-assay variability exists when measuring creatinine at low serum levels, risking inaccurate eGFR estimation and CKD staging.

What can we learn from this study?

The strengths of this study include a large patient cohort, allowing many specimens to be analyzed in all 4 patient categories, strongly supporting their conclusions. Despite this well-executed study, limitations include poor differentiation amongst age cohorts, most notably in the prepubertal patients. Further areas of research should include taking a closer look at differences in serum creatinine measurements in the neonatal and preterm infant population. Additionally, in looking at patients solely by age as well as race, the study does not specify what proportion of patients continue to have a low muscle mass, even in their early adolescent years, such as patients with spina bifida, cerebral palsy, or progressive neuromuscular conditions [4, 5]. There are special populations that really require a careful approach on how to assess kidney function, which may not be creatinine based at all [6]. In addition to this, the authors highlight having the specimens come from one center preventing generalizability. Nonetheless, this study contributes to literature that addresses worldwide efforts to standardize creatinine measurements and highlights awareness to gaps of studies that focused on adult patients only.

Opportunities for future research and translation into clinical practice

In our center, in addition to serum creatinine, we are able to utilize cystatin C-based eGFR [7], which is well documented to more accurately reflect kidney function, given that it comes from all nucleated cells, not just the muscle [8]. Unfortunately, widespread implementation of cystatin C remains a challenge [9]. The best way of estimating eGFR is probably the new approach with the online calculator, using both cystatin C and creatinine [10]. As for creatinine, there are international reference materials for cystatin C [11]; however, unlike creatinine, these reference materials do not require an augmentation of the low and high concentrations, because of the independence of cystatin C from muscle mass [8]. Lao's study points to the urgent need of augmenting the existing calibration materials to creatinine measurements as low as 0.05 mg/dL. Calibration at the lower limit of detection is a problem as there is always a higher imprecision at both ends of the spectrum of measurements for a given biomarker [12]. Apart from the need for calibrated reference materials, new methodologies may have to be utilized to improve the lower limit of detection, and there may be a need to measure creatinine with novel methods necessary for precision at the lower limit of detection [12]. This is especially true in the most vulnerable population, prematurely born and term infants, who require accurate assessment of kidney function [13], not only for the diagnosis of acute kidney injury, but also for proper drug dosing of the over 60% renally excreted drugs [14].

The current approach to measurement of serum creatinine in most places is insufficient for the accurate assessment of kidney function in patients with low muscle mass. Further studies looking at the availability of cystatin C-based eGFR calculation in a variety of health care settings and variability in results when compared to creatinine-based for same blood collections would allow physicians to better interpret eGFR values for a variety of patients.

Conclusions

In summary, Lao et al. demonstrate the impact on misclassification of eGFR due the lack of creatinine reference materials at the lower level of detection needed for children with low muscle mass. The creation of pediatric adjusted reference materials for accurate measurement of creatinine is imperative and remains an active area of research. We hope to see this study develop momentum to open the doors for further studies and build stronger understanding of how to best measure creatinine in all children, adolescents, and young adults.

References

1. Filler G, Yasin A, Medeiros M (2014) Methods of assessing renal function. Pediatr Nephrol 29:183–192
2. Srivastava T, Alon US, Althahabi R, Garg U (2009) Impact of standardization of creatinine methodology on the assessment of glomerular filtration rate in children. Pediatr Res 65:113–116
3. Lao K, Sykes E, van Wijk X, Williams J, Gherasim C, Sun Q (2021) Large inter-assay difference of serum creatinine in pediatric population: a threat to accurate staging of chronic kidney disease. Pediatr Nephrol. https://doi.org/10.1007/s00467-021-05335-x
4. Pham-Huy A, Leonard M, Lepage N, Halton J, Filler G (2003) Measuring glomerular filtration rate with cystatin C and Œ≤-trace protein in children with spina bifida. J Urol 169:2312–2315
5. Morgan C, Senthilselvan A, Bamforth F, Hoskinson M, Gowrishankar M (2008) Correlation between cystatin C- and renal scan-determined glomerular filtration rate in children with spina bifida. Pediatr Nephrol 23:329–332

6. Filler G, Lee M (2018) Educational review: measurement of GFR in special populations. Pediatr Nephrol 33:2037–2046
7. Filler G, Lepage N (2003) Should the Schwartz formula for estimation of GFR be replaced by cystatin C formula? Pediatr Nephrol 18:981–985
8. Filler G, Bökenkamp A, Hofmann W, Le Bricon T, Martínez-Brú C, Grubb A (2005) Cystatin C as a marker of GFR - History, indications, and future research. Clin Biochem 38:1–8
9. Ismail OZ, Bhayana V, Kadour M, Lepage N, Gowrishankar M, Filler G (2017) Improving the translation of novel biomarkers to clinical practice: the story of cystatin C implementation in Canada: a professional practice column. Clin Biochem 50:380–384
10. Pierce CB, Munoz A, Ng DK, Warady BA, Furth SL, Schwartz GJ (2021) Age- and sex-dependent clinical equations to estimate glomerular filtration rates in children and young adults with chronic kidney disease. Kidney Int 99:948–956
11. Grubb A, Blirup-Jensen S, Lindstrom V, Schmidt C, Althaus H, Zegers I, IFCC Working Group on Standardisation of Cystatin C (WG-SCC) (2010) First certified reference material for cystatin C in human serum ERM-DA471/IFCC. Clin Chem Lab Med 48:1619–1621
12. Sukhang M, Junkuy A, Buckley N, Mohamed F, Wunnapuk K (2020) An LC-MS/MS method for creatine and creatinine analysis in paraquat-intoxicated patients. J Environ Sci Health B 55:273–282
13. Filler G, Bhayana V, Schott C, Díaz-González de Ferris ME (2021) How should we assess renal function in neonates and infants? Acta Paediatr 110:773–780
14. Filler G, Kirpalani A, Urquhart BL (2015) Handling of drugs in children with abnormal renal function. In: Avner ED, Harmon WE, Niaudet P, Yoshikawa N, Emma F, Goldstein S (eds) Pediatr Nephrol. Springer, Berlin Heidelberg, pp 1–28