Kidney Stone Disease and Progression Risk in Autosomal Dominant Polycystic Kidney Disease: A *Post Hoc* Analysis of OVERTURE

Berenice Y. Gitomer[1], *Michel Chonchol*[1], *Xiaolei Zhou*[2], *Diana Garbinsky*[2], *Jinyi Wang*[2], *Sasikiran Nunna*[3], *Ancilla W. Fernandes*[3], *and Dorothee Oberdhan*[3]

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Introduction

Autosomal dominant polycystic kidney disease (ADPKD) is characterized by the formation and growth of cysts that result in kidney volume expansion, parenchymal damage, and gradual loss of kidney function.[1] Progression is highly variable among affected individuals, necessitating methods for prognostic estimation.[2] Prediction models on the basis of magnetic resonance imaging-determined total kidney volume in conjunction with patient age or incorporating genetic and clinical data into a scoring algorithm are available.[3,4] In the clinic, proteinuria and symptoms such as hematuria and urinary tract infection are useful indicators of a rapidly progressive phenotype.[5] Nephrolithiasis is a common ADPKD complication, present in 20%–35% of patients,[1] but its potential relationship with progression risk has not been systematically evaluated. Accordingly, we compared ADPKD progression in patient subgroups with and without a history of kidney stone disease (KSD).

Methods

Data were from a global, longitudinal, observational study (OVERTURE; NCT01430494) of patients with ADPKD receiving care in routine clinical settings before the commercial availability of tolvaptan. The design and primary results of OVERTURE have been reported.[6] The study cohort (N=3409) represented a broad spectrum of disease progression (CKD stages G1–G5) and demographic characteristics (*e.g.*, ages 12–78 years) at baseline and was enriched for risk factors for rapid progression.

Data on adult participants with or without a history of KSD, who were not in ESKD (baseline eGFR ≥15 ml/min per 1.73 m^2), and who had 1-year data on change from baseline in eGFR or height-adjusted total kidney volume (htTKV) were extracted (Table 1). To account for potential confounding, participants with KSD were matched with up to four participants without KSD by baseline age (±2 years), sex, race/ethnicity, eGFR (±5 ml/min per 1.73 m^2), CKD stage (G1, G2, G3a, G3b, G4), and htTKV (±150 ml/m). Participants with KSD had a wide range in duration since first diagnosis of KSD (from <1 to 44 years), and so, the study analyses were performed for subgroups defined by time since first KSD diagnosis: (*1*) <5 years, (*2*) 5 to <10 years, and (*3*) ≥10 years. These time intervals since KSD diagnosis were based on the possible responses available to study participants when surveyed about their medical histories.

Counts were tabulated for the weighted proportions of matched participants with or without KSD who experienced a composite endpoint of two clinically relevant indicators of disease progression (*i.e.*, had both ≥25% decline in eGFR and >7% increase in htTKV) at the 12-month follow-up. Annual growth of >7% in htTKV was chosen as an indicator of rapid progression to be consistent with our previous analyses of data from the Halt Progression of Polycystic Kidney Disease study[7] and from the Tolvaptan Efficacy and Safety in Management of ADPKD and Its Outcomes 3:4 trial.[8] The association between KSD and the composite endpoint was examined using conditional logistic regression models that account for variable matching ratios.[9]

[1]Division of Renal Diseases and Hypertension, University of Colorado School of Medicine, University of Colorado Anschutz Medical Campus, Aurora, Colorado
[2]RTI Health Solutions, Research Triangle Park, North Carolina
[3]Otsuka Pharmaceutical Development & Commercialization, Inc., Rockville, Maryland

Correspondence: Dr. Berenice Y. Gitomer, email: berenice.gitomer@cuanschutz.edu

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Table 1. Weighted and unweighted counts of matched patients by cohort, time since first diagnosis of kidney stone disease, and outcome

Outcome/Time since First Diagnosis of KSD	With KSD	Without KSD Weighted[a]	Without KSD Unweighted
Composite endpoint at month 12			
<5 yr	34/99 (34.3%)	38/99 (38.0%)	71/193 (36.8%)
5 to <10 yr	25/52 (48.1%)	21/52 (39.6%)	38/105 (36.2%)
≥10 yr	50/95 (52.6%)	35/95 (36.8%)	63/176 (35.8%)
≥25% decline in eGFR from baseline to month 12			
<5 yr	6/99 (6.1%)	7/99 (7.1%)	13/193 (6.7%)
5 to <10 yr	3/52 (5.8%)	4/52 (7.9%)	6/105 (5.7%)
≥10 yr	11/95 (11.6%)	11/95 (11.1%)	15/176 (8.5%)
>7% increase in htTKV from baseline to month 12			
<5 yr	28/99 (28.3%)	33/99 (33.0%)	62/193 (32.1%)
5 to <10 yr	22/52 (42.3%)	18/52 (33.7%)	33/105 (31.4%)
≥10 yr	43/95 (45.3%)	28/95 (29.4%)	54/176 (30.7%)

htTKV, height-adjusted total kidney volume; KSD, kidney stone disease.
[a]Each patient with kidney stone disease was matched with up to four patients without kidney stone disease. Consequently, counts and percentages for patients without kidney stone disease were weighted using 1/(number of matches).

Results

The initial matched analysis set included 250 patients with KSD and 478 without KSD. Of the 250 with KSD, the first diagnosis of KSD was <5 years before baseline in 99 (39.6%), 5 to <10 years before baseline in 52 (20.8%), and ≥10 years before baseline in 95 (38.0%) (Table 1). Four participants (1.6%) were missing the time since first KSD diagnosis. The proportion of patients who still had KSD at baseline was lower in the subgroups with longer times since first KSD diagnosis (<5 years: 48.5%; 5 to <10 years: 32.7%; ≥10 years: 22.1%).

The subgroup with <5 years since first KSD diagnosis was notably younger and with a higher mean baseline eGFR compared with the other subgroups (Supplemental Table 1). However, within each subgroup, baseline characteristics were generally balanced between matched cohorts with and without a history of KSD, as indicated by weighted absolute standardized mean differences of ≤0.2 (Supplemental Table 2).

The percentage of participants with KSD who met the composite endpoint was greater than that for participants without KSD in the two subgroups with at least 5 years since their first KSD diagnosis (Table 1). The differences were driven by the proportions of patients with >7% increase in htTKV from baseline to month 12, whereas there were no substantial differences between the cohorts for ≥25% eGFR decline at month 12. The proportions of participants with KSD who experienced the composite endpoint or >7% increase in htTKV alone were higher in the subgroups with greater time since first KSD diagnosis. Absolute and percentage changes in htTKV to month 12 also differentiated between participants without KSD and the subgroups with at least 5 years since the first KSD diagnosis (Supplemental Table 3).

In the conditional logistic regression models performed for the composite endpoint, the adjusted odds ratio comparing cohorts increased from 1.11 (in the subgroup of <5 years since KSD diagnosis) to 2.06 (in the subgroup of ≥10 years) and was significant at $P < 0.05$ for those with ≥10 years since first KSD diagnosis (Table 2), supporting a higher likelihood of reaching the composite endpoint of disease progression for patients with KSD compared with matched patients without KSD.

Table 2. Adjusted odds ratio estimates from conditional logistic regression models for the composite endpoint

Time Since First Diagnosis of KSD, yr	Odds Ratio Estimate (with KSD versus without KSD, 95% CI); *P* Value
<5	1.11 (0.62 to 1.99); 0.721
5 to <10	1.45 (0.67 to 3.14); 0.341
≥10	2.06 (1.12 to 3.77); 0.019

The conditional logistic regression models accounted for age, sex, race, eGFR, CKD stage, and height-adjusted total kidney volume by conditioning on the matched sets and adjusted for the following additional variables as regression covariates: cohort (with/without kidney stone disease), baseline body mass index, use of antihypertensive medications with/without angiotensin-converting enzyme inhibitors/angiotensin 2 receptor blockers, use of antibiotics, history of cardiac disorders, urine albumin excretion, history of hematuria, and history of urinary tract infection. CI, confidence interval; KSD, kidney stone disease.

Discussion

These analyses suggest an increased likelihood of rapid disease progression in patients with ADPKD with a long history of KSD. Previously, research conducted in rodent models of polycystic kidney disease suggested a mechanistic basis for accelerated disease progression in the presence of nephrolithiasis.[10] The findings of our study are limited by the *post hoc* design, small sample sizes, and the short (1-year) follow-up. The fact that differences in progression endpoints were observed over such a short follow-up, however, is suggestive and warrants further study. Despite the limitations, the data support further evaluation of KSD, with consideration of time since KSD onset, as a prognostic factor in ADPKD.

Disclosures

Disclosure forms, as provided by each author, are available with the online version of the article at http://links.lww.com/KN9/A605.

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Author Contributions

Conceptualization: Michel Chonchol, Ancilla W. Fernandes, Berenice Y. Gitomer, Sasikiran Nunna, Dorothee Oberdhan.
Data curation: Diana Garbinsky, Jinyi Wang, Xiaolei Zhou.
Formal analysis: Diana Garbinsky, Jinyi Wang, Xiaolei Zhou.
Methodology: Michel Chonchol, Ancilla W. Fernandes, Diana Garbinsky, Berenice Y. Gitomer, Sasikiran Nunna, Dorothee Oberdhan, Jinyi Wang, Xiaolei Zhou.
Writing – review & editing: Michel Chonchol, Ancilla W. Fernandes, Diana Garbinsky, Berenice Y. Gitomer, Sasikiran Nunna, Dorothee Oberdhan, Jinyi Wang, Xiaolei Zhou.

Data Sharing Statement

Anonymized data created for the study are or will be available in a persistent repository upon publication. To submit inquiries related to Otsuka clinical research, or to request access to individual participant data (IPD) associated with any Otsuka clinical trial, please visit https://clinical-trials.otsuka.com/. For all approved IPD access requests, Otsuka will share anonymized IPD on a remotely accessible data sharing platform.

Supplemental Material

This article contains the following supplemental material online at http://links.lww.com/KN9/A604.

Supplemental Table 1. Baseline characteristics by years since first diagnosis of kidney stone disease.

Supplemental Table 2. Baseline characteristics of participants without kidney stone disease by matched subgroup.

Supplemental Table 3. Summary of eGFR and htTKV by matched subgroups of years since first diagnosis of kidney stone disease.

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