Pediatr Nephrol (2013) 28:991–994
DOI 10.1007/s00467-013-2428-5

EDITORIAL COMMENTARY

Cystatin C adaptation in the first month of life

Guido Filler · Nathalie Lepage

Received: 23 January 2013 / Revised: 24 January 2013 / Accepted: 25 January 2013 / Published online: 23 February 2013

Abstract Je-Hyan Lee et al. have published a study on cystatin C concentrations in the first 30 days of life in 127 pre-term and 119 term neonates in this edition of *Pediatric Nephrology*, thereby closing a knowledge gap of detailed cystatin C concentrations beyond 72 h of life by day of life and by post-conceptional age. While the study objective has merit and a large number of measurements were included, there are some methodological limitations that bring the validity of the data into question as pure reference intervals for children up to 1 month of age, mostly because of the inclusion of patients that potentially could have an impaired glomerular filtration rate (GFR), for instance due to exposure to nephrotoxic drugs. We discuss the strengths and weaknesses of the study and outline an approach to definitely close this knowledge gap. We call for a worldwide collaboration to use Box–Cox transformations similar to the methodology used with growth charts to calculate age-independent *z*-scores and percentiles of neonatal and infant markers of GFR. This could also lead to better definitions of acute kidney injury in infants if GFR markers cross the percentiles based on post-conceptional or chronological age.

Keywords Cystatin C · Post-conceptional age · Reference intervals · Renal function · Postnatal adaptation of renal function

G. Filler (✉)
Departments of Pediatrics, Medicine and Pathology and Laboratory Medicine, Schulich School of Medicine & Dentistry, Western University, 800 Commissioners Road, East London, ON, Canada N6A 5W9
e-mail: guido.filler@lhsc.on.ca

N. Lepage
Department of Pathology and Laboratory Medicine, University of Ottawa and Biochemical Genetics laboratory, Children's Hospital of Eastern Ontario, 401 Smyth Road, Ottawa, ON, Canada K1H 8L1

Introduction

Accurate measurements of renal function are important for the dosing of drugs excreted by the kidneys. This is particularly challenging in neonates. While all nephrons are terminally differentiated at birth, they are recruited sequentially after birth in a similar sequence as they were formed through branching of the ureteric bud [1–3]. Renal function is typically measured by assessment of the glomerular filtration rate (GFR) [4], which is also important for assessing renal prognosis, especially in children with congenital renal anomalies [5]. There is also an increased appreciation that nephron endowment is not the same for every neonate and that congenital abnormalities may be associated with substantial nephron loss, especially if there was intermittent or persistent increased pressure in the urinary collecting system. The key mechanism is believed to be the induction of apoptosis-promoting molecules by increased pressure in the urinary collecting system [6]. However, there are challenges associated with the accurate assessment of GFR in neonates. Popper and Mandel proposed the use of serum creatinine in 1937 [7], and this measurement remains to this day the most widely used marker for GFR estimation despite its shortcomings. However, serum creatinine is largely affected by maternal GFR as creatinine crosses the placenta [8]. Over the last decade, cystatin C, a low molecular weight cysteine protease that is constantly produced by all nucleated cells [9], has evolved as a promising alternative to serum creatinine, with a better diagnostic sensitivity [10] and independence of muscle mass [11] and body composition [12]. Currently, the best estimated (e)GFR formulae in children can be derived from cystatin C alone or in combination with creatinine and/or urea [13]. Plebani et al. [14] and Cataldi et al. [15] have suggested that cystatin C does not cross the placenta. Bökenkamp et al. have shown that fetal cystatin C may be a useful predictor of postnatal kidney function [16]. Some evidence for diaplacental transport of cystatin C has recently been presented [5, 17],

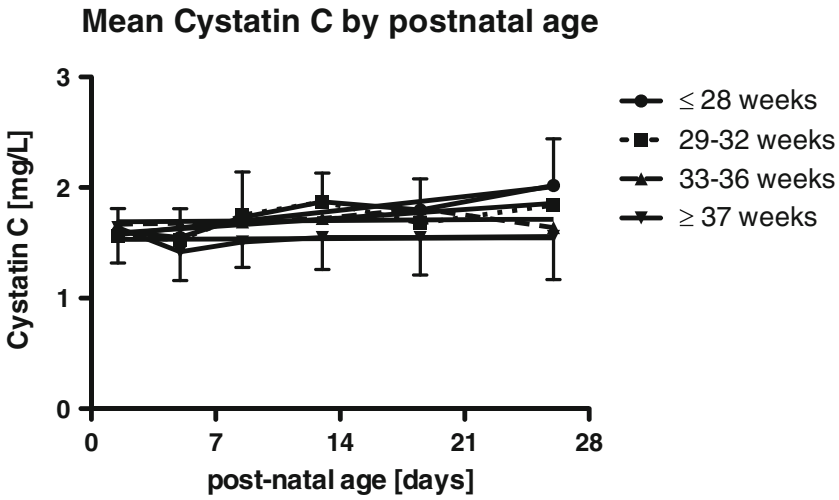

Fig. 1 Relationship between postnatal age (days), grouped by gestational age, and cystatin C concentrations as reported by Ji-Hyan Lee et al. [20] based on the results of their study at Soon Chun Hyang University, Seoul, Republic of Korea. The graph is derived from data presented in Table 2 of their article. While term babies had the lowest cystatin C concentrations and maintained these low concentrations throughout the study period, the cystatin C concentrations of premature infants actually increased

although the effect was much less pronounced than that of serum creatinine, even 72 h postpartum. However, pediatric reference intervals of cystatin C beyond 72 h postpartum to 1 year of age have to date lacked the necessary high resolution of post-conceptual age that is necessary to assess the rapid ontogeny of nephron recruitment in the first few months of life [3, 5, 18, 19]. In that context, we are delighted to see an important attempt at closing the knowledge gap, at least for the first 30 days of life, in the study of Ji-Hyun Lee and coworkers in this edition of *Pediatric Nephrology* [20].

Serum cystatin C in the first 30 postnatal days in neonates

Ji-Hyan Lee and colleagues measured cystatin C in 883 blood samples from 246 neonates, of whom 127 were premature. The exclusion criteria for prematurity were well selected, even though it always remains a challenge to truly define premature babies as healthy individuals. For premature babies with a post-conceptional age of <28 to 32 weeks, the authors demonstrated a gradual decline of serum cystatin C from 1.60±0.21 on day 0–3 to 1.50 mg/L on day 4–6, followed by gradually increasing levels up to 22–30 days. For full-term babies, the trends in cystatin C levels did not show such marked changes from 0–3 day to 22–30 days.

The strengths of the study include the large number of patients [15 infants at≤28 weeks of gestation, 40 at 29–32 weeks of gestation, 72 at 33–36 weeks of gestation, and 119 term infants (≥37 weeks of gestation)] and the large number of measurements (883). However, some patients presented with a wide variety of treatment procedures, with 34.1 and 31.0 % of measurements obtained while the patient was ventilated or receiving nephrotoxic drugs, respectively. This variation in treatment procedures significantly limits the designation of values presented in Table 2 of the article as reference intervals. Interestingly, when all groups were analyzed separately and longitudinally, the cystatin C values can be seen to have increased slightly (Fig. 1, derived from Table 2 in the article of Je-Hyan Lee et al. [20]). The slope of the regression line of the averages increases significantly in the extremely preterm group. Because each of the four study groups comprises a different number of infants, the results are heavily weighted towards term infants.

Interestingly, there was no difference in cystatin C concentrations among the four gestational age groups during the first 3 postnatal days. We had the opportunity to check the results against our own data from a previous study and also found no difference with regards to the initial cystatin C values on day 3 of life (Fig. 2). The data in that study reflect truly cross-sectional data.

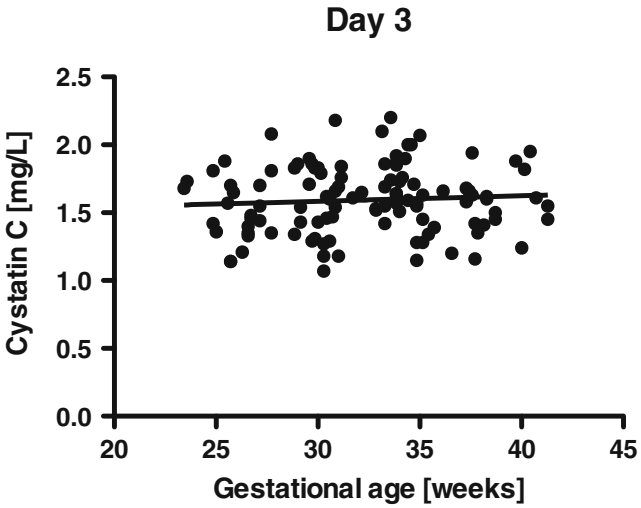

Fig. 2 The relationship between post-conceptional age in weeks and serum cystatin C level on day 3 of life in 111 healthy term and pre-term neonates from Children's Hospital of Eastern Ontario. The slope of the regression line was not significantly non-zero (Y=slope × X+ Y-intercept, with the slope=0.004080±0.005375, Y-intercept when X=0.0= 1.461±0.1751; p=0.4494)

Future directions

There is clearly a need to assess whether the GFR is normal in relationship to post-conceptional age. The GFR increases by threefold by 24 h after delivery; this is followed by a continuous slow increase until steady state is reached at 18 months [21]. Thereafter, the absolute GFR increases with body length; as such, the GFR is normalized to body surface area, which makes it an age-independent parameter, while serum creatinine continues to increase [22]. In infants, even with normalization to body surface area, GFR increases from about 10 to 90–150 mL/min/1.73 m^2 in 2-year-old children [3]. Pediatric nephrologists have significant difficulties determining exactly what the normal GFR would be for the exact age. Typically, reference intervals are provided as the 2.5th and 97.5th percentile for a given age range, but ideally, a modeled regression line using polynomial regression is more applicable to reflect the gradual changes. The undersigned are only aware of one such model for serum creatinine [23]. However, polynomial regression analysis also does not allow for assessment of age-independent normal values.

So, how can we derive whether cystatin C (or creatinine) or the eGFR derived from this [24] is actually normal for a given age in days post conception or days of life for a term infant? Luckily, an approach for a similar problem can be applied to markers of GFR in the first 24 months of life, namely the calculation of age-independent percentiles or *z*-scores. The Center of Disease Control and the World Health Organization have developed feasible and accurate methods for calculating percentiles or *z*-scores for height, weight, weight for height, and body mass index. We have applied these to children with chronic kidney disease [25]. If a sufficient sample size exists, Box–Cox transformations can be applied to calculate age-independent *z*-scores. Briefly, parameters of the median (M), the generalized coefficient of variation (S), and the power in the Box–Cox transformation (L) are calculated to generate exact percentiles and *z*-scores. To obtain the value (X) of a given physical measurement at a particular *z*-score or percentile, we used the following equation: X=M (1+LSZ)**(1/L), where L, M, and S are the values corresponding to the age in months of the child, and Z is the *z*-score that corresponds to the percentile. An example can be found in a recent study on the effects of preconception age of mothers on the body mass index percentiles of their offspring [26]. For the current issue, the aim is to collate cystatin C values of healthy infants less than 2 years of age obtained in pooled samples from multiple centers with standardized cystatin C measurements. The patient data need to be analyzed in sufficiently small age groups for the calculation of the L, M, and S scores by day for the first 4 weeks, thereafter by week until 6 months of life, and thereafter monthly, then age-independent percentiles. This approach will determine cystatin C reference intervals based on post-conceptual age and on age in days, and would assess whether a marker of renal function is crossing percentiles or not. This method would also allow for a much better way of assessing acute kidney injury in neonates [3]. The undersigned call for a multicenter collaboration to identify all infant cystatin C measurements in healthy children or children without any obvious disease or nephrotoxic medication or dehydration to generate these percentiles. Some of the measurements obtained by Je-Hyan Lee et al. [20] can be included. We suggest that the International Pediatric Nephrology Association could play a key role in coordinating such efforts.

Conclusion

Je-Hyan Lee et al. [20] have made a significant contribution towards closing the knowledge gap of cystatin C concentrations in the first month of life, despite the many limitations of their study. Further work and a coordinated effort across the globe is needed to develop a useful tool using the Box–Cox transformation of normal cystatin C data in infants to generate appropriate LMS charts for the calculation of age-independent percentiles that will enable accurate determination of the cystatin C percentiles based on post-conceptional and postnatal age.

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