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Association Between Newborn Metabolic Profiles and Pediatric Kidney Disease

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Introduction: Metabolomics offers considerable promise in early disease detection. We set out to test the hypothesis that routine newborn metabolic profiles at birth, obtained through screening for inborn errors of metabolism, would be associated with kidney disease and add incremental information to known clinical risk factors.

Methods: We conducted a population-level cohort study in Ontario, Canada, using metabolic profiles from 1,288,905 newborns from 2006 to 2015. The primary outcome was chronic kidney disease (CKD) or dialysis. Individual metabolites and their ratio combinations were examined by logistic regression after adjustment for established risk factors for kidney disease and incremental risk prediction measured.

Results: CKD occurred in 2086 (0.16%, median time 612 days) and dialysis in 641 (0.05%, median time 99 days) infants and children. Individual metabolites consisted of amino acids, acylcarnitines, markers of fatty acid oxidation, and others. Base models incorporating clinical risk factors only provided c-statistics of 0.61 for CKD and 0.70 for dialysis. The addition of identified metabolites to risk prediciton models resulted in significant incremental improvement in the performance of both models (CKD model: c-statistic 0.66 NRI 0.36 IDI 0.04, dialysis model: c-statistic 0.77 NRI 0.57 IDI 0.09). This was consistent after internal validation using bootstrapping and a sensitivity analysis excluding outcomes within the first 30 days.

Conclusion: Routinely collected screening metabolites at birth are associated with CKD and the need for dialytic therapies in infants and children, and add incremental information to traditional clinical risk factors.

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Chronic kidney disease (CKD) is a leading contributor to cardiovascular morbidity and mortality, with a global prevalence of 8% to 16% in adults. Although large population-based studies have examined the epidemiology of CKD in adult populations,[1–3] comparable studies of CKD in children are few.[4] The current literature suggests that 70% of children with CKD will develop end-stage kidney disease (ESKD) by age 20 years, and mortality rates for children with ESKD on dialysis therapy are 30 to 150 times higher than those in the general pediatric population.[5,6]

As there are limited therapies available after kidney disease onset, early identification of individuals at risk is critical to the implementation of measures to minimize complications, to improve quality of life, and to reduce mortality. Through its role as an excretory organ the kidney plays a significant role in nutritional and metabolic regulation. Alterations in glomerular filtration, secretion, and tubular reabsorption therefore result in detectable changes in small molecule concentrations in the blood and urine. Routinely used markers of kidney function including serum creatinine and blood urea nitrogen are limited, however, by their inability to support detection of CKD in the earliest stages of the disease.

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Metabolic derangements are well described in patients with CKD. Plasma and urinary amino acid profiles are demonstrably affected by acute and chronic kidney disease and by glomerulonephritis.[7–11] Dysregulation of acylcarnitine excretion as a result of renal failure has also been observed in CKD and diabetic nephropathy. It is unknown whether the biological processes associated with acute illness, inflammatory processes, and kidney disease are established at the time of birth. Humans are born with a set number of functioning nephrons per kidney,[12] and reduced nephron mass is hypothesized to underlie individual susceptibility to hypertension and CKD.[13–15] Whereas *antemortem* measurement of nephron mass is not currently possible, metabolic profiling of circulating amino acids and acylcarnitines in the neonatal period may reveal differential renal function and susceptibility to pediatric kidney disease before clinical onset of the condition.

In this study, we set out to examine the association between routinely collected newborn metabolite profiles with development of CKD or the need for dialysis in infants and children up to 9 years of age. We hypothesized that patterns of analytes and anatlye ratios at birth would be associated with CKD or dialysis and would add incremental information to known clinical kidney disease–related risk factors.

METHODS

Design and Setting

We conducted a population-based cohort study to determine the association between newborn metabolic profiles and the risk of CKD or dialysis. We used data collected from infants born in Ontario, Canada, through routine newborn screening and provincial outcome data from administrative databases housed at the Institute for Clinical Evaluative Sciences (ICES). The study was conducted according to a prespecified protocol with ethics approval by the Ottawa Health Science Network Research Ethics Board (20140724-01H) and the Children's Hospital of Eastern Ontario Research Ethics Board (15/143X).

Data Sources

Newborn metabolite data, maternal and newborn clinical data, and study outcome information were obtained by linkage between the Newborn Screening Ontario, the Better Outcomes Registry and Network, Gamma Dynacare, Canadian Organ Replacement Registry, and other ICES datasets using encrypted patient health card numbers as unique identifiers.

Newborn Screening Ontario

The Newborn Screening Ontario (NSO) program screens nearly all (>99%) children born in Ontario, Canada, for the presence of rare, treatable diseases using blood samples collected within the first few days of life. The newborn screening program collects data on more than 40 distinct analytes, many of which are markers of metabolism. The markers available for study from NSO are listed in Supplementary Table S1.

The Better Outcomes Registry and Network

The Better Outcomes Registry and Network (BORN) is a prescribed registry that includes a broad collection of prenatal and perinatal data. BORN was launched in 2012 as the integration of 5 stand-alone databases: congenital anomalies surveillance (Fetal Alert Network); pregnancy, birth, and newborn information for women in hospitals (Niday Perinatal Database); pregnancy, birth, and newborn information for women giving birth at home (Ontario Midwifery Program database); prenatal screening (Ontario Maternal Multiple Marker Serum Screening); and newborn screening (the Newborn Screening Ontario database). Data within the BORN Information System (BIS) are available to researchers for the purposes of facilitating or improving the provision of health care.

Institute for Clinical Evaluative Sciences

The Institute for Clinical Evaluative Sciences (ICES) houses all of Ontario's health administrative databases. The study cohort was limited to children who were continuously registered in the Ontario Health Insurance Plan (OHIP) Claims database during the study period to ensure capture of all potential study outcomes. ICES datasets used for this study included the MOMBABY dataset, which links the admission records of delivery mothers and their newborns; the Discharge Abstract Database, which captures all administrative, clinical, and demographic information on hospital discharges; Gamma Dynacare, which captures laboratory tests; the Canadian Organ Replacement Registry, which captures all ESKD patients in Canada; and the National Ambulatory Care Registration System database, which contains data for all hospital- and community-based ambulatory care. A list of diagnostic codes used for this study is presented in Supplementary Table S2.

Study Population

Children born between 1 April 2006 and 26 September 2015 for whom newborn screening data were available (n = 1,504,459) were included for analysis. Children for whom OHIP coverage was not continuous during the study period, cases with missing clinical data, children

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