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Empagliflozin in ADPKD with suspected IgA nephropathy: antiproteinuric response without adverse events

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Abstract

SGLT2 inhibitors have demonstrated robust cardiorenal benefits across diverse chronic kidney disease populations but remain underutilized in autosomal dominant polycystic kidney disease (ADPKD) due to lack of disease-specific data and theoretical safety concerns. We report a 58-year-old man with genetically confirmed *PKD2*-associated ADPKD who developed progressive proteinuria (0.8 g/24 h increasing to 2.0 g/24 h over three years) despite optimal ACE inhibition. Clinical findings suggested concomitant IgA nephropathy, but biopsy was contraindicated. Empagliflozin 10 mg/day was initiated off-label. Proteinuria decreased progressively to 0.9 g/24 h at one month, 0.645 g/24 h at three months, 0.4 g/24 h at six months, and stabilized between 0.3 and 0.4 g/24 h through 18 months (82–85% reduction sustained to date). Renal function remained stable (eGFR 33–35 mL/min/1.73 m^2). No infections or adverse events occurred. This case supports safety and antiproteinuric efficacy of empagliflozin in ADPKD with superimposed glomerular disease and provides context for broader therapeutic potential of SGLT2i in this systemic cardiorenal-metabolic disorder.

Keywords ADPKD, Proteinuria, SGLT2 inhibitors, Empaglifozin, IgA nephropathy

Introduction

Autosomal dominant polycystic kidney disease (ADPKD) affects approximately 4 in 10,000 individuals worldwide and represents the fourth leading cause of kidney failure in the United States [1–3]. Contemporary understanding recognizes ADPKD as a systemic cardiorenal–metabolic disorder, characterized by early cardiovascular involvement, metabolic dysregulation, and multiorgan manifestations [3–7], requiring a multidisciplinary approach [8]. Cardiovascular disease remains the leading cause of mortality, often manifesting before significant renal impairment [3, 7, 9].

Although cyst enlargement drives glomerular filtration decline, significant proteinuria is uncommon in ADPKD [3, 10]. Values exceeding 1 g/day typically indicate superimposed glomerular disease rather than cystic pathology alone [11].

Despite robust cardiorenal benefits across chronic kidney disease populations [12–14], SGLT2 inhibitors (SGLT2i) are not recommended for ADPKD by current guidelines [3]. This reflects ADPKD exclusion from

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major trials and theoretical concerns that osmotic diuresis might stimulate vasopressin release (accelerating cyst growth) and that glycosuria could increase genitourinary infections. However, mechanistic evidence suggests SGLT2i may address ADPKD's metabolic and cardiovascular pathophysiology, prompting calls for reconsideration [15, 16].

We report a patient with *PKD2*-associated ADPKD and progressive proteinuria suggestive of IgA nephropathy, treated with empagliflozin with marked sustained antiproteinuric response and no adverse events.

Case report

A 58-year-old Caucasian man presented with hypertension (controlled on perindopril 4 mg/day), proteinuria (0.8 g/24 h), and microhematuria. Ultrasound revealed bilateral renal and hepatic cysts. Serum creatinine was 0.98 mg/dL (eGFR 79 mL/min/1.73 m^2). Echocardiography showed mild left ventricular hypertrophy. Genetic testing identified a pathogenic *PKD2* mutation (NM_000297.4:c.1774 C > T, p.Arg592Ter), a truncating variant classified as Pathogenic per ACMG/AMP criteria [17]. MRI confirmed slight nephromegaly (TKV 950 mL) without complicated cysts. Tolvaptan was not indicated (age > 55 years, TKV below threshold).

Table 1 Immunological and serological tests

Test	Result	Reference Range
Serum IgA (mg/dL)	800	90–450
Serum IgG (mg/dL)	1120	700–1600
Serum IgM (mg/dL)	98	40–230
C3 (mg/dL)	115	90–180
C4 (mg/dL)	28	10–40
ANA	Negative	-
Anti-dsDNA	Negative	-
ANCA (MPO, PR3)	Negative	-
Anti-GBM antibodies	Negative	-
Cryoglobulins	Negative	-
HBsAg	Negative	-
Anti-HCV	Negative	-
Serum protein electrophoresis analysis	Normal pattern	-
Urinary protein characterization	Predominant glomerular albuminuria	-

Laboratory evaluation performed to investigate suspected glomerular disease. Markedly elevated serum IgA (800 mg/dL; nearly double the upper limit of normal) with normal IgG and IgM levels, combined with negative autoimmune serological markers and infectious disease screening, supported the clinical suspicion of IgA nephropathy superimposed on ADPKD. ANA, antinuclear antibodies; anti-dsDNA, anti-double-stranded DNA antibodies; ANCA, anti-neutrophil cytoplasmic antibodies (MPO, myeloperoxidase; PR3, proteinase 3); anti-GBM, anti-glomerular basement membrane antibodies; HBsAg, hepatitis B surface antigen; anti-HCV, anti-hepatitis C virus antibodies

Over three years, despite optimal blood pressure control (consistently < 135/85 mmHg) and continued ACE inhibition, proteinuria increased to 2.0 g/24 h (UPCR 2050 mg/g) with renal function decline (creatinine 2.0 mg/dL, eGFR 35 mL/min/1.73 m^2, CKD G3b). This trajectory was highly atypical for *PKD2*-associated ADPKD, which typically exhibits favorable renal outcomes with minimal proteinuria and slower progression [17].

Therefore coexisting glomerular disease was suspected. Laboratory evaluation revealed markedly elevated serum IgA (800 mg/dL; normal 90–450 mg/dL), with normal IgG and IgM. Serum C3 was normal (1.15 g/L; reference 0.90–1.80 g/L), yielding a markedly elevated IgA/C3 ratio of 6.96 (threshold for IgA nephropathy: >3.01). Urinary sediment demonstrated dysmorphic erythrocytes (>80%) and casts; urinary protein characterisation confirmed predominant glomerular albuminuria. Comprehensive workup was negative: normal C3/C4, negative ANA, anti-dsDNA, ANCA panel, anti-GBM antibodies, cryoglobulins, and hepatitis serology (Table 1). Findings strongly suggested IgA nephropathy. Biopsy was contraindicated due to extensive cystic replacement and bleeding risk.

Immunosuppressive therapy was not pursued given normal complement levels, arguing against an active immune-complex–mediated process, and the substantially increased infection risk associated with the polycystic renal anatomy.

Given progressive proteinuria, *PKD2* genotype, eGFR decline despite optimal therapy, and cardiovascular risk (left ventricular hypertrophy), empagliflozin 10 mg/day was initiated off-label for antiproteinuric effect and cardiorenal protection.

Clinical response

Response was remarkable. Proteinuria decreased from 2.0 g/24 h to 0.9 g/24 h (month 1), 0.645 g/24 h (month 3), 0.4 g/24 h (month 6), 0.35 g/24 h (month 9), and stabilized at 0.3–0.4 g/24 h through 18 months, an 82–85% sustained reduction continuing to date (Table 2; Fig. 1). Renal function remained stable (creatinine 2.0-2.2 mg/dL, eGFR 33–35 mL/min/1.73 m^2) without accelerated decline.

Following empagliflozin initiation, a transient eGFR dip was observed within the first two weeks, consistent with the well-recognized hemodynamic effect of SGLT2 inhibitors mediated by tubuloglomerular feedback-induced reduction in afferent arteriolar tone; this early decline was followed by stabilization of renal function, confirming its hemodynamic rather than nephrotoxic nature; subsequent stabilization, in a patient with advanced cystic nephropathy, represents arrest of decline rather than further deterioration.

Table 2 Clinical parameters over time

Parameter	Index visit	3 years later	Month 1	Month 3	Month 6	Month 9	Month 18
Serum creatinine (mg/dL)	0.98	2.00	2.20	2.10	2.10	2.20	2.10
eGFR (mL/min/1.73 m^2)	79	35	33	35	33	35	31
24 h proteinuria (g/24 h)	0.80	2.00	0.90	0.64	0.50	0.40	0.35
UPCR (mg/g)	825	2050	925	663	411	360	339
Body weight (kg)	76	78	78	78	78	78	78
HbA1c (%)	5.5	5.6	-	5.7	-	5.8	5.8
Serum Na (mmol/L)	141	140	140	144	142	140	140
Serum K (mmol/L)	4.2	4.3	4.4	3.9	4.1	4.3	4.8
Uric acid (mg/dL)	6.8	7.2	6.8	6.6	6.5	6.4	6.4

Serial measurements of renal function, proteinuria, and metabolic parameters from initial presentation (baseline), at the time of empagliflozin initiation (3 years later, pre-empagliflozin), and during 18 months of follow-up. Proteinuria progressively decreased from 2.0 g/24 h at empagliflozin initiation to 0.3–0.4 g/24 h at 18 months (82–85% reduction), while renal function remained stable (eGFR 33–35 mL/min/1.73 m^2). No significant changes were observed in body weight, metabolic parameters, or electrolytes. UPCR, urine protein-to-creatinine ratio; HbA1c, glycated hemoglobin; Na, sodium; K, potassium

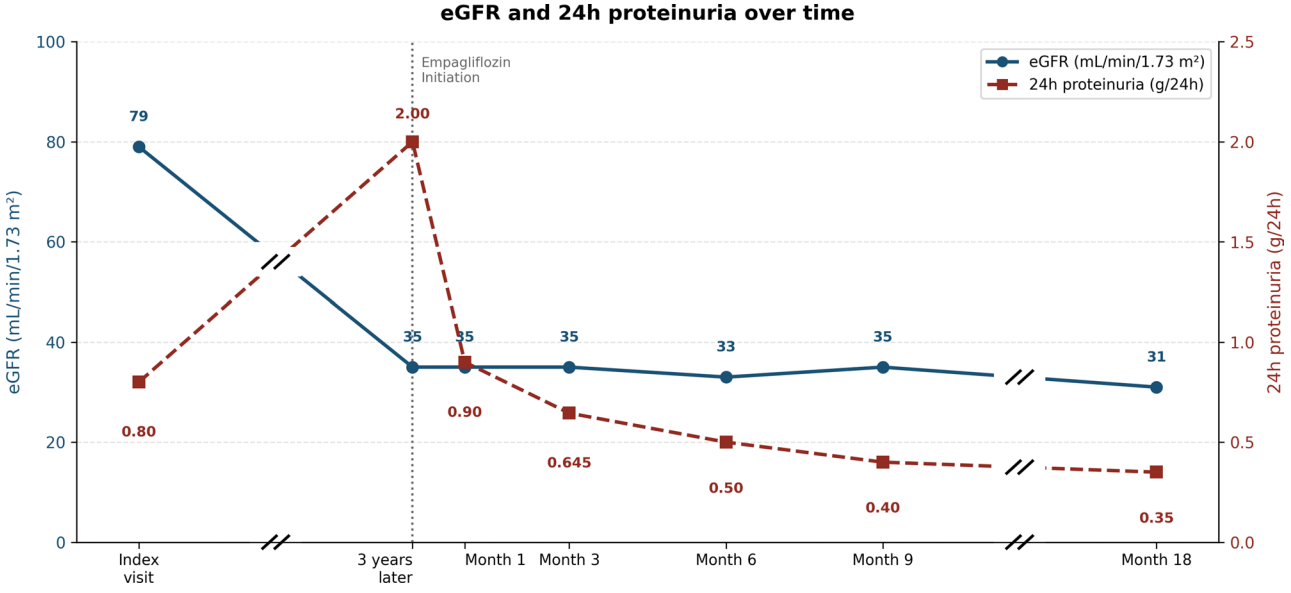


Fig. 1 Time course of eGFR and 24-hour proteinuria during empagliflozin treatment. The horizontal axis represents real time and reflects the actual unequal intervals between observations: the three-year period of progressive proteinuria preceding empagliflozin initiation is followed by visits at month 1, 3, 6, 9, 12 and 18 after the start of treatment. The empagliflozin start point is indicated by a vertical reference line, and an axis break is used to make the unequal time spacing visually explicit

Notably, in the three years preceding empagliflozin, eGFR had declined from 79 to 35 mL/min/1.73 m^2 (approximately – 14.7 mL/min/1.73 m^2/year), a rate substantially faster than expected for *PKD2*-associated ADPKD and likely driven by the superimposed glomerular disease; following empagliflozin initiation, renal function remained essentially stable over 18 months, representing a clear inflection point in the trajectory.

No urinary tract infections, genital mycotic infections, or other adverse events occurred. Blood pressure remained stable (always < 135/85 mmHg) without medication changes. Body weight was unchanged. Patient reported no symptoms and demonstrated excellent adherence. Notably, blood pressure had been consistently well-controlled below 135/85 mmHg throughout the entire three-year period prior to empagliflozin initiation, arguing against a blood pressure-mediated explanation for the subsequent proteinuria reduction.

Discussion

This case illustrates empagliflozin safety and antiproteinuric efficacy in *PKD2*-associated ADPKD with suspected IgA nephropathy, with 82–85% proteinuria reduction sustained over 18 months without adverse events. Beyond this specific scenario, the case provides context for reconsidering SGLT2i therapeutic potential in ADPKD.

ADPKD with concomitant glomerular disease

Progressive proteinuria exceeding 1 g/24 h is distinctly uncommon in *PKD2*-associated ADPKD [3, 10, 11, 18], which typically manifests minimal proteinuria. *PKD2*

mutations confer a substantially milder phenotype than *PKD1*, with later onset of hypertension, slower kidney growth, and more favorable renal survival [3, 18]. The identified variant (*NM_000297.4*:c.1774C>T, p.Arg592Ter) is a truncating mutation. Although genotype–phenotype correlations are less well established in *PKD2* than in *PKD1*, available evidence still suggests a potential impact of mutation class on renal function. In the Genkyst cohort, Cornec-Le Gall et al. reported that nontruncating *PKD2* variants were associated with higher age-adjusted eGFR than truncating ones, although mutation type was not an independent predictor of age at end-stage renal disease and contributes 0 points to the PROPKD score regardless of subtype. The same study explicitly recommends that, when accelerated kidney function decline is observed in *PKD2*-associated ADPKD, a concomitant nephropathy should be ruled out, the precise rationale that guided the diagnostic and therapeutic approach in our patient [19].

In this patient, progressive proteinuria (0.8 to 2.0 g/24 h over three years) despite continuous ACE inhibition, markedly elevated IgA (nearly double upper normal limit), dysmorphic hematuria with casts, and negative comprehensive workup strongly suggested IgA nephropathy, though histological confirmation was impossible.

The rapid, substantial, sustained response argues against spontaneous fluctuation or delayed ACE inhibitor effect. Proteinuria had been persistently elevated for three years without fluctuation before empagliflozin, and the consistent downward trajectory after SGLT2i initiation (baseline 2.0 → month 1: 0.9 → month 3: 0.645 → month 6: 0.4 → month 9–18: 0.3–0.4 g/24 h) strongly supports causality. This pattern is consistent with SGLT2i effects in other proteinuric glomerulopathies [12, 13].

This carries practical relevance. Coexisting glomerular diseases in ADPKD often remain undiagnosed because biopsy is contraindicated, leaving clinicians managing proteinuria empirically [11].

In our patient, as aforementioned immunosuppression was not pursued given normal complement levels and the heightened infection risk in polycystic kidneys; empagliflozin was therefore selected as the antiproteinuric agent of choice, yielding a marked and sustained response.

SGLT2 inhibitors offer evidence-based therapy with established antiproteinuric effects across diverse glomerulopathies [12, 13]. This case demonstrates SGLT2i can be safely administered despite cystic renal anatomy without precipitating infections.

Safety profile

Theoretical concerns have historically limited SGLT2i use: that osmotic diuresis stimulates vasopressin (accelerating cyst growth) and that glycosuria increases infection risk. Our patient experienced no infections despite 18 months treatment, with stable renal function.

These observations align with emerging data. Uchiyama et al. demonstrated dapagliflozin added to tolvaptan in 34 ADPKD patients was safe, caused no infections, and showed no detrimental effects on kidney volume or eGFR over 12 weeks [18]. Multiple observational cohorts report favorable safety profiles with no ADPKD-specific adverse events [20].

Broader therapeutic potential

While this case primarily demonstrates SGLT2i efficacy with superimposed glomerular disease, it prompts consideration of broader potential across ADPKD. ADPKD is increasingly recognized as systemic cardiorenal-metabolic disease [3, 5–7]. Polycystin deficiency triggers metabolic reprogramming: shift to aerobic glycolysis, mitochondrial dysfunction, oxidative stress, inflammation, insulin resistance, and dysregulated AMPK-mTOR signaling, alterations appearing causative in cyst growth [5, 6]. Simultaneously, cardiovascular abnormalities (left ventricular hypertrophy, diastolic dysfunction, endothelial dysfunction) manifest early, even with preserved eGFR [7].

SGLT2 inhibitors modulate multiple relevant pathways. By inducing glycosuria and promoting a nutrient deprivation state, they shift metabolism toward fatty acid oxidation and mild ketogenesis [21]. Ketone bodies and the resulting metabolic changes activate nutrient deprivation sensors including AMPK and SIRT1, while suppressing nutrient surplus pathways such as mTOR [21]. These coordinated responses improve mitochondrial function, reduce oxidative stress and inflammation, and promote cellular housekeeping mechanisms including autophagy [21]. Preclinical studies show interventions targeting these pathways can attenuate cyst growth, suggesting SGLT2i effects may extend beyond hemodynamic renoprotection [20].

Critically, SGLT2 inhibitors provide robust cardiovascular protection: left ventricular hypertrophy regression, heart failure reduction, cardiovascular mortality reduction [14]. These benefits address ADPKD's leading cause of death and distinguish SGLT2i from tolvaptan, whose action remains cyst-directed without cardiovascular benefit [3]. Effective ADPKD therapeutics must address the broader cardiorenal-metabolic landscape, not solely cyst burden.

Emerging evidence supports this potential. Beyond Uchiyama's trial, observational studies report stable/improved renal outcomes, reduced albuminuria, and favorable tolerability with SGLT2i in ADPKD, with no study demonstrating accelerated kidney volume growth or eGFR decline [20].

Expert consensus statements have called for dedicated trials evaluating SGLT2i in ADPKD with comprehensive endpoints including not only renal outcomes (eGFR, kidney volume) but also cardiovascular outcomes (left ventricular mass, cardiovascular events, mortality), quality of life, and metabolic parameters.

Such trials are essential to determine whether mechanistic rationale and early signals translate into population-level benefits. The EMPA-PKD randomized controlled trial [22] is currently evaluating the efficacy and safety of empagliflozin specifically in ADPKD patients, with pre-specified endpoints including eGFR slope and TKV change. Additional prospective trials are also underway. Our observation provides complementary real-world data pending these results, which will be pivotal in determining whether SGLT2i merit a formal indication in ADPKD.

Clinical implications

This case suggests SGLT2 inhibitors may benefit ADPKD across scenarios: patients with proteinuria from superimposed glomerulopathy (as demonstrated), those with cardiovascular disease/high risk, and potentially broadly by targeting metabolic pathophysiology. Until dedicated trial data emerge, carefully selected individualized use appears reasonable with appropriate informed consent and monitoring.

Limitations

Single-case observation precludes definitive causality determination. Lack of histological confirmation introduces diagnostic uncertainty, though clinical findings strongly supported IgA nephropathy. Relatively short follow-up (18 months) precludes long-term safety. Additional limitations specifically related to ADPKD pathophysiology should also be acknowledged. Given the mechanistic concern that SGLT2 inhibitors may increase circulating vasopressin levels, with theoretical implications for cyst growth, the absence of copeptin (or other vasopressin surrogate) measurement before and during empagliflozin therapy represents a relevant limitation. Similarly, follow-up MRI was not performed because it was not clinically indicated, and the lack of longitudinal total kidney volume (TKV) assessment after SGLT2 inhibitor initiation precludes any direct conclusion regarding the impact of empagliflozin on cyst growth in this patient. Nevertheless, response magnitude, rapidity, durability, and temporal relationship provide compelling support for SGLT2i efficacy and safety.

Conclusions

This case supports safety and marked antiproteinuric efficacy of empagliflozin in *PKD2*-associated ADPKD with suspected IgA nephropathy, with sustained response over 18 months without adverse events. Beyond this specific scenario, the case provides context for reconsidering broader SGLT2i therapeutic potential based on ADPKD's metabolic and cardiovascular pathophysiology and emerging clinical evidence. Dedicated prospective trials evaluating comprehensive renal, cardiovascular, and metabolic endpoints are warranted to determine whether mechanistic rationale and encouraging signals translate into population-level benefits.

Abbreviations

ADPKD	Autosomal Dominant Polycystic Kidney Disease
SGLT2i	Sodium-Glucose Cotransporter 2 Inhibitors
eGFR	estimated Glomerular Filtration Rate
CKD	Chronic Kidney Disease
TKV	Total Kidney Volume
UPCR	Urine Protein-to-Creatinine Ratio
ACE	Angiotensin-Converting Enzyme
IgA	Immunoglobulin A
ANA	Antinuclear Antibodies
ANCA	Anti-Neutrophil Cytoplasmic Antibodies
GBM	Glomerular Basement Membrane

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12882-026-05045-2.

Supplementary Material 1

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Not applicable.

Author contributions

RFR, MTSA, and GV conceived and designed the study. RFR, AB, and MTSA provided clinical care and follow-up of the patient. SU, ET, PB, MP, KK, LIDR, and MC contributed to data collection and analysis. SU, MC, and RFR drafted the manuscript. All authors critically reviewed and approved the final manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

This research was conducted in accordance with the Declaration of Helsinki. Ethical approval was obtained from the Institutional Review Board (Ethics Committee) of IRCCS San Raffaele Scientific Institute, Milan, Italy.

Consent for publication

Written informed consent for publication of clinical details was obtained from the patient. A copy of the consent form is available for review by the Editor of this journal.

Competing interests

The authors declare no competing interests.

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