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Clinical and laboratory characteristics of nephropathic cystinosis in a resource-limited region

Adem Yasin Köksoy[1], Orhan Görükmez[2]

[1]Department of Pediatric Nephrology, Samsun Training and Research Hospital, Samsun, Türkiye, [2]Department of Genetics, Bursa Yüksek İhtisas Training and Research Hospital, Bursa,Türkiye

Correspondence Author: **Adem Yasin Köksoy**
e-mail: ayasin71@gmail.com
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ABSTRACT

Objective: Cystinosis remains a significant cause of morbidity in developing countries. Key challenges include limited access to specialized clinics, availability of cysteamine treatment, and difficulties in monitoring treatment efficacy, such as measuring leukocyte cystine levels. The aim of this study was to describe the clinical characteristics, growth patterns, and renal outcomes of pediatric patients with nephropathic cystinosis in a resource-limited region

Material and Methods: This retrospective study included 17 patients diagnosed with cystinosis who were followed in the Pediatric Nephrology Clinic of a tertiary care center between June 2016 and April 2023. Clinical and laboratory characteristics were evaluated, and statistical analyses were performed using IBM SPSS Statistics.

Results: After a median follow-up period of 69.24 months, no significant change was observed in weight SDS ((median [IQR]; baseline vs. follow-up; -3.6 [1.35] vs. -2.8 [1.55], p=0.255). However, height SDS significantly decreased (median [IQR]; baseline vs. follow-up; -2.8 [2.44] vs. -3.9 [2.35], p=0.034). Ocular involvement was present in all patients, and six were diagnosed with hypothyroidism. The majority of patients (n=9) exhibited biochemical features consistent with renal Fanconi syndrome. One patient initially presented with persistent hypochloremic hypokalemic metabolic alkalosis and subsequently developed Fanconi syndrome during follow-up, while another showed transient metabolic alkalosis at presentation. The median estimated glomerular filtration rate (eGFR) significantly declined from diagnosis (116.66 [62.69] mL/min/1.73 m^2) to the last follow-up (77.40 [95.18] mL/min/1.73 m^2, p=0.007). Twelve patients had an eGFR <90 mL/min/1.73 m^2; three progressed to stage 3 chronic kidney disease, and three required renal replacement therapy.

Conclusion: Growth retardation and progression to chronic kidney disease are significant challenges for cystinosis patients in resource-limited settings. Improving access to specialized care and monitoring is essential to enhance patient outcomes.

Keywords: Cystinosis, chronic kidney disease, cysteamine, nephropathic cystinosis, resource-limited settings

Introduction

Cystinosis is a rare disease caused by mutations in the CTNS gene, with an estimated incidence of 1 in 100000 to 1 in 200000 in the USA. It is characterized by the accumulation of intralysosomal cystine crystals due to dysfunction of cystinosin, a lysosomal transport protein (1). In regions with high rates of consanguineous marriages, such as Türkiye and various countries in the Middle East and East Mediterranean, the prevalence of cystinosis may be significantly elevated (1, 2). Given the high burden of autosomal recessive disorders in populations with elevated consanguinity rates, the regional prevalence of cystinosis is expected to surpass that reported in Western countries. The disease can affect multiple organs and is categorized into three distinct types: nephropathic, infantile, and ocular cystinosis (3-5). Nephropathic cystinosis, the most common form, is an orphan disease that necessitates early diagnosis and intervention due to its potential to progress to end-stage renal disease in childhood. Since cysteamine therapy functions by reducing intracellular cystine accumulation, its introduction in the 1980s has markedly improved renal survival and overall outcomes in affected patients. Cysteamine achieves this by converting intralysosomal cystine into metabolites that can exit the lysosome via alternative transport pathways, thereby preventing crystal formation and

reducing cellular toxicity (6). Despite these advancements, cystinosis continues to be a major cause of morbidity in developing countries compared to developed nations (7). In such settings, access to specialized metabolic and pediatric nephrology centers is often limited, cysteamine therapy may be difficult to obtain due to logistical or financial barriers, and regular monitoring—particularly leukocyte cystine measurement—is frequently unavailable. Socioeconomic challenges may further compromise treatment adherence and follow-up continuity. These factors collectively increase the risk of growth retardation, progression to kidney failure, and extrarenal complication (8). The study centre, located in a city in eastern Türkiye with a population of 1.1 million and a crude birth rate of 17.1 per 1000 inhabitants in 2023, serves as a focal point for pediatric nephrological consultations. Given the region's high natality rate and the relatively high prevalence of rare genetic disorders like cystinosis—likely due to elevated consanguinity rates—we manage a substantial number of these patients each year. The aim of this study was to evaluate the clinical characteristics of pediatric patients with cystinosis from a resource-limited region, with a particular focus on growth outcomes and progression to kidney failure.

Materials and Methods

This retrospective study included 17 patients diagnosed with cystinosis who were followed in the Pediatric Nephrology Clinic of a Van Research and Education Hospital between June 2016 and April 2023. The diagnosis of cystinosis is fundamentally based on clinical and laboratory criteria associated with renal Fanconi syndrome, including growth failure, polyuria, electrolyte imbalances, glucosuria, phosphaturia, and generalized proximal tubular dysfunction. The confirmation of cystinosis is established through the detection of corneal cystine crystals during ophthalmic examination and/or the measurement of elevated leukocyte cystine levels at an external centre (exceeding 2 nmol half-cystine per mg of protein) and/or the identification of mutations in the CTNS gene (3).

The medical records of patients were obtained from the hospital patient records and the included patients were evaluated in terms of demographic, clinical, and laboratory data. The evaluated demographic characteristics included gender, age, body weight, weight standard deviation score (SDS), height, height SDS, body mass index (BMI), BMI SDS.

Clinical characteristics included eye involvement, hypothyroidism and hypophosphatemic rickets, existence of nephrocalcinosis, evolution of chronic kidney disease during follow up. Laboratory characteristics included serum creatinine at the time of first and last admission, estimated glomerular filtration rate (eGFR) at the time of first and last admission, blood gas status at admission and genetic testing if available.

Weight (kg), height (cm), and BMI (kg/m^2) values, along with their corresponding standard deviation scores (SDS), were obtained and assessed based on predefined reference ranges for Turkish children (9). Serum creatinine levels were measured using an enzymatic assay, and the estimated glomerular filtration rate (eGFR) was calculated utilizing the bedside Schwartz equation (10, 11).

Molecular genetic analyzes of the patients included in this study were performed at an external center. A clinical exome sequencing kit (SOPHIA GENETICS, Boston, MA, USA) was applied to patients using an NGS-based system (NextSeq 500 system Illumina, San Diego, CA, USA). Data analyzes were carried out with the help of the kit manufacturer's analysis program (SOPHIA DDM). Reported variants were identified using the Human Gene Mutation Database (HGMD) database. Other variants were classified according to American College of Medical Genetics (ACMG) criteria.

In our cohort, alkali therapy was administered using a citrate solution containing sodium citrate 100 g, potassium citrate 100 g, and citric acid 70 g per liter. This corresponds to a sodium dose of 1.16–4.65 mEq/kg/day and potassium dose of 0.98–3.92 mEq/kg/day when administered at 1–4 mL/kg/day.

Neutral phosphate supplementation was provided using Joulie solution ($Na_2HPO_4{\cdot}7H_2O$ 136 g + H_3PO_4 58.8 g per liter), corresponding to a sodium and phosphate dose of 1.02–4.07 mEq/kg/day each, administered at 1–4 mL/kg/day. Cysteamine bitartrate was prescribed to all patients at a dose of 60–90 mg/kg/day, and cysteamine eye drops were administered four times daily.

Statistical analysis

Statistical analyses were conducted using IBM SPSS Statistics version 24.0 (IBM Corp., Armonk, NY, USA). The normality of the variables was assessed through both visual methods (histograms) and analytical methods (Kolmogorov-Smirnov and Shapiro-Wilk tests). Descriptive statistics for categorical variables were presented as frequencies. For variables that did not follow a normal distribution, medians and interquartile ranges (IQR) were reported. When evaluating differences between patients' weight SDS, height SDS, BMI SDS and eGFR values at the first and last admission, the Wilcoxon signed-ranks test was used. A p value <0.050 was considered statistically significant

Results

Primary complaints and epidemiological characteristics of the patients are summarized in Table I. Among the 17 patients, there were 8 girls (44.4%) and 9 boys (55.6%). The median age at presentation was 10.92 (IQR; 8.40) months, and the median follow-up time was 69.24 (IQR;61.20) months. Most patients were admitted with growth retardation, evidenced by a median weight SDS of -3.66 (IQR; 1.35), median height SDS of -2.89 (IQR; 2.44), and BMI SDS of -1.93 (IQR; 1.46). At the time of admission, the median serum creatinine (Cr) level was 0.33 (0.18) mg/dL, and the estimated glomerular filtration rate (eGFR) was 116.66 (IQR; 62.69) mL/min/1.73 m^2 (Table I).

After a median follow-up duration of 69.24 (IQR; 61.20) months, reassessment of height and weight showed no

Table I: Epidemiological properties of cytinosis patients

Variable	Values	p
Number of patients	17	-
Age at onset*	10.92 (8.40)	-
Follow up duration*	69.24 (61.20)	-
Gender (Female)†	8 (44.4)	-
Prensence of consanguinity†	13 (72.2)	-
Weight at onset (kg)*	6.6 (1.55)	-
Weight SDS at onset*	-3.66 (1.35)	-
Height at onset*	68 (7.5)	-
Height SDS onset*	-2.89 (2.44)	-
BMI at Oonset*	14.27 (1.53)	-
BMI SDS at onset*	-1.93 (1.46)	-
Creatinine levels*		
Diagnosis	0.33 (0.18)	0.001‡
Last visit	0.72 (0.87)	
eGFR*		
Diagnosis	116.66 (62.69)	0.007‡
Last Visit	77.40 (95.18)	
Primary complaints*		
Growth retardation	11 (64.7)	-
Vomiting	1 (5.9)	
Family history	4 (23.5)	
Walking difficulty	1 (5.9)	

: median (IQR), †: n(%), ‡: Wilcoxon signed-ranks test,* ***eGFR:* *estimated glomerular filtration rate,* ***SDS:*** *Standard deviation scrore,* ***BMI:*** *Body mass index*

statistically significant difference in weight standard deviation scores (SDS). Baseline median body weight SDS was -3.6 (IQR; 1.35), compared with -2.8 (IQR; 1.55) at follow-up (p = 0.255). However, height SDS significantly deteriorated from a baseline median of -2.8 (IQR; 2.44) to -3.9 (IQR; 2.35) (p=0.034), indicating a notable decline in lineer growth (Figure 1).

Among the initial laboratory data available for 11 patients, the following findings were noted. First, all patients demonstrated tubulopathy as anticipated. And also the majority (n=9) had profiles consistent with incomplete or complete renal Fanconi syndrome (Table II). Additionally, metabolic alkalosis was identified in two patients during blood gas analyses: one (P3) had transient alkalosis, while another (P12) exhibited persistent hypochloremic hypokalemic metabolic alkalosis without ocular cystine crystals, initially leading to a provisional diagnosis of Bartter syndrome. However, upon the development of renal Fanconi syndrome, cystine levels were assessed externally, confirming cystinosis (Table II).

During periodic follow-up evaluations, ocular involvement was documented in all patients. Additionally, hypothyroidism necessitating treatment was detected in six patients (35.2%), and clinical manifestations of rickets were observed in four patients (23.5%) (Table II). Nephrocalcinosis was identified in six patients (35.2%). Treatment adherence was assessed clinically; good adherence was documented in 9 (52.9%) patients, whereas poor adherence was noted in 8 (47.1%) patients (Table II). Poor adherence was more common among those who progressed to advanced CKD.

Table II: Clinical and laboratory characteristics of patients

Patient No	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Age at diagnosis (months)	13.9	6.9	24.6	10.9	14.7	7.9	7.6	9.9	9	15	7.08	26.4	15.3	22.9	17.0	6	10.9
Follow up time (months)	91.6	86.1	1	82.0	54.8	28.0	11.5	123.0	69.2	76.8	89.1	56.6	42.4	25.0	129.7	30.3	120.1
Tubulopathy at onset																	
Glycosuria	+	+	-	NA	+	+	-	NA	NA	+	+	-	+	NA	NA	+	NA
Hypophosphatemia	+	+	+	NA	+	+	+	NA	NA	+	+	+	+	NA	NA	+	NA
Metabolic acidosis	-	-	-	+	+	+	+	+	+	-	-	-	+	+	+	-	+
Metabolic alkalosis	-	-	+	-	-	-	-	-	-	-	-	+	-	-	-	-	-
Normal blood gas	+	+	-	-	-	-	-	-	-	+	+	-	-	-	-	+	-
Extrarenal Findings (during follow up)																	
Ocular involvement	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hypothyroidism	-	-	-	+	-	-	-	+	-	-	-	-	+	-	+	+	+
Rickets	-	-	-	-	-	-	-	-	-	-	-	+	-	-	+	+	+
Treatment Adherence	G	G	G	P	P	G	G	G	P	P	P	P	G	G	P	G	P
Nephrocalcinosis (Present)	+	-	-	+	-	+	-	+	+	-	-	-	-	-	-	-	+
Kidney function status/eGFR (Last)																	
eGFR	155.8	146.2	113.2	10.3	44.0	89.5	193.8	62.4	55.0	75.8	80.9	32.2	133.3	80.6	9.7	77.4	9.10
CKD stage (KDIGO)	G1	G1	G1	G5	G3	G2	G1	G2	G3	G2	G2	G3	G1	G2	G5	G2	G5

G: *Good* ***P:*** *Poor,* ***NA:*** *not avaliable,* ***CKD:*** *Chronic Kidney Disease,* ***KDIGO:*** *Kidney Disease: Improving Global Outcomes*

Table III: Genetic analysis of patients

Patient	Gene (Transcript)	Zygosity	Variation	R/N	ACMG	OMIM	IP
P1	CTNS (NM_001031681)	Homozygous	c.681G>A (p.Glu227Glu)	CS099126	P	Cystinosis (OMIM: 606272)	AR
P2	CTNS (NM_001031681)	Homozygous	c.681G>A (p.Glu227Glu)	CS099126	P	Cystinosis (OMIM: 606272)	AR
P6	CTNS (NM_001031681)	Homozygous	c.681G>A (p.Glu227Glu)	CS099126	P	Cystinosis (OMIM: 606272)	AR
P7	CTNS (NM_004937)	Heterozygous	c.681G>A (p.Glu227Glu)	CS099126	P	Cystinosis (OMIM: 606272)	AR
		Heterozygous	c.1015G>A (p.Gly339Arg)	CM980461	P		AR
P8	CTNS (NM_004937)	Homozygous	c.681G>A (p.Glu227Glu)	CS099126	P	Cystinosis (OMIM: 606272)	AR
P9	CTNS (NM_004937)	Homozygous	c.681G>A (p.Glu227Glu)	CS099126	P	Cystinosis (OMIM: 606272)	AR
P13	CTNS (NM_001031681)	Homozygous	c.681G>A (p.Glu227Glu)	CS099126	P	Cystinosis (OMIM: 606272)	AR
P16	CTNS (NM_004937)	Homozygous	c.18_21delGACT (p.Thr7Phefs*7)	CD982561	P	Cystinosis (OMIM: 606272)	AR

R/N: *reported/nove,* ***ACMG:*** *American College of Medical Genetics and Genomics,* ***OMIM:*** *Online Mendelian Inheritance in Man,* ***IP:****Inheritance pattern,* ***AR:***Autosomal reccessive***, P:*** *pathogenic,* ***CTNS:*** *cystinosis*

When comparing patients' eGFR values at diagnosis (116.66 [62.69] mL/min/1.73 m²) with those at the final follow-up (77.40 [95.18] mL/min/1.73 m²), the median eGFR at follow-up was significantly lower (p=0.007) (Table I). According to the KDIGO classification, 5 patients were in stage G1, 6 in G2, 3 in G3, and 3 in G5 at the final visit, with no patients in G4. In total, 12 patients had an eGFR below 90 mL/min/1.73 m², and 3 of them had progressed to stage 3 chronic kidney disease, while another 3 had developed end-stage kidney disease requiring renal replacement therapy (Table II). Genetic results were available for 8 of the 17 patients, with the identified genetic variants detailed in Table III.

Discussion

In this study, growth retardation, recurrent vomiting, and a positive family history were the most common presenting features that prompted referral to the nephrology clinic. The distribution of presenting symptoms was consistent with previous reports (2, 4). In addition to these primary complaints, parents frequently reported polyuria and polydipsia, reflecting the early onset of tubular dysfunction typical of nephropathic cystinosis. Older patients also described a pronounced tendency toward salt craving, which is commonly observed in the context of chronic electrolyte losses associated with the disease.

Bertholet-Thomas et al. (7) reported that in developing countries patients were slightly older at the time of diagnosis compared to patients diagnosed in developed countries, 1.5 years vs.1.3 years, respectively but the proportion of patients with a diagnosis before 2 years of age was not different between developing and develeped countries. Soliman et al. (12) reported that mean age at the time of diagnosis was above four years (52.7 months) and almost half (44%) of their patients were diagnosed after the age of five years. In our study median age at diagnosis was 10.9 months. Despite limited resources, the relatively younger age at diagnosis in this study group compared to other developing countries may be attributed to heightened clinical awareness, likely influenced by the increased prevalence of consanguineous marriages in the region and the consequent higher incidence of autosomal recessive disorders.

In this study, there were three patients without glucosuria at baseline. Of these, two were patients with a known family history of cystinosis in a sibling (P2, P7), and one presented with a phenotype of Bartter syndrome (P12). In other patients, glucosuria was observed as a reflection of generalized proximal tubular dysfunction. In the same patient group (P2 and P7), bicarbonate levels in blood gas at the time of diagnosis were within low-normal limits. Although renal Fanconi syndrome typically presents with pronounced clinical and laboratory findings, it should be noted that some cases may present with incomplete proximal tubular dysfunction, and it may take time for generalized tubular dysfunction findings to fully manifest (13, 14). In the presence of incomplete renal Fanconi syndrome or metabolic alkalosis instead of metabolic acidosis, diagnosis may delay (12-16).

Failure to thrive is almost a universal finding in cystinosis and other hereditary renal tubular disorders. On the other hand, it has been reported that effective and appropriate treatment can improve weight and height parameters and that catch-up growth can occur in these patients particularly in dRTA (17). However in more complex renal tubular disorders such as cystinosis and renal fanconi syndrome and proximal RTA achieving catch up growth may differ than other hereditary renal tubular disorders such as dRTA (17-20).

In this study, the significant decrease in median height SDS scores observed at the end of a median follow-up period of 69 months was notable. Although all patients included were receiving oral cysteamine therapy, the decline in height SDS scores may be attributed to several potential factors. Despite treatment, patients with renal Fanconi syndrome experience loss of final adult height, due to a variety of factors such as chronic hypokalemia, persistant metabolic acidosis and consequences, phospate loss and resultant defective bone mineralisation and inadequate intake of required daily energy due to polydypsia and loss of appetite (18-21). Also nutritional deficiencies and the effects of hormones such as growth hormone and thyroid hormones may play a role in growth retardation. Particularly in patients with cystinosis, the feeling of fullness and abdominal distention due to polyuria and polydipsia can restrict adequate caloric intake, leading to

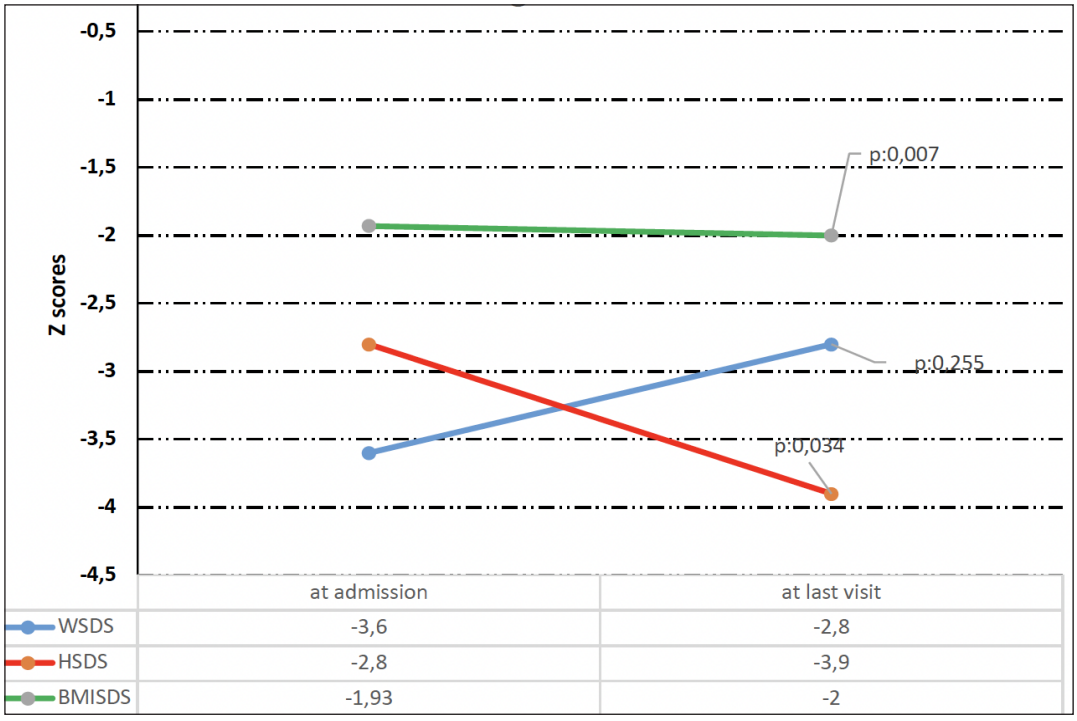

Figure 1: Changes in median weight for age,height for age and body mass index Z scores

nutrient deficiencies and anemia. Additionally, hypothyroidism is not uncommon in patients with cystinosis and may contribute to retarded growth (22). In our study, patients were screened for hypothyroidism during their follow-ups and 6 out of 17 patients were started on levothyroxine. Furthermore, given that 6 of the 17 patients had advanced-stage chronic kidney disease (3 patients with stage 3 CKD and 3 with end-stage renal disease requiring dialysis), we can speculate that the impact of hormonal factors, particularly within the growth hormone axis, becomes increasingly evident as chronic kidney disease progresses and renal function deteriorates.

In this study, nephrocalcinosis was detected in 6 patients. Nephrocalcinosis in patients with cystinosis may develop due to significant calcium and phosphorus loss and the balance between fluid intake and loss, but it can also arise as a complication related to supportive therapies containing active vitamin D, calcium, and phosphorus (23). Although this study does not permit definitive conclusions regarding the impact of nephrocalcinosis on renal function, we contend that it is essential to evaluate the relationship between nephrocalcinosis and GFR loss in larger cohorts.

Upon analysis of patients over the age of 1 at admission, a total of 8 patients exhibited eGFR greater than 90 ml/min/1.73 m^2 at baseline, which subsequently declined to below 90 at the final follow-up. Among these patients, 3 were undergoing peritoneal dialysis, while 3 had progressed to stage 3 chronic kidney disease in a pre-dialysis state. Despite all patients having initiated cysteamine therapy, the relatively high incidence of renal failure in this cohort is a matter of concern. We believe that this situation may be significantly related to the treatment adherence related with socioeconomic conditions and family structures in the region. Specifically, low literacy rates and large family sizes appear to be factors that reduce treatment adherence. From a clinician's perspective, the regular monitoring of leukocyte cystine levels, alongside essential clinical and laboratory parameters, is crucial for assessing treatment efficacy. Unfortunately, due to the inability to measure leukocyte cystine levels in the region, patients are required to seek care at larger centers for this assessment. This situation poses socioeconomic challenges for families and complicates optimal treatment monitoring. Additionally, side effects related to the medication, such as taste disturbances and vomiting, can hinder the attainment of effective dosing, potentially leading to treatment non-adherence.

Conclusion

While the progression to kidney failure in patients with cystinosis undergoing cysteamine treatment may be manageable the optimal management of these patients continues to pose a substantial challenge for clinicians, particularly in developing countries and in regions that are remote from major experienced medical centers. We think that, in light of the literature, cystinosis can be viewed as two distinct entities—before and after the initiation of cysteamine treatment—particularly in developed countries. However, in resource-limited settings, cystinosis remains an orphan condition and continues to be a significant cause of chronic kidney failure.

Limitations

The limitations of this study include its retrospective nature and the challenges in accessing data for some patients who were referred from different centers. Although all patients were followed periodically, treatment adherence was evaluated

subjectively, which may introduce potential misclassification bias. Additionally, the inability to routinely measure leukocyte cystine levels limited the objective assessment of metabolic control and prevented a more accurate correlation between adherence and renal outcomes. The relatively small sample size, inherent to the rarity of the disease, may also restrict the generalizability of our findings.

Ethics committee approval

This study was conducted in accordance with the Helsinki Declaration Principles. The study was approved by Van Research and Education Hospital (15.09.2023, number: 2023/09-06).

Contribution of the authors

Study conception and design: AY, OG; data collection: AY; analysis and interpretation of results: AY,OG; draft manuscript preparation: AY. All authors reviewed the results and approved the final version of the article.

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Conflict of interest

The authors declare that there is no conflict of interest.

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