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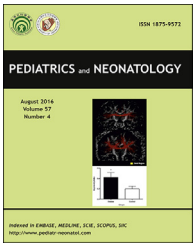

ORIGINAL ARTICLE

Childhood Albuminuria and Chronic Kidney Disease is Associated with Mortality and End-Stage Renal Disease

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Key Words
childhood heavy albuminuria;
chronic kidney disease;
congenital anomaly of kidney and urinary tract;
glomerulonephritis;
metabolic syndrome

Background: We do not yet fully grasp the significance of childhood albuminuria. Based on mass urinary screening (MUS) using albumin-specific dipsticks in school children, we studied the independent association of estimated glomerular filtration rate (eGFR) and albuminuria with mortality and end-stage renal disease (ESRD) in children with chronic kidney disease (CKD).
Methods: A prospective cohort of 5351 children with albuminuria detected by school MSU during the period 1992–1996, followed up to 2009.
Results: Cumulative mortality rate, prevalence of CKD, and ESRD were higher in children with albuminuria than those without. Albuminuria category was associated with the risk of mortality [hazard ratio (HR) 3.4] and ESRD (HR 3.24). Lower eGFR and albuminuria predicted mortality and ESRD among children with albuminuria and CKD. We found that being below a threshold of 45 mL/min/1.73 m^2 was significantly associated with ESRD. The highest renal function decline, along with the steepest slope of cumulative ESRD number, occurred in Stage 3, the critical point in renal progression. Risk factors for renal progression among different age groups with albuminuria were hypercholesterolemia and low serum albumin at 7–17 years of age. Beyond 18 years of age, besides the risk factor, a higher fasting blood sugar (BS) was also noted.
Conclusion: Childhood albuminuria is a risk factor for CKD in later life, albuminuria provides additional prognostic information, and complications of CKD should be defined in each case.

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1. Introduction

Chronic kidney disease (CKD) is recognized as a major global public health problem.[1,2] The prevalence and annual incidence of end-stage renal disease (ESRD) in Taiwan have risen dramatically since 1990,[1] with the nationwide prevalence of CKD and ESRD in adults at 11.93% and 0.15%, respectively.[1] For children, the annual incidence of ESRD was 8.12/million of age-related population.[3] With no definite statistical report of the annual incidence of CKD in children, adult data cannot be extrapolated to children without further study. It remains unclear whether higher ESRD incidence reflects a higher burden of renal progression from children to adults.

Heavy albuminuria is a risk factor. Several studies reported an association between albuminuria or estimated glomerular filtration rate (eGFR) and clinical outcomes in the general population.[4] Meta-analysis of observation study showed albuminuria to be an independent risk factor associated with mortality and kidney outcome.[2] Association between albuminuria and mortality was linear on the log-log scale:[2] eGFR and albuminuria were cumulatively associated with risk of mortality.[2] At any given GFR, graded mortality risk climbed with the amount of albuminuria, with the highest rates for those with overt and the lowest for those with negative albuminuria.[5,6] Studies of Taiwanese adults showed trace albuminuria by urine dipstick to be a powerful predictor of mortality.[5] Correlation between all-cause mortality risk and albuminuria in a cohort of approximately 500,000 Taiwanese showed a hazard ratio (HR) of 1.44 for all-cause mortality.[5] This result was similar to the Canadian cohort of nearly one million individuals with 2.1 all-cause mortality risk.[7] Still, the significance of childhood albuminuria is not fully understood, and no study has linked it with CKD. An increasing number of studies[8–10] called our attention to the importance of albuminuria in childhood CKD.

Albuminuria has been linked to a greater risk of future cardiovascular disease, renal disease, atherosclerosis, and cardiovascular disease mortality in adults.[11–14] However, no study linked it with childhood albuminuria. Among childhood ESRD cases in Taiwan, over the initial 5 years, cerebrovascular disease (14.81%), cardiovascular disease (12.11%), and infection (11.11%) were major causes of death.[3] Identifying and treating individual complications in early stages of CKD is increasingly being proposed for the prevention of childhood ESRD as well as cardiac and cerebrovascular events.[3,15,16]

Mass urinary screening (MUS) has been performed for Taiwanese elementary and junior high students since 1990.[17,18] Dipstick screening, as part of the office routine, offers an effective way to reach out to the public in improving awareness of CKD. In our MUS, sensitivity was 98.7% and specificity was 90.2% for albuminuria. Cases of heavy albuminuria were monitored closely from 1992 to 2008, enabling us to calculate mortality and renal progression risk for all five stages of CKD and to probe initial complications. Based on prior established research[19–23] and cohort, we analyzed mortality and percentage of complications in children according to CKD stage at first positive MUS with albuminuria and risk factors for renal progression among age groups.

2. Methods

2.1. MUS procedures

Health status measurement included measurement of height, weight, and blood pressure (BP). Three consecutive standardized BP measurements were recorded in the sitting position, using a standardized automatic oscillometer method. Midstream first-morning urine at home was obtained in order to avoid orthostatic proteinuria and it was sent by refrigerated vehicle to 21 local laboratories. Medical technicians ascertained pH, protein, occult blood, and glucose in urine samples via semiautomatic Ames CTK-200 with standardization.[17,18] Those testing positive underwent a second urinary albumin screening 10—15 days later. The first urine screening was done with an albumin-sensitive urine dipstick and sulfosalicylic acid. If it was $>$ 100 mg/dL, urinary albumin/creatinine (Cr) ratio (ACR) was performed simultaneously. Second urine samples from positive cases and serum samples were collected by public health nurses at local health stations in each township and district. Serum Cr was gauged by an automatic RA2000 serum analyzer and the international standard calibrated serum Cr assay. Serum from positive cases was sampled for baseline data twice per annum by urinary screening in the first semester, and from new cases in the second semester. Fasting time before sampling was over 8 hours. Baseline data included age, body weight, height, body mass index, BP, fasting blood sugar (BS), blood urea nitrogen, Cr, albumin, immunoglobulin (Ig)A, Complement 3 (C3), antistreptolysin O, and cholesterol. Pediatric nephrologists analyzed and identified grades of abnormalities. Heavy albuminuria was defined as urinary albumin $>$ 100 mg/dL by the albumin-specific paper dip strip method and ACR $>$ 200 mg/g.[5,17–19] In our MUS, the screening rate was 99.8%, sensitivity was 95.1%, and specificity was 90.2% for albuminuria.[17,18]

Follow-up began from August 1992. For individuals with albuminuria in MUS, all data were stored in a computer and analyzed each semester. If there was any change in the grade, individuals were notified as rapidly as possible. Because many positive individuals did not respond to the first notification, second and third notifications were sent. This system proved highly successful: there was a