RESEARCH ARTICLE

Role of dipstick albuminuria in progression of paediatric chronic kidney disease

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Abstract

Objective: Renal function of patients with chronic kidney disease (CKD) is typically evaluated by detecting proteinuria because it is a major predictor of CKD progression. In paediatric patients with CKD, urine albumin-to-creatinine ratio (ACR) is used to detect CKD progression, which is similar to urine protein-to-creatinine ratio (PCR). However, facilities for evaluation of urine ACR and urine PCR may not be widely available. To date, this is the first study that investigated the predictive value of baseline dipstick albuminuria for 1-year and 3-year CKD progression in Indonesian children. We assessed the association between baseline level of dipstick albuminuria and CKD progression in paediatric patients.

Methods: This retrospective cohort study was conducted at the Cipto Mangunkusumo Hospital (CMH) involving 43 children with CKD between 2016 and 2019. The patients were followed up for 1 year and 3 years after enrolment. Risk ratios (RR) for 1-year and 3-year CKD progression were calculated using Fisher's exact test.

Results: The RR for 1-year CKD progression in children with baseline dipstick albuminuria <2+ was 2.16 (95% CI: 1.13-4.14, p = 0.02), and the corresponding RR for 3-year CKD progression in these children was 1.70 (95% CI: 0.73-3.97, p=0.21).

Conclusion: Dipstick albuminuria was not associated with 1-year and 3-year CKD progression in children.

Keywords: Kidney failure, chronic; chronic renal insufficiency; albuminuria; proteinuria. (JPMA 71: S-103 [Suppl. 2]; 2021)

Introduction

In 2010, an estimated 497 million adults aged 20 years had chronic kidney disease (CKD) worldwide; of these, an estimated 236 million patients presented with CKD stage 3-5.[1] The reported average annual incidence rate of paediatric end-stage renal disease (ESRD) is approximately 8.12 per million population in this age-group.[2] Early identification of patients with CKD who are at risk of rapid decline in kidney function (those with annual estimated glomerular filtration rate (eGFR) decline of >5% from baseline) is a key imperative to institute appropriate interventions.[3,4]

Proteinuria is an important indicator of progression of CKD. The Effect of Strict Blood Pressure Control and Angiotensin-converting Enzyme (ACE) Inhibition on Progression of Chronic Renal Failure in Paediatric Patients (ESCAPE) trial in children with CKD demonstrated a correlation between higher proteinuria level and faster decline in GFR.[5] In Chronic Kidney Disease in Children (CKiD) study, the total urine protein-to-creatinine ratio (PCR) of > 0.5 mg/mg in children with glomerular CKD showed an association with 94% accelerated initiation time of renal replacement therapy and 50% decline in eGFR.[6]

In adult patients with CKD, albuminuria is a stronger indicator of renal disease progression than proteinuria.[7] However, in children with CKD who do not present with diabetes, the utility of initial urine ACR for characterisation of CKD progression is similar to that of urine PCR.[8] However, facilities for evaluation of urine ACR and urine PCR might not always be available at every hospital, particularly in resource-constrained settings. Therefore, some studies have suggested the use of dipsticks for measuring albumin as a convenient indicator of CKD progression. Dipstick albuminuria was shown to exhibit 75.4% sensitivity and 99.5% specificity for prediction of urine with ACR > 300 mg/g in adults.[9]

However, the role of urine dipstick albuminuria in predicting renal disease progression has not been well-studied in children with CKD. In this study, we aimed to assess the association between albuminuria, as assessed by dipsticks, and progression of paediatric CKD.

Material and Methods

This retrospective cohort study was conducted at the Cipto Mangunkusumo Hospital (CMH) between July 2016 and December 2019. Institutional review board approval was obtained from the CMH Board and Ethics Committee of Faculty of Medicine, University of Indonesia (KET-818/UN2.F1/ETIK/PPM.00.02/2019).

Clinical data of patients were obtained from medical

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records. The inclusion criteria were the following: children aged < 18 years with CKD stage 3-5 who were not on dialysis (ND CKD stage 5) and who visited outpatient clinic of Pediatric Nephrology at CMH between July 2016 and December 2019. The patients were followed up for at least 1 year and up to 3 years after enrolment.

We described the aetiology and comorbid conditions and analysed the association of baseline dipstick albuminuria level with 1-year and 3-year CKD progression, using CKD categories based on the Kidney Disease Improving Global Outcomes (KDIGO) 2012 classification. CKD progression was defined as the presence of one or more of the following: a drop in GFR category accompanied by ≥ 25% drop in eGFR from baseline or initiation of dialysis.[10,11] Blood pressure was measured according to the standard protocol and was categorised according to 2017 American Academy of Pediatrics Guidelines for Childhood Hypertension.[12] The criteria for normal haemoglobin levels in our study was WHO criteria.[13]

Random urine samples (first morning void, if possible) were obtained, and urine albumin level was measured using a urine dipstick test strip (Aim Uri Test 10LTM) on one occasion, that was dipped in urine sample for 2 seconds. The dipstick test strip was then read using Siemens CLINITEK Advantus Urine Chemistry Analyzer with result scales of 0, 1+, 2+, 3+ and 4+. Result of 0 and 1+ are categorized into < 2+, while 2+, 3+, and 4+ are categorized into ≥2+.

The association of baseline dipstick albuminuria level with 1-year and 3-year CKD progression in children was described as the risk ratio (RR) with 95% confidence interval (CI). Categorical variables were compared using Fisher's exact test. All statistical analyses were performed using the IBM SPSS software version 24.0 (IBM Corp., Armonk, NY, USA); p values < 0.05 were considered indicative of statistical significance.

Results

In all, 52 patients fulfilling the inclusion criteria were selected for the study. Patient characteristics are summarised in Table-1. Twenty-eight (53.8%) patients exhibited baseline dipstick albuminuria level of < 2+, while 24 (46.1%) patients exhibited baseline dipstick albuminuria level of ≥ 2+. The distribution of CKD stage was as follows: 17 (32.7%) patients were at stage 3a, 10 (19.2%) patients at stage 3b, 15 (28.8%) patients at stage 4, and 10 (19.2%) patients at non-dialysis stage 5.

Over 1-year follow-up period, 27 (51.9%) patients maintained their kidney function at the same level and 25 (48.1%) patients showed aggravation of kidney function. The RR of dipstick albuminuria level of ≥ 2+ for 1-year CKD progression was 2.16 (95% CI: 1.13-4.14, p = 0.02). The rate of ESRD progression in 1 year from CKD stage 3-4 was 31%.

Over 3-year follow-up, 17 (43.6%) patients maintained their kidney function at the same level and 22 (56.4%) patients showed aggravation of kidney function. The RR of dipstick albuminuria level of ≥ 2+ for 3-year CKD progression was 1.70 (95% CI: 0.73-3.97, p=0.21). The rate of ESRD progression in 3 year from CKD stage 3-4 was 39%

Table-1: Characteristics of the study population.

Patient characteristics	Values (n = 52)
Age (years), median, range	11.2 (0.3-17.9)
Gender	
Male	28 (53.9%)
Female	24 (46.1%)
Primary disease	
Cystic/hereditary/congenital diseases	19 (36.6%)
Interstitial nephritis/pyelonephritis	5 (9.6%)
Glomerulonephritis	1 (1.9%)
Secondary glomerulonephritis	26 (50.0%)
Miscellaneous	1 (1.9%)
Comorbidities	
Hypertension	29 (55.8%)
Anaemia	44 (84.6%)
Hb (g/dL), median, range	10.2 (6.3-14.3)
Albumin serum (g/L), median, range	4 (1.2-5.4)
Dipstick urine albumin at baseline	
< 2+	28 (53.8%)
≥ 2+	24 (46.1%)
CKD stage	
3a	17 (32.7%)
3b	10 (19.2%)
4	15 (28.8%)
5ND	10 (19.2%)

CAKUT: congenital anomalies of kidney and urinary tract; Hgb: haemoglobin; CKD: chronic kidney disease; CI: confidence interval.

Table-2: Patient outcomes at 1- and 3-year follow-up.

Outcome	Values n (%)
1-year CKD progression compared to baseline	n=52
- Stable	27 (51.9%)
- Deteriorate (without dialysis)	14 (26.9%)
- Deteriorate (with dialysis)	11 (21.2%)
3-year CKD progression compared to baseline	n=40
- Stable	17 (43.6%)
- Deteriorate (without dialysis)	11 (28.2%)
- Deteriorate (with dialysis)	11 (28.2%)
- Missing value*	1 (2.5%)

*patients who have not reached 3-year follow-up at our centre. CKD: chronic kidney disease.

in this study.

Discussion

In previous studies, the typical primary diseases responsible for CKD were congenital anomalies of kidneys and urinary tract (CAKUT) disorders (36%-50%) followed by glomerulonephritis (19%-32%),[14-16] whereas in our study population, glomerulonephritis had a greater proportion compared to CAKUT (51.9% and 46.2%, respectively).

In our study, 84.6% of paediatric patients with CKD were affected by anaemia, which was largely attributable to erythropoietin (EPO) and functional iron deficiencies.[17] This rate is higher than the previously reported prevalence of anaemia in children with CKD (range, 37%-63%).[18,19] Anaemia was poorly managed in our unit; the median haemoglobin level was 10.2 g/dL (range 6.3-14.3). Poor haemoglobin control in our patients was likely attributable to suboptimal utilisation of erythropoietin-stimulating agents (ESAs) and intravenous (IV) iron therapy. Owing to the gaps in national universal health coverage, our centre has a limited budget for treatment. Therefore, ESA therapy is limited to a maximum dosage of 50-100 unit/kg body weight twice weekly, while IV iron therapy is reserved only for patients with haemoglobin level < 100 g/L.[20]

Hypertension is another comorbidity of CKD, which was found in 55.8% of patients in our study. This finding is consistent with results of previous studies wherein 50-57.5% children with CKD were affected by hypertension.[18,21] Blood pressure control was not well achieved at our unit due to poor adherence to multiple antihypertensive medications. The high rate of anaemia and hypertension in children with CKD suggests considerable room for improving the quality of CKD care at our facilities.

In the North American Paediatric Renal Transplant Cooperative Study (NAPRTCS), children with CKD stage 2-4 experienced progression to ESRD with a rate of 17% at 1-year follow-up and 39% at 3-year follow-up; the median time to ESRD was 4.5 years.[16] Therefore, developing methods to predict cases at risk of CKD progression is necessary; these patients might be targeted with preventive interventions, such as improving blood pressure control and managing dietary intake of salt, phosphate, potassium and protein. In our study population, urine ACR evaluation based on immunoassay was not performed due to its high cost.[21] Given the resource-constrained setting, a dipstick was used for this purpose.

In a study involving screening of healthy children, the presence of albuminuria was found to be a risk factor for the development of ESRD within the next 13-17 years. Children with albuminuria were at a 3.24-times greater risk of developing ESRD, as compared to those without albuminuria.[22] As for biomarkers in adult patients with CKD, the severity of albuminuria shows a strong correlation with the risk of CKD progression to ESRD.[23,24] In adults with CKD who exhibit urine ACR 30, 300 and 1000 mg/g, the risk of developing ESRD was 4.87 (95% CI 2.3 - 10.3), 13.4 (95% CI 5.49 - 32.7) and 28.4 (95% CI 14.9 - 54.2), respectively, as compared to adults with CKD who exhibit urine ACR of 5 mg/g.[24] Nonetheless, there are currently no guidelines for predicting the 1-year and 3-year risk of CKD progression in children.

Our results suggested that dipstick albuminuria $\geq$ 2+ might not be a useful predictor of 3-year CKD progression in children. The results are consistent with Park et al. (2016), who compared dipstick albuminuria and urine ACR.[9] That study showed the dipstick test demonstrated poor sensitivity and high false-discovery rate for ACR $\geq$ 30 mg/g; therefore, measurement of albuminuria to predict CKD progression using urine ACR is better than using a dipstick.[9]

To the best of our knowledge, this is the first study that investigated the predictive value of baseline dipstick albuminuria for 1-year and 3-year CKD progression in Indonesian children. Nevertheless, some limitations of the study should be considered while interpreting the results. The sample size in our study was smaller as compared to previous studies that investigated correlation between albuminuria and CKD progression. For example, Fuhrman et al. (2017) investigated the association of albuminuria and proteinuria with renal disease progression in a cohort of 202 children with CKD.5 Moreover, comparing dipstick albuminuria with urine ACR and 24-hour albuminuria is necessary. The result of our study indicated that association could not be determined from nominal data (albuminuria dipstick <2+ and $\geq$2+). Ordinal data would be able to describe association if more categories are applied, i.e. albuminuria negative, trace, +1, +2, +3, and +4 toward 3-year-progression to CKD grade 3, grade 4, grade 5 without dialysis, and grade 5 with dialysis. However, quantitative data such as numerical data would describe decline of kidney function better.

Evaluation of baseline dipstick albuminuria level could be used as one of the methods to predict the risk of 1-year and 3-year CKD progression in children in resource-constrained settings.

Conclusion

In this study, baseline dipstick albuminuria level of $\geq$2+ was not associated with the progression of CKD. Our results

suggested that dipstick albuminuria might not be a useful predictor of 1-year and 3-year CKD progression in children.

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References

1. Mills KT, Xu Y, Zhang W, Bundy JD, Chen CS, Kelly TN, et al. A systematic analysis of worldwide population-based data on the global burden of chronic kidney disease in 2010. Kidney Int 2015;88:950-7. doi: 10.1038/ki.2015.230.
2. Lin HH, Tsai CW, Lin PH, Cheng KF, Wu HD, Wang IK, et al. Survival analysis of pediatric dialysis patients in Taiwan. Nephrology (Carlton) 2012;17:621-7. doi: 10.1111/j.1440-1797.2012.01613.
3. Wasung ME, Chawla LS, Madero M. Biomarkers of renal function, which and when? Clin Chim Acta 2015;438:350-7. doi: 10.1016/j.cca.2014.08.039.
4. Clark WF, Macnab JJ, Sontrop JM, Jain AK, Moist L, Salvadori M, et al. Dipstick proteinuria as a screening strategy to identify rapid renal decline. J Am Soc Nephrol 2011;22:1729-36. doi: 10.1681/ASN.2010111217.
5. Fuhrman DY, Schneider MF, Dell KM, Blydt-Hansen TD, Mak R, Saland JM, et al. Albuminuria, Proteinuria, and Renal Disease Progression in Children with CKD. Clin J Am Soc Nephrol 2017;12:912-20. doi: 10.2215/CJN.11971116.
6. Warady BA, Abraham AG, Schwartz GJ, Wong CS, Muñoz A, Betoko A, et al. Predictors of Rapid Progression of Glomerular and Nonglomerular Kidney Disease in Children and Adolescents: The Chronic Kidney Disease in Children (CKiD) Cohort. Am J Kidney Dis 2015;65:878-88. doi: 10.1053/j.ajkd.2015.01.008.
7. Matsushita K, van der Velde M, Astor BC, Woodward M, Levey AS, de Jong PE, et al. Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. Lancet 2010;375:2073-81. doi: 10.1016/S0140-6736(10)60674-5.
8. Methven S, MacGregor MS, Traynor JP, Hair M, O'Reilly DS, Deighan CJ. Comparison of urinary albumin and urinary total protein as predictors of patient outcomes in CKD. Am J Kidney Dis 2011;57:21-8. doi: 10.1053/j.ajkd.2010.08.009.
9. Park JI, Baek H, Kim BR, Jung HH. Comparison of urine dipstick and albumin:creatinine ratio for chronic kidney disease screening: A population-based study. PLoS One 2017;12:e0171106. doi: 10.1371/journal.pone.0171106.
10. KDIGO. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int 2013;3(Suppl 1):1-150.
11. Caravaca-Fontán F, Azevedo L, Luna E, Caravaca F. Patterns of progression of chronic kidney disease at later stages. Clin Kidney J 2018;11:246-53. doi: 10.1093/ckj/sfx083.
12. Flynn JT. 2017 AAP Guidelines for Childhood Hypertension. [Online] 2017 [Cited 2020 October 30]. Available from URL: https://solutions.aap.org/DocumentLibrary/pcowebinars/2017%20Hypertension%20Webinar.pdf
13. World Health Organization. Haemoglobin concentrations for the diagnosis of anaemia and assessment of severity. [Online] 2011 [Cited 2020 October 30]. Available from URL: https://www.who.int/vmnis/indicators/haemoglobin/en/
14. European Society for Paediatric Nephrologist. ESPN/ERA-EDTA Registry. [Online] 2016 [Cited 2020 October 30]. Available from URL: https://www.espn-reg.org/index.jsp
15. Hattori S, Yosioka K, Honda M, Ito H. The 1998 report of the Japanese National Registry data on pediatric end-stage renal disease patients. Pediatr Nephrol 2002;17:456-61. doi: 10.1007/s00467-002-0848-8.
16. NAPRTCS. North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS) 2011 Annual Dialysis Report. [Online] 2011 [Cited 2020 October 30]. Available from URL: https://naprtcs.org/system/files/2011_Annual_Dialysis_Report.pdf
17. Babitt JL, Lin HY. Mechanisms of anemia in CKD. J Am Soc Nephrol 2012;23:1631-4. doi: 10.1681/ASN.2011111078.
18. Al Riyami MS, Al Shehhi M, Al Sulaimi T, Al Mamary L, Al Maskari A, Al Ghaithi B, et al. Epidemiology and Outcome of CKD in Omani Children. Kidney Int Rep 2019;4:727-32. doi: 10.1016/j.ekir.2019.02.014.
19. Koshy SM, Geary DF. Anemia in children with chronic kidney disease. Pediatr Nephrol 2008;23:209-19. doi: 10.1007/s00467-006-0381-2.
20. Ambarsari CG, Trihono PP, Kadaristiana A, Tambunan T, Mushahar L, Puspitasari HA, et al. Five-year experience of continuous ambulatory peritoneal dialysis in children: a single center experience in a developing country. Med J Indones 2019;28:329-37. Doi: 10.13181/mji.v28i4.3807
21. Flynn JT, Mitsnefes M, Pierce C, Cole SR, Parekh RS, Furth SL, et al. Blood pressure in children with chronic kidney disease: a report from the Chronic Kidney Disease in Children study. Hypertension 2008;52:631-7. doi: 10.1161/HYPERTENSIONAHA.108.110635.
22. Lin CY, Huang SM. Childhood Albuminuria and Chronic Kidney Disease is Associated with Mortality and End-Stage Renal Disease. Pediatr Neonatol 2016;57:280-7. doi: 10.1016/j.pedneo.2015.09.013.
23. Amdur RL, Feldman HI, Gupta J, Yang W, Kanetsky P, Shlipak M, et al. Inflammation and Progression of CKD: The CRIC Study. Clin J Am Soc Nephrol 2016;11:1546-56. doi: 10.2215/CJN.13121215.
24. Gansevoort RT, Matsushita K, van der Velde M, Astor BC, Woodward M, Levey AS, et al. Lower estimated GFR and higher albuminuria are associated with adverse kidney outcomes. A collaborative meta-analysis of general and high-risk population cohorts. Kidney Int 2011;80:93-104. doi: 10.1038/ki.2010.531.