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Urologic Care and Progression to End-Stage Kidney Disease: A Chronic Kidney Disease in Children (CKiD) Nested Case-Control Study.

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Summary

Introduction—Children with chronic kidney disease (CKD) risk progressing to end-stage kidney disease (ESKD). The majority of CKD causes in children are related to congenital anomalies of the kidney and urinary tract, which may be treated by urologic care.

Objective—To examine the association of ESKD with urologic care in children with CKD.

Study Design—Nested case-control study within the Chronic Kidney Disease in Children (CKiD) prospective cohort study that included children ages 1-16 years with non-glomerular causes of CKD. The primary exposure was prior urologic referral with or without surgical intervention. Incidence-density sampling matched each case of ESKD to up to 3 controls on duration of time from CKD onset, sex, race, age at baseline visit, and history of low birthweight. Conditional logistic regression analysis was performed to estimate rate ratios (RR) for the incidence of ESKD.

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Results—66 cases of ESKD were matched to 153 controls. Median age at baseline study visit was 12 years; 67% were male, 7% were black. Median follow-up time from CKD onset was 14.9 years. 70% received urologic care, including 100% of obstructive uropathy and 96% of reflux nephropathy diagnoses. Cases had worse renal function at their baseline visit and were less likely to have received prior urologic care. After adjusting for income, education, and insurance status, urology referral with surgery was associated with 50% lower risk of ESKD (RR 0.50 [95% Confidence Interval [CI] 0.26-0.997), compared to no prior urologic care (Figure). After excluding obstructive uropathy and reflux nephropathy diagnoses, which were highly correlated with urologic surgery, the association was attenuated (RR 0.72, 95% CI 0.24-2.18).

Conclusion—Within the CKiD cohort, children with non-glomerular causes of CKD often received urologic care. Urology referral with surgery was associated with lower risk of ESKD compared to no prior urologic care, but depended on specific underlying diagnoses.

Graphical Abstract

Keywords

Chronic kidney disease; end-stage kidney disease; urologic care; incidence-density sampling; nested case-control

Introduction

Chronic kidney disease (CKD) is estimated to affect 12-14% of the United States general population [1], with a lifetime incidence of up to 60% [2]. Among children, CKD is less common compared to adults, but with potentially more dire consequences for those it affects: progression to end-stage kidney disease (ESKD) results in a 30-fold increase in risk of death compared to age-matched healthy children [3, 4]. Even without reaching ESKD, CKD among children has been associated with heart disease [5], hypertension [6], fractures [7], impaired neurocognition [8], and poor growth [9]. Given the longer life expectancy of a child compared to an adult, the subsequent cumulative comorbidity burden associated with CKD progression can be significantly greater.

One modifiable risk factor for preventing CKD progression and improving outcomes is access to specialist care. Earlier care by a nephrologist has been shown to improve outcomes among both children [10, 11] and adults [12–15] at risk for ESKD. Multi-disciplinary teams, usually including a combination of nephrologists, dieticians, and primary care providers, also have been demonstrated to slow CKD progression compared to standard care among children [16]. The impact of access to a pediatric urologist, however, on CKD progression and outcomes has never been previously assessed. This is critical among children, because

the majority of pediatric CKD causes are non-glomerular in origin and related to congenital anomalies of the kidney and urinary tract (CAKUT) [17]. Recent large-scale epidemiologic data support a significant association between CAKUT in childhood and development of ESKD in adulthood [18].

The objective of this study was therefore, to assess the association between urologic care and development of ESKD in a prospective cohort of children with CKD. We hypothesized that receipt of urologic care would be associated with lower risk of ESKD.

Methods

Study Design and Data Source

This is a nested case-control study within the Chronic Kidney Disease in Children (CKiD) study, a multicenter prospective cohort study of children conducted at 54 pediatric nephrology centers across North America. The study has been previously described [5, 7, 8, 17, 19–21]. In brief, the study has enrolled two cohorts of participants aged 1-16 years with estimated glomerular filtration rate (eGFR) of 30-90 ml/min/1.73m²: the first from April 2005 to August 2009, and the second from February 2011 to March 2014. Each study site's Institutional Review Board approved the study protocol, and each participating family provided informed consent.

In 2015, completely de-identified data from CKiD was made publicly available through the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) website; these data were accessed and analyzed for this study. Our analysis of the de-identified dataset was determined not to constitute human subjects research by our institutional review board and was therefore exempt from oversight.

Participants

At enrollment into CKiD, participants were 1-16 years of age with an eGFR between 30 and 90 ml/min/1.73m² for the first cohort and between 45 and 90 ml/min/1.73m² for the second cohort. Participants underwent an initial baseline visit where detailed medical history, examination, blood pressure, eGFR, and laboratory values were obtained. Subsequent study follow-up visits were performed annually until need for renal replacement therapy (RRT) (*i.e.*, transplant or dialysis) or in a few cases, death. Because glomerular etiologies of CKD are unlikely to be referred to urology, this analysis was restricted to CKiD children with non-glomerular etiologies of CKD. The most common specific non-glomerular diagnoses as coded within CKiD include obstructive uropathy, reflux nephropathy, and aplastic/hypoplastic/dysplastic kidneys. Diagnoses were considered by CKiD to be mutually exclusive (*i.e.*, each child could only have one specific diagnosis). Participants lacking complete data on urologic care were excluded.

Selection of Cases and Controls

Cases were defined as individuals who developed ESKD, as defined by the need for RRT. Selection of the control group was performed using incidence-density sampling [22] using CKD onset reported by the participant at the baseline visit as the time origin and time from

CKD onset as the time metric. Incidence-density sampling produces odds ratios that are unbiased estimates of incidence rate ratios (RR) [23]. Eligible controls for each case consisted of participants without ESKD at the date the case developed ESKD. For each case, up to three eligible controls were matched on: time from CKD onset to follow-up, race (black versus non-black), sex, low birthweight (<2500g), and age at the baseline visit. Cases that were not able to be successfully matched were excluded since finding a comparable match is a key component of incidence-density sampling.

Exposures and Covariates

The primary exposure was parent or patient report of prior urologic care consisting of urologic referral with or without surgical intervention. Thus, our exposure was composed of three mutually exclusive groups: no referral, referral without surgery, and referral with surgery.

Other potential confounders in the adjusted models included baseline household income (\$36,000/year, \$36,001-\$75,000/year, >\$75,000/year), highest maternal education (college graduate versus not), and participant insurance status (none, non-private/public, private) at time of enrollment into CKiD. The few missing values for income and maternal education were grouped as a dummy variable. Data were not available on geographic region or center characteristics.

Statistical Analysis

Conditional logistic regression analysis of matched sets of cases and controls was used to assess associations of ESKD with our exposure of interest. We analyzed an initial unadjusted model and an adjusted model, which included income, maternal education, and insurance status.

Two post-hoc sensitivity analyses were performed. First, we initially noted 7 participants who reported urologic procedures but no referral. As this is unlikely and attributable to recall error, these 7 participants were considered to have received urologic referral in the primary analysis. A sensitivity analysis was conducted with these 7 participants excluded. Second, as several specific diagnoses completely determined (*e.g.*, obstructive uropathy) or were highly correlated (*e.g.*, reflux nephropathy) with referral status, we performed a sensitivity analysis removing these diagnoses.

All analyses were performed with Stata v.14 (StataCorp, College Station, TX), with a two-tailed alpha of 0.05.

Results

Of 483 participants meeting eligibility criteria with non-glomerular CKD etiology within CKiD, 76 developed ESKD. Of these, 66 cases of ESKD were successfully matched to 153 controls according to our multiple criteria. The remaining 10 cases could not be matched to a suitable control. Median age at the enrollment baseline visit was 12 years; 67% were male and 7% were black (Table 1). Median follow-up time from CKD onset was 14.9 years. Cases had worse markers of kidney function at CKiD study enrollment with lower eGFRs and

higher urine protein-to-creatinine ratios. Cases were also less likely to have received urologic care prior to enrollment than controls.

When participants were stratified by type of urologic care received, 67 received no care, 26 received a referral without surgery, and 126 received a referral with surgery (Table 2). At enrollment into CKiD, those with no prior urologic care had lower eGFR but similar urine protein-to-creatinine ratio compared with the other two exposure groups. No associations were seen between urologic care and household income, maternal education, or insurance status. Among specific non-glomerular diagnoses, 100% (45 of 45) of participants with obstructive uropathy and 96% (47 of 49) of participants with reflux nephropathy reported urologic referral with or without surgery. Frequencies of specific diagnoses and sub-diagnoses within “other” are shown in the Supplemental Table.

On unadjusted regression analysis, urologic referral with surgery was associated with a 52% reduction in risk of ESKD (RR 0.48, 95% Confidence Interval [CI] 0.25-0.91, $p=0.03$; Table 3) compared to no urologic care. This association remained after adjustment for income, education, and insurance status, with a 50% risk reduction associated with urologic referral with surgery (RR 0.50, 95% CI 0.26-0.997, $p=0.049$). Children who had a urologic referral without surgery had a risk of ESKD comparable to that of children with no reported urologic care.

In the first sensitivity analysis, excluding those participants with possibly misclassified referral information did not change point estimates (data not shown). In the second sensitivity analysis, exclusion of participants with obstructive uropathy or reflux nephropathy attenuated the association between urologic referral with surgery and ESKD (RR 0.72, 95% CI 0.24-2.18, $p=0.56$), compared to no referral.

Discussion

We have shown that receipt of urologic care with surgical intervention, compared to no urologic care, was significantly associated with decreased progression to ESKD for children who develop CKD secondary to non-glomerular disease pathologies. These children face a potentially life-altering burden of morbidity and even mortality, compared to their healthy peers. Identification of modifiable risk factors has thus been important in efforts to slow CKD progression. However, our results must be interpreted in light of possible residual confounding or effect modification from specific underlying diagnoses.

We found that the strongest point estimate for decreased risk of progression was associated with urologic care with surgery. Since we found no significant difference between participants who reported a referral but no surgery and those who reported no urologic care, surgical intervention appeared to be a potential mechanism with which a reduced risk of ESKD was associated. However, we were unable to fully adjust for specific non-glomerular diagnosis, given that certain diagnoses were highly correlated with referral status and thus the positivity assumption was violated. This is important given the heterogeneity of disease pathologies that constitute non-glomerular etiologies, including CAKUT [17]. Within CAKUT, the most common subtypes include obstructive uropathy, such as posterior urethral

valves, and reflux nephropathy. Both of these specific primary diagnoses may require surgical intervention (*e.g.*, valve ablation or ureteral reimplantation, respectively) more than other CAKUT diagnoses, such as renal aplasia/dysplasia/hypoplasia. Indeed, for diagnoses such as posterior urethral valves, surgical intervention is paramount and the clinical standard for preservation of renal function.

Reassuringly, we found that 98% of our matched participants with obstructive uropathy reported having undergone urologic surgery. Similarly, 84% of matched participants with reflux nephropathy reported undergoing surgery. Despite most of these children having undergone urologic surgery, however, some still progressed to ESKD. The natural history of the underlying disease processes, rather than urologic intervention, may therefore appear to dictate the progression of renal deterioration in these select children. However, because no adequate comparison could be made against children with obstructive uropathy or reflux nephropathy who received no urologic surgery, our results must be interpreted as exploratory with need for future validation.

After excluding those specific diagnoses that were highly correlated with urologic surgery, we found that the association between receipt of urologic surgery and ESKD was attenuated and no longer significant. This may be due in part to the smaller sample size, as well as the fact that the remaining non-glomerular diagnoses, such as renal aplasia/hypoplasia/dysplasia, seldom require urologic surgical management. Studies of solitary functional kidneys suggest that renal injury may result in 25-50% of children who have an isolated solitary functional kidney [24, 25]. Preservation of renal function in these diagnoses may be more medical, such as intensified control of blood pressure [6], rather than surgical. When surgery is indicated, such as for removal of a poorly-functioning dysplastic renal moiety, it is thus not surprising that renal outcomes are unaffected.

In certain other urologic conditions, associations and trends have been noted between appropriate surgery and reductions in CKD development or progression. In spina bifida, for example, a cross-sectional study observed increasing nationwide temporal rates of CKD simultaneously with declining rates in spina-bifida-related urological surgery [26]. A systematic review found bladder augmentation for adult neurogenic bladders to be associated with stable renal function [27]. Similarly, in nephrolithiasis, kidney stones are associated with higher risk of incident CKD [28, 29], while surgical procedures to remove the stones have not been associated with increased incident CKD [29]. Preservation of renal function through surgery may therefore depend on the underlying condition. Caution must be given, however, to the other non-renal risks of surgery that may counterbalance the preservation of renal function. Determining the appropriate surgery remains a case-by-case determination with necessary joint decision-making between the urologist and the patient or patient's family.

Our study has several strengths that differentiate it from previous studies. First, we were able to study the potential association between ESKD and prior urologic care. Previous studies of specialist care among children at risk for ESKD have predominantly examined associations with nephrologic care [10–15, 30] or multi-disciplinary care, excluding urology [16]. Second, we were able to adjust for social determinants of health. One prior study examined

how pediatric access to a urologist in California varied by insurance status [31], but the disease pathology mentioned was cryptorchidism and not one that affected long-term renal function. In our study, urologic care was not associated with insurance status, income, or maternal education at time of study enrollment. Additional research is needed to explore the mechanisms through which social determinants of health, such as income [20], can affect renal outcomes. Third, we were able to utilize the largest prospective cohort study of children with CKD within North America. Fourth, our study design of a nested case-control study allowed an unbiased estimate of the rate ratio for the effect of urologic care on the rate of ESKD. One previous CKiD study reported the number of urology referrals and procedures [17], but it did not examine their association with ESKD, was a cross-sectional study, and only included the first cohort enrolled in CKiD.

Our study does have several limitations. First, CKiD did not enroll its participants at the time of CKD onset. Therefore, recall bias at the baseline visit is possible, and misclassification of exposures may be present. For example, if more cases incorrectly recalled absence of urology exposure than controls at the baseline CKiD visit, results could be biased away from the null. However, to further minimize differences between cases and controls in time since CKD onset, we also matched on several covariates and additionally conducted a sensitivity analysis of potential misclassified exposures with no change in point estimate. Second, we did not have data on initial disease severity at CKD onset. However, since more severe cases are more likely to be referred to urology, and risk of ESKD is greater in these more severe cases, there is the possibility that our estimates are conservative and biased towards the null. Third, CAKUT often can have overlapping diagnoses, such as both obstructive uropathy and renal dysplasia. This could bias results either towards or away from the null. For example, a case classified with renal dysplasia in CKiD but secondary to posterior urethral valves who received urologic care, could be matched with a control classified with renal dysplasia alone who did not receive urologic care. This would bias an association towards the null, as seen in our second sensitivity analysis. Unfortunately, CKiD only assigns one specific underlying diagnosis per participant. Fourth, because the time metric for this study was time from CKD onset until ESKD, potentially important intermediaries along the CKD progression pathway such as medications or timing of surgery were not included in the analysis as adjustment for such intermediate variables can induce collider bias [32], which can be towards or farther from the null. Furthermore, despite the stringent matching criteria for cases and controls, this is still an observational study with its inherent selection biases and unmeasured confounders. For example, an unmeasured confounder in CKiD is hospital characteristics, which, without being matched across cases and controls, can bias the results in either direction, depending on whether the case or control received care at a higher-quality hospital. Matched characteristics, such as race, are essentially removed from being analyzed, but this sharpens the comparison of cases versus controls in relation to the exposure of interest. Lastly, because CKiD is a highly referred cohort of children already diagnosed with CKD, the results may not be generalizable to all children born with CAKUT, since not all develop CKD. Further study in children with CAKUT without CKD is certainly warranted. However, since prevention of ESKD is a universally common goal, a referral to urology is still recommended. Even the delay of ESKD offers a substantial improvement in the patient's quality of life [33].

In summary, our results suggest that for children with non-glomerular causes of CKD, receipt of urologic surgery was associated with lower progression to ESKD compared to no urologic care. However, this association may be modified by the specific underlying diagnosis, whose natural history may ultimately determine the fate of kidney function in these children.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

CAKUT	congenital anomalies of the kidney and urinary tract
CKD	chronic kidney disease
CKiD	Chronic Kidney Disease in Children
ESKD	end-stage kidney disease
RR	relative risk
RRT	renal replacement therapy

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Table 1.

Characteristics of cases and controls.

Variable	Controls	Cases	p
Total No.	153	66	-
Age at cohort entry [*] (yr)	12 (9-15)	12 (9-14)	0.78
Male sex [*]	68 (104)	65 (43)	0.68
AA race [*]	6 (9)	11 (7)	0.22
Low birthweight [*] (<2500g)	11 (16)	18 (12)	0.12
Household income			0.22
<=\$36k/yr	25 (39)	38 (25)	
\$36k-\$75k/yr	37 (56)	30 (20)	
>\$75k/yr	37 (57)	30 (20)	
Missing	1 (1)	1 (1)	
Maternal education			0.90
Less than college graduate	68 (104)	71 (47)	
College graduate	30 (46)	27 (18)	
Missing	2 (3)	2 (1)	
Insurance			0.56
None	3 (4)	2 (1)	
Non-private/public	31 (47)	38 (25)	
Private	67 (102)	61 (40)	
eGFR at baseline visit (ml/min/1.73m ²)	49 (39-64)	33 (28-39)	<0.001
CKD-stage at cohort entry			<0.001
eGFR <30	7 (10)	32 (21)	
eGFR 30-59	63 (97)	67 (44)	
eGFR ≥60	30 (46)	1 (1)	
Urine protein to creatinine ratio at cohort entry (mg/mg)	0.3 (0.1-0.6)	1.3 (0.5-2.1)	<0.001
Prior urologic care			0.01
No referral	26 (40)	41 (27)	
Referral without surgery	10 (15)	17 (11)	
Referral with surgery	64 (98)	42 (28)	
Follow-up from CKD onset (yr) [*]	14.9 (11.6-16.7)	14.6 (11.3-16.7)	0.87
Specific Diagnoses			0.03
Obstructive Uropathy	22 (34)	17 (11)	
Reflux Nephropathy	27(41)	12 (8)	
Aplastic/hypoplastic/dysplastic kidneys	20 (30)	23 (15)	
Other	31 (48)	48 (32)	

Values are median (interquartile range) or % (n). P-values are from Wilcoxon rank-sum, chi-square, or Fisher exact tests.

^{*} matched characteristic

CKD = chronic kidney disease; AA = African-American; eGFR = iohexol or estimated glomerular filtration rate

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Table 2.

Characteristics by urologic care status.

Variable	No referral	Referral without surgery	Referral with surgery	p
Total No.	67	26	126	-
Age at cohort entry (yr)	11 (8-14)	12 (7-15)	12 (10-15)	0.40
Male sex	60 (40)	50 (13)	75 (94)	0.02
AA race	2 (1)	12 (3)	10 (12)	0.08
Low birth weight*(<2500g)	19 (13)	19 (5)	8 (10)	0.04
Household income				0.20
<=\$36k/yr	37 (25)	35 (9)	24 (30)	
\$36k-\$75k/yr	30 (20)	31 (8)	38 (48)	
>\$75k/yr	31 (21)	31 (8)	38 (48)	
Missing	1 (1)	4 (1)	0 (0)	
Maternal education				0.55
Less than college graduate	75 (50)	65 (17)	67 (84)	
College graduate	22 (15)	35 (9)	32 (40)	
Missing	3 (2)	0 (0)	2 (2)	
Insurance				0.87
None	3 (4)	0 (0)	1 (1)	
Non-private/public	33 (42)	38 (10)	30 (20)	
Private	63 (80)	62 (16)	69 (46)	
eGFR at baseline visit (ml/min/1.73m ²)	37 (32-49)	44 (36-54)	48 (34-67)	<0.001
CKD-stage at cohort entry				<0.001
eGFR <30	19 (13)	12 (3)	12 (15)	
eGFR 30-59	75 (50)	85 (22)	55 (69)	
eGFR ≥60	6 (4)	4 (1)	33 (42)	
Urine protein to creatinine ratio at cohort entry (mg/mg)	0.4 (0.1-1.8)	0.6 (0.1-1.4)	0.5 (0.1-1.1)	0.72
Follow-up from CKD onset (yr)	12.9 (11.2-16.6)	12.5 (8.7-16.4)	15.1 (12.2-16.9)	0.03
Specific Diagnoses				<0.001
Obstructive Uropathy	0 (0)	4 (1)	35 (44)	
Reflux Nephropathy	3 (2)	23 (6)	33 (41)	
Aplastic/hypoplastic/dysplastic kidneys	30 (20)	35 (9)	13 (16)	
Other	67 (45)	38 (10)	20 (25)	

Values are median (interquartile range) or % (n). P-values are from Kruskal-Wallis, chisquare, or Fisher exact tests.

CKD = chronic kidney disease; AA = African-American; eGFR = iohexol or estimated glomerular filtration rate

Table 3.

Conditional logistic regression models analyzing risk of ESKD.

	RR	95% CI	p
Unadjusted Model			
No referral	<i>referent</i>		
Referral without surgery	1.19	0.47-3.01	0.71
Referral with surgery	0.48	0.25-0.91	0.03
Adjusted Model *			
No referral	<i>referent</i>		
Referral without surgery	1.09	0.40-2.93	0.87
Referral with surgery	0.50	0.26-0.997	0.049

* adjusted for: income, maternal education, insurance status.

ESKD = end-stage kidney disease; RR = rate ratio; CI = confidence interval.