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EDITORIAL

Standardized urine biomarkers in assessing neonatal kidney function: are we there yet?☆

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A reliable biomarker is a measurable indicator of a biological function or process that can be consistently reproduced and applied to differentiate physiologic normality from disease.[1,2] Biomarkers are needed for a more accurate assessment of kidney function and injury in the preterm infant. Preterm infants are notable for a relatively low glomerular filtration rate (GFR) compared to term-born infants as well as an increased vulnerability to acute kidney injury (AKI).[3–5] In turn, AKI is independently associated with adverse consequences such as increased mortality, prolonged hospitalization and a presumed increased propensity to chronic kidney disease (CKD), as well as shorter longevity.[5,6] Developing a clear understanding of the application of biomarkers to neonatal kidney function is essential if AKI is to be promptly diagnosed, appropriately treated and adverse consequences followed prospectively in critically ill neonates. An important component of this conundrum is to have reliable reference standards derived from ''healthy controls''. During the past 2 decades, some pioneers have focused on identifying the role of both serum and urine biomarkers to accurately assess renal injury and preemptively diagnose AKI in the neonate.[7–10] Unfortunately, only a few studies have focused on developing reference standards derived from ''healthy controls'' including those of term gestation and/or case-matched gestational age (GA) controls.[8–10]

Although serum creatinine (SCr) is the traditional biomarker of kidney function across all ages, its imprecision is particularly problematic in the neonate.[11–13] Creatinine is a derivative of muscle mass that is low in newborns. The maternal burden of creatinine transferred through the placenta may elevate the neonate's SCr for at least 2 days after birth during physiologic adaptations to the extrauterine environment.[11–13] More importantly, there is the role of preterm birth and gestational age on the vulnerability of kidney function since those born before 34 weeks' GA have not completed nephrogenesis.[12] Even ''healthy'' preterm infants are known to have lower GFR and slower declines in SCr relative to GA.[12,13] Hence, the accurate assessment of neonatal kidney function remains elusive and the enlistment of new and precise markers of kidney function and injury is essential for clinical management and investigation. Nevertheless, SCr remains an important reference biomarker that is affordable and universally available to define both normal and abnormal kidney function.[12,13]

All newborns, when exposed to a noxious postnatal environment of nephrotoxic drugs or ischemia are vulnerable to AKI. Most contemporary definitions of neonatal AKI rely on subtle increases in SCr or decreases in urine output that reflect a loss of function rather than an injury.[1,11–13] These definitions predict increased mortality but do not signal early injury that might potentially allow for mitigating interventions that might arrest or reverse the process. Since 2013, the consensus has been to apply the modified KDIGO

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definition in an effort to allow consistency in the interpretation of results of clinical trials.[14]

In the current issue of *Jornal de Pediatria*, Correa et al. have provided an important prospective analysis of a multiplex panel of 17 urine biomarkers of tubular and glomerular function/injury in 40 clinically stable preterm infants at 72 h and 3 weeks' post-natal age.[15] The results provide several distinct contributions to the current literature. The initial array of 17 biomarkers is probably too big to be a useful panel that differentiates mechanisms of adaptive function versus injury. However, when comparing the same urinary biomarkers at gestational ages < 32 weeks and ≥ 32 weeks at 72 hours and 3 weeks postnatal age, there were no differences.[7,9,10] These include urinary albumin, epithelial growth factor (EGF), kidney injury molecule-1 (KIM-1), osteoprotegenin (OPN), neutrophil gelatinase-associated lipocalcin (NGAL), and cystatin-C (CysC). The authors note that changes in these biomarkers from birth to 3 weeks may reflect *maturational* as well as *developmental* changes in glomerular and tubular function in preterm infants rather than *injury*. There has been one other prospective study of urinary biomarkers in unstressed preterm infants compared to term controls from birth to 3 months' post-natal age.[9] These differences were more distinct, presumably due to the achievement of completion of post-natal nephrogenesis. Both studies are limited by small numbers of subjects. There is much to be learned in establishing reference values which is essential for applying these biomarkers for early estimation of renal function and injury.

Although Correa et al. did not measure renal function by either SCr or serum CysC, they recognize the imperative that future studies should address the need to refine the assessment of neonatal renal function by an accurate, timely and affordable marker to replace SCr. At this point, serum CysC seems to be the most likely candidate. A prospective study across all gestational ages comparing SCr and CysC in 2014 determined that serum CysC was more reliable as a measure of kidney function.[11] All studies have been limited by inadequate numbers. Recently, in the Preterm Erythropoietin Neuroprotection Trial (PENUT) renal function was examined by both SCr and CysC in 923 extremely low gestational age neonates (ELGAN) of <29 weeks' GA. The PENUT trial offers comparable values for SCr and CysC in the largest cohort studied to date.[16]

Other caveats regarding the accurate assessment and reporting of reference standards of biomarkers in preterm infants are that gestational age, birth weight, postnatal age, and maternal factors such as maternal hypertension have been reported to significantly affect renal biomarkers.[7–10] In the Correa et al. study, 80% of the subjects were products of hypertensive pregnancies.[15] This could result in inherent bias and perhaps explain the lack of significant variation in all the biomarkers from birth to 3 weeks in the present cohort. Clearly, more robust studies are needed to better define the utilization and application of urinary biomarkers in preterm infants in order to differentiate adaptive function from injury. Correa et al. should be applauded for their innovation and initiative in a clinical translational study of biomarkers in preterm neonates. The global community is eager for more research in this sphere which will require a global collaborative.

Conflicts of interest

The authors declare no conflicts of interest.

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