Paediatrics Publications   Paediatrics Department

9-1-2021

Discrepant changes of urinary cystatin C and other urinary biomarkers in preterm neonates

Guido Filler
Schulich School of Medicine & Dentistry, guido.filler@lhsc.on.ca

Maria E.Díaz González de Ferris
The University of North Carolina at Chapel Hill

EDITORIAL

Discrepant changes of urinary cystatin C and other urinary biomarkers in preterm neonates☆

Guido Filler ⓘ [a,b,c,*], **Maria E. Díaz-González de Ferris** ⓘ [d]

[a] *Western University, Schulich School of Medicine & Dentistry, Departments of Paediatrics and Medicine, London, Canada*
[b] *Western University, The Lilibeth Caberto Kidney Clinical Research Unit, London, Canada*
[c] *Western University, Schulich School of Medicine & Dentistry, Department of Pathology and Laboratory Medicine, London, Ontario, Canada*
[d] *The University of North Carolina at Chapel Hill, Department of Pediatrics, Chapel Hill, North Carolina, USA*

Introduction

Adaptation of neonatal function is a complex process where nephrons are slowly recruited in the order of their formation, especially in the first few weeks after birth, when kidney function changes daily.[1,2] Whereas only 3% of the renal blood flow goes to the kidneys before birth, this increases slowly to 25% at 18−24 months of age.[3,4] In preterm neonates, there is added complexity because depending on their gestational age, they may not have completed nephrogenesis (usually by 34−36 weeks).[5] It is believed that renal development is interrupted by premature delivery, affecting nephron endowment.[6] However, some recent work suggests that some altered nephrogenesis can take place postnatally.[7] Nephron development is also affected by hyperglycemia.[7] Postnatally, these infants often experience additional stress, and neonatal acute kidney injury (AKI).[8] There are multiple processes occurring in the developing neonatal kidney of a prematurely born infant, namely recruitment of more nephrons, improved isosthenuria, handling of sodium, altered or halted nephrogenesis, hypoxic-ischemic processes, nephrotoxin exposures, and hemodynamic changes. The process of recruiting nephrons and the aforementioned processes are understudied in preterm neonates. In this context, we are pleased to read the recent study by Correa et al.[9] examining urinary biomarkers of kidney function and kidney injury in preterm neonates, both at 72 h and 3 weeks of age.

The study by Correa et al.

Correa et al.[9] studied a wide array of urinary biomarkers in 40 preterms (55% male) with an average gestational age of 30 weeks and an average birth weight of 1477 g. All deliveries were by Cesarian section and preeclampsia was the major cause of prematurity in 80% of cases. The vast majority of these neonates were exposed to antenatal glucocorticoids, and 24/40 had respiratory distress. Fourteen out of 40 patients had low or extremely low birth weight for gestational age.

The array of urinary biomarkers included: Calbindin − a 28 kD biomarker found predominantly in the distal tubule that is used for monitoring nephrotoxic chemotherapy: Osteoprotegerin (OPN) − produced by the kidneys and lym-

phoid cells and used as a potential biomarker of lupus nephritis disease activity; Collagen IV; Fatty Acid binding protein 1 (FABP1) – a biomarker of hypoxia in the proximal tubule; Glutathione Transferase Alpha (alpha GST) – an early biomarker for renal dysfunction; urinary interferon gamma induced protein 10 (IP-10) – a chemokine involved in the alloimmune response of an allograft; kidney injury molecule 1 (KIM-1); Osteoactivin – an early marker that is upregulated in acute kidney injury; Renin; Trefoid Factor 3 (TFF-3) – a urinary biomarker that is markedly reduced in AKI; TIMP-1 – the inhibitor of the matrix metalloproteinase MMP9, used for congenital hydronephrosis and reflux workup on an experimental basis; alpha-1-Microglobulin – a low molecular weight protein associated with tubular injury; Albumin; Clusterin – a 75–80 kDa disulfide-linked heterodimeric protein associated with the clearance of cellular debris and apoptosis; Cystatin C; epidural growth factor (EGF); Lipocalin-2; neutrophil gelatinase-associated lipocalin (NGAL) and Osteopontin – higher urinary osteopontin specifically predicts incident chronic kidney disease. These molecule tests were performed using panels 1 and 2 of multiplex kits of AKI. Studies on such a wide panel of urinary biomarkers in preterm neonates have been elusive.

Correa et al.[9] found significant increases of some of the urinary biomarkers in their preterm neonates between 3–21 days, namely for urinary albumin, EGF, microglobulin, clusterin, OPN, osteoactivin, KIM-1, and NGAL.

When interpreting these results, it is important to consider what is actually being assessed, and which direction is concerning. For instance, with worsening renal function, urinary EGF decreases; whereas urinary cystatin C or KIM-1 increases. Urinary albumin, EGF, macroglobulin, clusterin, OPN, NGAL, and osteoactivin all increased significantly between 3–21 days, whereas urinary KIM-1 barely reached statistical significance. Urinary cystatin C remained unchanged.

Urinary EGF has been used as a biomarker for the progression of Alport syndrome.[10] Unlike the molecular weight proteins that increase with decreased tubular function (e.g., urinary cystatin C or KIM-1),[11] urinary EGF is derived from the kidneys and has been demonstrated to be downregulated in human kidney diseases.[12] An increase of urinary EGF would therefore reflect better tubular function, potentially due to increased nephron recruitment after 21 days of age.

Urinary 28-kD calbindin is a vitamin D-dependent calcium-binding protein found predominantly in the central nervous system and is a marker of distal tubular function in the kidneys,[13] and like urinary KIM-1, its increased urinary concentration is a biomarker for tubular injury.[14] Urinary albumin and beta-2 microglobulin and in the case of this study, alpha-1 microglobulin (which is similar but more stable),[15] are known to increase in the neonatal period, with urinary beta 2-microglobulin showing a peak level at 7 days. In sick preterm neonates, both markers were increased for at least two weeks.[16] Urinary NGAL is known to be increased with lower birth weight and may serve as a marker of AKI.[17]

The authors also analyzed if there was a difference between these markers for less than and greater than 31 weeks of gestational age. Interestingly, and in contrast to what was expected (namely that the higher gestational age group would show fewer increases), there was no difference between both groups.

How to make sense of these observed increases in several urinary markers while urinary cystatin C remains unchanged?

The first important finding was that cystatin C did not change. It is known that serum cystatin C does not change much with gestational age until the post-conceptual age reaches 40 weeks.[1] The amount of serum cystatin C is a marker of glomerular filtration rate, and it is freely filtered across the glomerular filtration barrier.[18] Urinary cystatin C is reflecting the amount of cystatin that is not degraded by pinocytosis in the proximal tubule.[18] As the recruitment of nephrons after birth parallels the tubules that are being recruited, maintaining the same urinary cystatin C levels would make sense.

Most of the kidney injury molecules studied increased in keeping with tubular damage. Given the high proportion of respiratory distress in Correa's cohort, tubular damage would be expected. This may explain the increase of alpha-1 microglobulin, clusterin, OPN, osteoactivin, NGAL, and the barely significant increase of urinary KIM-1. The increase of EGF from a median of 1.89–2.97 is an interesting finding. This increase would be in keeping with the increased recruitment of nephron endowment.[12] Unfortunately, the rate of nephron recruitment in prematurity remains understudied, however, pharmacokinetic studies of Vancomycin would support the findings that nephrons are being recruited continuously after delivery, as indicated by increasingly shorter dosing intervals with increased postnatal age.[19]

The need for future research

Correa's study demonstrated that the kidneys of preterm neonates are subject to considerable stress as detected by the urinary metabolomic profile, suggesting that there is not only a creatinine-blind range of AKI, but possibly also a cystatin C-blind range. Since prematurity and AKI (with associated morbidity/mortality and length of stay) continue to increase, despite overall reduced pediatric admissions[20,21]; reliable tools for the detection of AKI are required. The incidence of AKI in critically ill preterm neonates is 40–70%.[22] Current definitions for AKI in these patients still have shortcomings. We need reference intervals for urinary biomarkers of AKI by post-conceptual age, to identify injury and target possible interventions. The study conducted by Correa et al. strongly suggests that most prematurely born neonates experience significant tubular distress 21 days after birth regardless of the gestational age, which may contribute to the risk of future chronic kidney disease and hypertension in these patients. We encourage ongoing research in this field.

Summary

Correa's study[9] suggests that the kidneys of pre-term neonates, and their tubules in particular (both proximal and distal), are subject to considerable stress as detected by the urinary metabolomic profile, which does not include changes in urinary cystatin C. This stress worsens between 3 and 21 days of life and is probably unnoticeable by conventional tests.

Conflicts of interest

Acknowledgments

References

1. Filler G, Bhayana V, Schott C, Díaz-González de Ferris ME. How should we assess renal function in neonates and infants? Acta Paediatr. 2021;110:773−80.

2. Arant BS Jr. Postnatal development of renal function during the first year of life. Pediatr Nephrol. 1987;1:308−13.

3. Filler G, Guerrero-Kanan R, Alvarez-Elías AC. Assessment of glomerular filtration rate in the neonate: is creatinine the best tool? Curr Opin Pediatr. 2016;28:173−9.

4. Filler G, Lopes L, Awuku M. The importance of accurately assessing renal function in the neonate and infant. Adv Clin Chem. 2015;71:141−56.

5. Thayyil S, Sheik S, Kempley ST, Sinha A. A gestation- and postnatal age-based reference chart for assessing renal function in extremely premature infants. J Perinatol. 2008;28:226−9.

6. Hinchliffe SA, Sargent PH, Howard CV, Chan YF, van Velzen D. Human intrauterine renal growth expressed in absolute number of glomeruli assessed by the disector method and Cavalieri principle. Lab Invest. 1991;64:777−84.

7. Callaway DA, McGill-Vargas LL, Quinn A, Jordan JL, Winter LA, Anzueto D, et al. Prematurity disrupts glomeruli development, whereas prematurity and hyperglycemia lead to altered nephron maturation and increased oxidative stress in newborn baboons. Pediatr Res. 2018;83:702−11.

8. Askenazi D, Abitbol C, Boohaker L, Griffin R, Raina R, Dower J, et al. Optimizing the AKI definition during first postnatal week using Assessment of Worldwide Acute Kidney Injury Epidemiology in Neonates (AWAKEN) cohort. Pediatr Res. 2019;85:329−38.

9. Correa LP, Marzano AC, Silva Filha R, Magalhães RC, Simoes-E-Silva AC. Biomarkers of renal function in preterm neonates at 72h and 3 weeks of life. J Pediatr (Rio J). 2021;97:508−13.

10. Li B, Zhang Y, Wang F, Nair V, Ding F, Xiao H, et al. Urinary epidermal growth factor as a prognostic marker for the progression of Alport syndrome in children. Pediatr Nephrol. 2018;33:1731−9.

11. Vanmassenhove J, Vanholder R, Nagler E, Van Biesen W. Urinary and serum biomarkers for the diagnosis of acute kidney injury: an in-depth review of the literature. Nephrol Dial Transplant. 2013;28:254−73.

12. Stangou M, Alexopoulos E, Papagianni A, Pantzaki A, Bantis C, Dovas S, et al. Urinary levels of epidermal growth factor, interleukin-6 and monocyte chemoattractant protein-1 may act as predictor markers of renal function outcome in immunoglobulin A nephropathy. Nephrology (Carlton). 2009;14:613−20.

13. Takashi M, Zhu Y, Miyake K, Kato K. Urinary 28-kD calbindin-D as a new marker for damage to distal renal tubules caused by cisplatin-based chemotherapy. Urol Int. 1996;56:174−9.

14. George B, Wen X, Mercke N, Gomez M, O'Bryant C, Bowles DW, et al. Time-dependent changes in kidney injury biomarkers in patients receiving multiple cycles of cisplatin chemotherapy. Toxicol Rep. 2020;7:571−6.

15. Lun A, Ivandic M, Priem F, Filler G, Kirschstein M, Ehrich JH, et al. Evaluation of pediatric nephropathies by a computerized Urine Protein Expert System (UPES). Pediatr Nephrol. 1999;13:900−6.

16. Tsukahara H, Fujii Y, Tsuchida S, Hiraoka M, Morikawa K, Haruki S, et al. Renal handling of albumin and beta-2-microglobulin in neonates. Nephron. 1994;68:212−6.

17. Lavery AP, Meinzen-Derr JK, Anderson E, Ma Q, Bennett MR, Devarajan P, et al. Urinary NGAL in premature infants. Pediatr Res. 2008;64:423−8.

18. Filler G, Bökenkamp A, Hofmann W, Le Bricon T, Martínez-Brú C, Grubb A. Cystatin C as a marker of GFR—history, indications, and future research. Clin Biochem. 2005;38:1−8.

19. Janssen EJ, Välitalo PA, Allegaert K, de Cock RF, Simons SH, Sherwin CM, et al. Towards rational dosing algorithms for vancomycin in neonates and infants based on population pharmacokinetic modeling. Antimicrob Agents Chemother. 2015;60:1013−21.

20. Selewski DT, Akcan-Arikan A, Bonachea EM, Gist KM, Goldstein SL, Hanna M, et al. The impact of fluid balance on outcomes in critically ill near-term/term neonates: a report from the AWAKEN study group. Pediatr Res. 2019;85:79−85.

21. Hidayati EL, Utami MD, Rohsiswatmo R, Tridjaja B. Cystatin C compared to serum creatinine as a marker of acute kidney injury in critically ill neonates. Pediatr Nephrol. 2021;36:181−6.

22. Sethi SK, Agrawal G, Wazir S, Rohatgi S, Iyengar A, Chakraborty R, et al. Neonatal acute kidney injury: a survey of perceptions and management strategies amongst pediatricians and neonatologists. Front Pediatr. 2020;7:553.