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The impact of asymptomatic kidney stones on disease progression in autosomal dominant polycystic kidney disease

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Abstract

Background Autosomal Dominant Polycystic Kidney Disease (ADPKD) is a common hereditary disorder leading to end-stage kidney disease due to the progressive formation of renal cysts. Nephrolithiasis is a frequent complication of ADPKD, with a prevalence significantly higher than in the general population. However, its role in disease progression remains underexplored. This study investigates the impact of asymptomatic nephrolithiasis on kidney function decline in ADPKD patients.

Methods A retrospective cohort of 195 ADPKD patients was followed at our nephrology clinic. Of these, 85 patients had nephrolithiasis (N+), and 110 did not (N-). Data on demographic characteristics, biochemical parameters, and kidney function were collected. ΔeGFR (change in eGFR over time) served as the primary outcome. Statistical analyses, including correlation and multiple linear regression, were performed to assess the predictors of ΔeGFR.

Results The N + group exhibited a significantly greater decline in kidney function compared to the N- group (ΔeGFR: 16.53 vs. 12.82 mL/min/1.73 m^2, $p = 0.008$). Lower calcium levels were observed in the N + group ($p = 0.007$), potentially reflecting metabolic abnormalities linked to nephrolithiasis. Nephrolithiasis was independently associated with kidney function decline (B = 3.159, $p = 0.038$). Follow-up duration was strongly associated with ΔeGFR ($p < 0.001$). Age showed a trend toward significance but did not reach statistical significance.

Conclusion Asymptomatic nephrolithiasis is associated with accelerated kidney function decline in ADPKD patients. These findings highlight the importance of monitoring kidney stones, even in the absence of symptoms, to mitigate their impact on renal dysfunction.

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Background

Autosomal Dominant Polycystic Kidney Disease (ADPKD) is one of the most common hereditary kidney disorders, with a prevalence of approximately 1:400 to 1:1000 live births, affecting millions worldwide [1]. ADPKD is characterized by the progressive formation of fluid-filled cysts in the kidneys, leading to a decline in renal function. It is a major cause of end-stage renal disease (ESRD), with more than 50% of patients reaching ESRD by the age of 60 [1, 2]. Mutations in the PKD1 and PKD2 genes, which regulate renal tubular epithelial cell function, are primarily responsible for the pathogenesis of ADPKD, contributing to abnormal cyst formation and progressive kidney damage [3].

Nephrolithiasis (kidney stone disease) is a frequent complication of ADPKD, occurring in 20–36% of patients, significantly higher than the approximately 8–10% prevalence observed in the general population [4–6]. The formation of kidney stones in ADPKD is often attributed to anatomical distortions caused by cysts and metabolic abnormalities, including urinary stasis and hypercalciuria [4, 5, 7]. Although these stones can remain asymptomatic, they may still contribute to disease progression by exacerbating renal dysfunction, causing urinary tract infections, hematuria, or obstruction [6, 8]. Despite the prevalence of nephrolithiasis in ADPKD, studies specifically investigating the impact of asymptomatic stones on the progression of chronic kidney disease are limited [8].

The role of asymptomatic kidney stones in ADPKD has not been thoroughly examined, creating a gap in the understanding of their clinical significance. Most current research focuses on symptomatic stone cases, leaving a need for further exploration of how asymptomatic stones may accelerate kidney function decline [1, 4, 5]. This study aims to assess the potential contribution of asymptomatic nephrolithiasis to the progression of renal dysfunction in ADPKD patients, while addressing key gaps in the literatüre, including the lack of consensus on imaging standards and comparative prevalence data.

Methods

Ethical statement

This study was in accordance with the ethical principles of the Declaration of Helsinki, the Good Clinical Practice guidelines of the International Conference on Harmonization, and local regulatory requirements. The study was approved by the local ethics committee with the approval/date and number: 13 March, 2024, 2024/19-E-54022451-050.04-146750.

Study design and population

This retrospective cohort study included patients diagnosed with Autosomal Dominant Polycystic Kidney Disease (ADPKD) who were followed at our nephrology clinic. Initially, 442 patients were under follow-up. After applying exclusion criteria, 195 patients were included in the final analysis: 85 with kidney stones (N+) and 110 without (N-). The diagnosis of ADPKD and patient selection criteria were based on the KDIGO guidelines, which represent current clinical standards for managing and monitoring ADPKD [9]. The inclusion criteria required a follow-up period of more than 90 days, a diagnosis of ADPKD according to current clinical guidelines, and confirmation of kidney stone diagnosis via imaging techniques such as computed tomography or ultrasonography. We chose a follow-up period of at least 90 days to ensure meaningful changes in eGFR could be observed, which aligns with standard clinical practices for kidney function monitoring. Additionally, this threshold allowed us to exclude patients with very short follow-up durations or those who visited the clinic only once, ensuring data reliability. Most patients with follow-up periods exceeding 90 days were monitored for over a year, capturing significant renal function changes. Furthermore, this criterion balanced the need for robust data while maintaining a sufficient sample size for analysis.

Exclusion criteria

Patients younger than 18 or older than 75 years of age, those with an initial estimated glomerular filtration rate (eGFR) below 15 ml/min/1.73 m^2, individuals who had undergone kidney stone surgery, those with a history of acute kidney injury, patients with a follow-up period shorter than 90 days, and individuals lacking available laboratory data were excluded from the study.

Data collection

Patients' demographic data, clinical history, laboratory results, and imaging findings were collected from medical records. eGFR was calculated using the CKD-EPI formula [10] at baseline and follow-up. The presence of kidney stones was confirmed using imaging techniques such as computed tomography (CT) or ultrasonography. All patients underwent at least one computed tomography (CT) imaging study to ensure accurate confirmation of kidney stones.

Statistical analysis

Descriptive statistics were used to summarize the baseline characteristics of the participants. Continuous variables were expressed as means with standard deviations or medians with interquartile ranges, depending on the distribution of the data. The normality of the data was assessed using the Kolmogorov-Smirnov test, along with skewness and kurtosis values, and visual inspection of histogram curves. Since the variables were not normally distributed, non-parametric tests were used for statistical

analysis. Differences between patients with and without kidney stones were evaluated using the Mann-Whitney U test. A p-value of < 0.05 was considered statistically significant. All analyses were conducted using SPSS Statistics for Windows (IBM Corp., Armonk, NY).

Results

Study Population

Initially, 442 patients diagnosed with Autosomal Dominant Polycystic Kidney Disease (ADPKD) were evaluated for inclusion in the study. After evaluating 442 patients, 169 were excluded due to a follow-up period of less than 90 days, 17 patients were excluded because their initial estimated glomerular filtration rate (eGFR) was below 15 ml/min/1.73 m^2, and 7 patients were excluded for being older than 75 years. After applying these criteria, 249 patients remained. From this cohort, 15 patients were excluded due to unavailable data, 24 patients were excluded because they experienced acute kidney injury during the follow-up, and 15 patients were excluded due to having undergone surgery for kidney stones. This left a final cohort of 195 patients: 85 nephrolithiasis-positive (N+) and 110 nephrolithiasis-negative (N-) patients. The patient selection process is illustrated in the flow chart in Fig. 1.

Demographic and clinical characteristics

The median age was 46.48 years (IQR: 35.60-55.71) in the N + group and 49.04 years (IQR: 38.36–58.87) in the N- group, with no statistically significant difference between the two groups ($p = 0.132$). The follow-up period was also similar between the groups, with a median of 1496.5 days (IQR: 897–2138) in the N + group and 1102 days (IQR: 626–2183) in the N- group ($p = 0.133$). There were no significant differences between the groups in terms of gender distribution, smoking status, or comorbidities such as hypertension and diabetes mellitus ($p > 0.05$ for all comparisons). Detailed demographic characteristics are presented in Table 1.

Biochemical parameters

Biochemical analyses revealed significant differences between the N + and N- groups. Most notably, the decline in kidney function, as measured by ΔeGFR, was significantly greater in the N + group (16.53 mL/min/1.73 m^2, IQR: 10.04–27.49) compared to the N- group (12.82 mL/min/1.73 m^2, IQR: 7.10-22.03, $p = 0.008$), indicating a more pronounced decline in renal function in patients with nephrolithiasis. The N + group also had a significantly lower median calcium level (9.48 mg/dL, IQR: 9.30–9.70) compared to the N- group (9.40 mg/dL, IQR: 9.10–9.53, $p = 0.007$), possibly reflecting underlying metabolic abnormalities such as hypercalciuria or altered calcium metabolism contributing to stone formation.

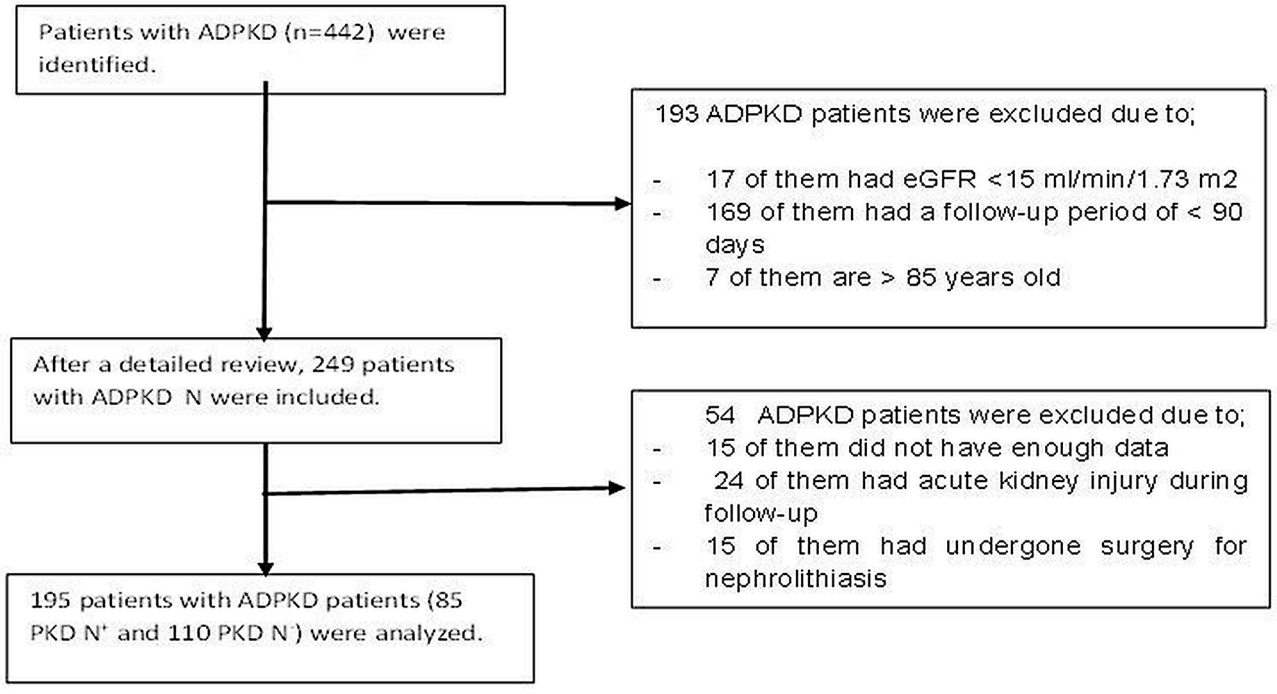

Fig. 1 Flow chart of the study. Abbreviations: ADPKD N+: autosomal polycystic kidney disease with nephrolithiasis. ADPKD N-: autosomal polycystic kidney disease without nephrolithiasis

Table 1 Demographic and clinical characteristics of patients

Characteristics		ADPKD_N$^+$ group ($n=85$)	ADPKD_N$^-$ group ($n=110$)	p
Age (years) IQR		46,48 (35,60 – 55,71)	49,04 (38,36–58,87)	0,132*
Follow-up Time (days), IQR		1496,5 (897–2138)	1102 (626–2183)	0,133*
Gender - Male (%)		41 (51,3%)	48 (41,7%)	0,190**
Smoking status	Smoker	21 (26,3%)	41 (35,7%)	0,070**
	Non-Smoker	52 (65%)	56 (48,7%)	
	Ex-Smoker	7 (8,8%)	18 (15,7%)	
Body mass index (kg/m^2)		28,05 (27,34 – 28,37)	28,05 (25,64 – 30,44)	0,658*
Hypertension		68 (85%)	94 (81,7%)	0,550**
Diabetes mellitus		18 (22,5%)	17(14,8%)	0,167**
Ischemic Heart Disease		2 (2,5%)	4 (3,5%)	0,697**
Heart failure		1 (1,3%)	1 (0,9%)	0,795**
Hypothyroidism		10 (12,5%)	7 (6,1%)	0,118**
Medications Used				
- Renin-Angiotensin-Aldosterone-Inhibitor		37 (61,7%)	49 (57%)	0,571**
- Thiazide Diuretics		14 (23,3%)	23 (26,7%)	0,641**
- Spironolactone		4 (2,7%)	3 (5%)	0,162**
- Calcium Channel Blocker		21 (35%)	32 (37,2)	0,785**
- Beta Blocker		25 (41,7%)	27 (31,4%)	0,202**
- Alpha Blocker		5 (8,3%)	12 (14%)	0,298**
- Allopurinol		5 (8,3%)	7 (8,1%)	0,967**
- Sodium bicarbonate		5 (8,6%)	12 (14%)	0,331**
- Polystyrene Sulfonate Calcium		4 (6,8%)	5 (5,8%)	0,813**
- Statin		4 (6,9%)	9 (10,5%)	0,464**
- Metformin		6 (10,3%)	4 (4,8)	0,201**
- Insulin		1 (1,7%)	2 (2,4%)	0,789**
- Anti-aggregant		10 (17,5%)	24 (28,1%)	0,091**
- Anti-coagulant		2 (3,4%)	3 (3,6%)	0,969**
- Proton Pump Inhibitor		6 (10,3%)	11 (13,1%)	0,620**
- Tolvaptan		6 (10,3%)	3 (3,5%)	0,099**

* Shows the p value obtained with the Mann Whitney U test

** Shows the p value obtained with the Chi-Square test

Parathyroid hormone (PTH) levels showed a trend toward being lower in the N + group, but the difference did not reach statistical significance ($p=0.064$). Other biochemical parameters, including albumin, magnesium, phosphorus, and potassium levels, were similar between the two groups ($p>0.05$ for all comparisons). These findings are summarized in Table 2.

Correlation analysis

Correlation analysis demonstrated that age (r=-0.184, $p=0.010$) and follow-up duration ($r=0.342$, $p<0.001$) were significantly correlated with ΔeGFR. Initial eGFR was also positively correlated with ΔeGFR ($r=0.197$, $p=0.006$), indicating that patients with higher initial eGFR experienced greater declines in kidney function over time. Other factors, such as body mass index, creatinine levels, calcium, and phosphorus levels, did not show significant correlations with ΔeGFR ($p>0.05$ for all). The correlations between ΔeGFR and other clinical and biochemical parameters are detailed in Table 3.

Multiple linear regression analysis

In the multiple linear regression model, nephrolithiasis was found to be an independent predictor of greater eGFR decline (B = 3.159, SE = 1.588, β = 0.132, $p=0.038$). Follow-up duration was strongly associated with ΔeGFR (B = 0.005, SE = 0.001, β = 0.330, $p<0.001$), indicating that longer follow-up was associated with greater declines in kidney function. Age showed a trend toward significance but did not reach statistical significance ($p=0.094$), and initial eGFR was not a significant predictor ($p=0.548$). The regression model explained 17.8% of the variance in ΔeGFR (R^2=0.178, adjusted R^2=0.161), as shown in Table 4.

Discussion

In this study, we demonstrated that the presence of asymptomatic nephrolithiasis (N+) in patients with ADPKD is associated with a significantly greater decline in renal function, as measured by ΔeGFR, compared to nephrolithiasis-negative (N-) patients. Specifically, we found that ΔeGFR was significantly higher in the

Table 2 Various biochemical parameters determined as mean values at baseline and during follow-up in patients with (ADPKD_N$^+$) and without (ADPKD_N$^-$) kidney stones (nephrolithiasis)

Biochemical parameters were expressed as median (IQR)	ADPKD_N + group ($n=85$)	ADPKD_N$^-$ group ($n=110$)	p*
Glucose_mean (mg/dl)	93,95 (87,65–103,88)	94,33 (87,33–101,89)	0,839
Urea_ mean (mg/dl)	41,33 (31,17–55,91)	42,67 (29,29–71,36)	0,605
Initial creatinine (mg/dl)	1,02 (0,82 – 1,39)	1,13 (0,79 – 1,64)	0,318
Creatinine-mean (mg/dl)	1,18 (0,88 – 1,64)	1,16 (0,83 – 1,95)	0,609
Initial_eGFR (ml/min/1.73m^2)	79,06 (58,26–112,73)	69,60 (42,93–103,66)	0,071
eGFR_mean (ml/min/1.73m^2)	62,58 (44,51–105,74)	59,34 (31,07–96,70)	0,199
ΔeGFR (ml/min/1.73m^2)	16,53 (10,04–27,49)	12,82 (7,10–22,03)	**0,008**
Albumin_mean (g/dl)	4,40 (4,24 – 4,55)	4,30 (4,15 – 4,50)	0,097
Calcium_mean (mg/dl)	9,48 (9,30 – 9,70)	9,40 (9,10 – 9,53)	**0,007**
Magnesium_mean (mg/dl)	1,92 (1,87 – 2,01)	1,92 (1,83 – 2,01)	0,511
Phosphorus_mean (mg/dl)	3,45 (3,14 – 3,75)	3,50 (3,18 – 3,80)	0,298
Sodium_mean (mmol/l)	139,73 (138,40–140,67)	139,67 (138,13–140,67)	0,749
Potassium_mean (mmol/l)	4,35 (4,22 – 4,60)	4,34 (4,17 – 4,64)	0,584
Bicarbonate_mean (mmol/l)	24,86 (24,39 – 24,86)	24,86 (24,86 – 24,86)	0,525
PTH_mean (pg/ml)	83,14 (60,93–121,08)	111,67 (56,90–143,73)	0,064
ALP_mean (IU/L)	74,84 (63,63–85,17)	74,84 (62,80 – 78,00)	0,770
Hemoglobin_mean (g/dl)	13,17 (11,98 – 14,72)	12,95 (12,09–14,29)	0,540
UPCR_mean (g/g)	13,17 (11,98 – 14,72)	12,95 (12,09–14,29)	0,834
Urine_Density_mean	1,012 (1,009 – 1,018)	1,011 (1,008 – 1,015)	0,079
Urine_pH_mean	6.0 (5,506,38)	6,0 (5,5–6,0)	0,978

Abbreviations: ALP: alkaline phosphatase, eGFR: estimated glomerular filtration rate, IQR: interquartile range, PTH: parathormone, UPCR: urine protein-to-creatinine ratio

P*: shows the p value obtained with the Mann Whitney U test

N + group (16.53 mL/min/1.73 m²) than in the N- group (12.82 mL/min/1.73 m², $p=0.008$). This finding underscores the potential role of asymptomatic nephrolithiasis in accelerating kidney function decline in ADPKD patients, even in the absence of overt symptoms, a relatively understudied area in the current literature.

Our findings are in line with previous studies that have suggested nephrolithiasis contributes to worsening kidney function in ADPKD patients. For example, Torres et al. reported a similar association between nephrolithiasis and increased risk of renal function decline in ADPKD patients [1]. Additionally, the prevalence of kidney stones in our cohort, approximately 36%, is consistent with the rates reported in other studies, which range from 20 to 36% [4, 5]. These findings reinforce the idea that nephrolithiasis is a common complication of ADPKD, and its presence should not be overlooked even in asymptomatic cases, as it may still contribute to long-term adverse outcomes.

Several factors may explain the association between nephrolithiasis and accelerated kidney function decline in ADPKD. One possible mechanism is urinary stasis caused by the anatomical deformities of the kidneys due to cyst formation, which can lead to stone formation and recurrent infections, further damaging renal tissue [6]. Additionally, the metabolic disturbances associated with ADPKD, such as hypercalciuria and hypocitraturia, may predispose patients to stone formation [5]. Our findings regarding significantly lower calcium levels in the N + group may indicate a compensatory mechanism or underlying metabolic abnormalities contributing to stone formation. This aligns with previous studies that have suggested altered calcium metabolism as a risk factor for nephrolithiasis [5, 7, 11]. While PTH levels were not significantly different between groups, the observed trend toward lower PTH levels in the N + group could reflect individual variations or differences in disease phenotype. Further prospective studies are necessary to clarify these observations. Our study found that calcium levels were significantly lower in the N + group, which may reflect compensatory mechanism or underlying abnormalities contributing to stone formation.

Interestingly, our study found no significant difference in parathyroid hormone (PTH) levels between the N + and N- groups, despite a trend toward lower PTH levels in the N + group. This contrasts with some reports in the literature that suggest elevated PTH levels in ADPKD patients with nephrolithiasis due to secondary hyperparathyroidism, which may be linked to stone formation [6]. However, the lack of significance in our findings may be due to the relatively small sample size or differences in patient characteristics compared to other studies. Further research is needed to clarify the relationship between PTH levels and nephrolithiasis in ADPKD patients.

Table 3 Correlation between ΔeGFR and other laboratory and clinical parameters

	ΔeGFR	
	R	***P***
Age (years)	-,184**	**0,010**
Follow-up Time (days)	,342**	**< 0.001**
Body mass index (kg/m^2)	0,092	0,201
Urea_ mean (mg/dl)	0,008	0,907
Initial creatinine (mg/dl)	-0,127	0,077
Creatinine-mean (mg/dl)	0,035	0,629
Initial_eGFR (ml/min/1.73m^2)	,197**	**0,006**
Last_eGFR (ml/min/1.73m^2)	-0,107	0,137
eGFR_mean (ml/min/1.73m^2)	0,009	0,901
Glucose_mean (mg/dl)	-0,008	0,913
HBA1C_mean (%)	0,066	0,534
Total protein_mean (g/dl)	0,082	0,257
Albumin_mean (g/dl)	0,123	0,086
Calcium_mean (mg/dl)	0,096	0,180
Phosphorus_mean (mg/dl)	0,074	0,305
Magnesium_mean (mg/dl)	0,059	0,410
Sodium_mean (mmol/l)	-0,018	0,798
Potassium_mean (mmol/l)	0,039	0,589
ALP_mean (IU/L)	-0,029	0,691
PTH_mean (pg/ml)	-0,040	0,574
25-hydroxy-vitamin_D_mean	-0,097	0,179
Bicarbonate_mean (mmol/l)	-0,096	0,182
CRP_mean (mg/l)	-0,007	0,920
Hemoglobin_mean (g/dl)	0,069	0,340
UPCR_mean (g/g)	0,091	0,205
Urine_Density_mean	,116	0,105
Urine_pH_mean	-0,029	0,688

R: Spearman Correlation Coefficient

Abbreviations: ALP: alkaline phosphatase, eGFR: estimated glomerular filtration rate, IQR: interquartile range, PTH: parathormone, UPCR: urine protein-to-creatinine ratio. Δ: Initial value– last follow-up value

Table 4 Multiple linear regression model of factors associated with ΔeGFR

	B	SE	β	*P*
ADPKD groups (N + and N$^-$)	3.159	1.588	**0.132**	**0.038**
Age	-0.131	0.077	-0.152	0.094
Follow-up period (days)	0.005	0.001	0.330	**< 0.001**
Initial_eGFR (ml/min/1.73m^2)	0.017	0.029	0.054	0.548

Abbreviations: ADPKD = Autosomal dominant polycystic kidney disease, N$^+$: with nephrolithiasis, N$^-$: without nephrolithiasis, SE: standard error

Δ: Initial value– last follow-up value

Variables with significant *p* value in simple linear regression were selected for multiple linear regression model. R2 = 0.178 and adjusted R2 = 0.161

The inclusion of prognostic tools such as Mayo's criteria, which utilize height-adjusted total kidney volume (htTKV) as a prognostic indicator, is widely recognized as a valuable approach to evaluating disease progression risk in ADPKD [12]. However, due to the retrospective nature of this study, standardized measurements required for htTKV calculation, such as precise kidney dimensions and consistent imaging protocols, were not uniformly available across all included patients. Consequently, we could not incorporate htTKV into the current analysis. While htTKV data were not available for all patients in this retrospective study, the established predictive power of Mayo's criteria underscores the importance of incorporating such metrics in future studies to provide a more comprehensive assessment of the relationship between nephrolithiasis and disease progression.

Another significant finding from our study is the strong correlation between follow-up duration and ΔeGFR. As expected, patients with longer follow-up periods experienced greater declines in kidney function, highlighting the progressive nature of ADPKD. This is consistent with existing literature, where long-term studies of ADPKD cohorts have consistently shown a gradual decline in kidney function over time [1, 8].

Our findings also suggest that age and initial eGFR are important predictors of kidney function decline in ADPKD. Older patients, as well as those with higher baseline eGFR, tend to experience more significant declines in renal function. This is consistent with the literature, which suggests that both age and baseline kidney function are critical determinants of disease progression in ADPKD [5, 8]. However, it is important to note that while age showed a trend toward significance in our regression analysis, it did not reach statistical significance ($p = 0.094$), likely due to sample size limitations.

While we examined the use of medications such as tolvaptan and other relevant treatments (Table 1), no significant differences were found between the N + and N- groups, which may mitigate concerns about their potential confounding effect. Similarly, comorbidities such as diabetes mellitus and hypertension were comparable between the groups, as shown in Table 1. These findings suggest that differences in kidney function decline are likely attributable to nephrolithiasis rather than these confounding factors.

Clinical implications

The identification of asymptomatic nephrolithiasis in ADPKD patients should prompt closer monitoring and management. Strategies such as optimizing hydration, correcting metabolic abnormalities, and regular imaging to detect changes in stone burden may help mitigate the potential impact of nephrolithiasis on disease progression. However, further studies are needed to evaluate whether early intervention can alter the natural history of the disease.

Limitations

Despite the strengths of our study, including the relatively large sample size and the focus on asymptomatic nephrolithiasis, there are several limitations that should be

acknowledged. First, this is a retrospective cohort study, and as such, there may be inherent biases in patient selection and data collection. Second, while we examined the use of medications such as tolvaptan and other relevant treatments (Table 1), no significant differences were found between the N + and N- groups, which may mitigate concerns about their potential confounding effect. However, other factors such as dietary habits or unmeasured comorbidities could still influence kidney function decline. Additionally, the reliance on imaging to diagnose nephrolithiasis may have resulted in the underdetection of small or non-obstructive stones. Finally, the follow-up duration varied among patients, which may have introduced variability in the ΔeGFR values.

Conclusion

In conclusion, our study demonstrates that asymptomatic nephrolithiasis is associated with accelerated kidney function decline in patients with ADPKD. These findings highlight the importance of monitoring kidney stone development, even in the absence of symptoms, as part of the comprehensive management of ADPKD. Further prospective studies are warranted to explore the mechanisms underlying this association and to develop strategies to mitigate the impact of nephrolithiasis on disease progression.

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Author contributions
All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by O. C. E., B.Y. and B.B.O. The first draft of the manuscript was written by O.C.E. and edited by S.M., M.G. and R.K. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.Corresponding author: Omer Celal ElciogluResponses to reviewers' criticisms were given by the corresponding author, O.C.E., and the final version of the manuscript was viewed and approved by all authors.

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Data availability
The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
This study was in accordance with the ethical principles of the Declaration of Helsinki, the Good Clinical Practice guidelines of the International Conference on Harmonization, and local regulatory requirements. The study was approved by the **Bezmialem Vakif University Ethics Committee** with the approval/ date and number: **13 March**, **2024**, **2024/19-E-54022451-050.04-146750.** Informed consent was waived by the **Bezmialem Vakif University Ethics Committee** due to the retrospective nature of the study, in accordance with national regulations (Decision No: 2024/19-E-54022451-050.04-146750).

Consent for publication
Not Applicable.

Competing interests
The authors declare no competing interests.

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