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Kidney Disease in Adenine Phosphoribosyltransferase Deficiency

Hrafnhildur Linnet Runolfsdottir, BS[1], **Runolfur Palsson, MD**[1,2], **Inger M. Sch. Agustsdottir, RN**[3], **Olafur S. Indridason, MD, MHS**[2], and **Vidar O. Edvardsson, MD**[1,3]

[1]Faculty of Medicine, School of Health Sciences, University of Iceland, Reykjavik, Iceland
[2]Division of Nephrology, Internal Medicine Services [3]Children's Medical Center, Landspitali - The National University Hospital of Iceland

Abstract

Background—Adenine phosphoribosyltransferase (APRT) deficiency is a purine metabolism disorder causing kidney stones and chronic kidney disease (CKD). The course of nephrolithiasis and CKD has not been well characterized. The objective of this study was to examine long-term kidney outcomes in patients with APRT deficiency.

Study Design—An observational cohort study.

Setting & Participants—All patients enrolled in the APRT Deficiency Registry of the Rare Kidney Stone Consortium.

Outcomes—Kidney stones, acute kidney injury (AKI), stage of CKD and kidney failure, estimated glomerular filtration rate (eGFR) and changes in eGFR.

Measurements—Serum creatinine and eGFR calculated using creatinine-based equations.

Results—Of 53 patients, 30 (57%) were female and median age at diagnosis was 37.0 (range, 0.6–67.9) years. The median duration of follow-up was 10.3 (range, 0.0–31.5) years. At diagnosis, kidney stones had developed in 29 patients (55%) and 20 (38%) had CKD stages 3–5, including 11 patients (21%) with stage 5. At latest follow-up, 33 patients (62%) had had kidney stones; 18 (34%), AKI; and 22 (42%), CKD stage 3–5. Of the 14 (26%) patients with CKD stage 5, 12 had

Corresponding author: Vidar Orn Edvardsson, MD, Children's Medical Center, Office 21-D, Landspitali – The National University Hospital of Iceland, Hringbraut, 101 Reykjavik, Iceland, Phone: +354-543-1000, Fax: +354-543-3021, vidare@lsh.is.

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Contributions: Conception and study design: RP, VOE; statistical analysis: HLR, OSI; critical review of results: HLR,, IMA, OSI, RP, VOE; supervision and mentorship: OSI, RP, VOE. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved. VOE takes responsibility that this study has been reported honestly, accurately, and transparently; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

initiated renal replacement therapy. Kidney stones recurred in 18 of 33 patients (55%). The median eGFR slope was −0.38 (range, −21.99 to 1.42) mL/min/1.73 m2 per year in patients receiving treatment with xanthine dehydrogenase inhibitor and −5.74 (range, −75.8 to −0.10) mL/min/1.73 m2 per year in those not treated prior to the development of stage 5 CKD (p=0.001).

Limitations—Use of observational registry data.

Conclusions—Progressive CKD and AKI episodes are major features of APRT deficiency, while nephrolithiasis is the most common presentation. Advanced CKD without history of kidney stones is more prevalent than previously reported. Our data suggest that timely therapy may retard CKD progression.

Index words

end-stage kidney disease; chronic kidney disease (CKD); Adenine phosphoribosyltransferase (APRT) deficiency; purine metabolism disorder; nephrolithiasis; kidney stone; crystal nephropathy; estimated glomerular filtration rate (eGFR); renal function; acute kidney injury (AKI), disease progression; kidney failure; renal replacement therapy (RRT)

Adenine phosphoribosyltransferase (APRT) deficiency is an uncommon autosomal recessive disorder of purine metabolism that leads to kidney stones and chronic kidney disease (CKD).[1, 2] Absence of APRT enzyme activity prevents the recycling of adenine, which instead is catabolized by xanthine dehydrogenase (XDH) to 2,8-dihydroxyadenine (2,8-DHA), a poorly soluble substance excreted by the kidney resulting in heavy crystalluria (Figure 1). Over 40 mutations in the coding region of *APRT* have been identified in more than 400 affected people from more than 25 countries,[3, 4] the majority of whom are from France, Iceland and Japan while less than 15 patients originate in the United States.[2] All known pathogenic mutations abolish enzyme function.[1, 5]

The phenotype is characterized by radiolucent kidney stones, the most commonly reported clinical manifestation of APRT deficiency, followed by progressive CKD secondary to crystal nephropathy. In fact, kidney failure requiring renal replacement therapy (RRT) is the presenting feature in approximately 15% of adult cases.[1, 5] In a number of instances, APRT deficiency has first been recognized after kidney transplantation, when allograft dysfunction occurs.[6, 7] Other reported clinical manifestations include hematuria and lower urinary tract symptoms. A significant number of patients are asymptomatic at diagnosis.[1, 2, 8] Treatment with the XDH inhibitor allopurinol has been shown to effectively prevent the progression of kidney disease and the recently introduced non-purine XDH inhibitor, febuxostat, has provided an alternative therapeutic option.

Limited data exist on kidney stone recurrence, and the course of kidney function over time has not been well characterized in patients with APRT deficiency. In order to closely examine long-term kidney outcomes, we analyzed data from all subjects currently enrolled in the APRT Deficiency Registry of the Rare Kidney Stone Consortium.

Methods

Study Design

This was an observational cohort study using data from the APRT Deficiency Registry of the Rare Kidney Stone Consortium (www.rarekidneystones.org/). The study was approved by the National Bioethics Committee of Iceland (NBC 09-072) and the Icelandic Data Protection Authority, and informed consent was obtained from all living participants. The clinical and research activities reported are consistent with the Principles of the Declaration of Helsinki. Data from all 53 patients (from Iceland, 33; United States, 13; Austria, 2; Italy, 2; United Kingdom, 1; India, 1; and from Norway of Turkish descent, 1) who enrolled in the registry before November 11, 2014 were included. Limited data on 23 of the 33 Icelandic patients have previously been reported by our group[1] and 5 of the non-Icelandic cases were included in earlier publications.[7, 9, 10]

Clinical Data

The registry data included age at diagnosis; kidney manifestations, including kidney stones, acute kidney injury (AKI) and stage of CKD; lower urinary tract symptoms; results of urological imaging studies, kidney stone analysis, and kidney biopsies; surgical treatment of kidney stones; XDH inhibitor treatment; RRT; and cause of death. For calculation of estimated glomerular filtration rate (eGFR) in children, height measurements were obtained from medical records or extrapolated from data points on the growth chart when recent measurements were not available. Laboratory studies included serum creatinine (Scr) measurements, results of urine microscopy, including assessment of 2,8-DHA crystals, *APRT* genotype, and APRT enzyme activity.

Definitions

Symptomatic kidney stone events were defined as either patient reported stone passage or abdominal pain associated with hematuria and/or a stone confirmed by an imaging study. Urinary tract stones identified by imaging only were considered asymptomatic. Stone recurrence was defined as detection of a stone in patients previously shown to be stone-free by imaging study. The eGFR was calculated from Scr, using the CKD-EPI (CKD Epidemiology Collaboration) creatinine equation in adults[11] and the modified Schwartz equation[12] in children. Non-standardized Scr values were reduced by 5% before eGFR was calculated, as previously described.[13] All patients were considered to have CKD based on presumed structural damage associated with renal 2,8-DHA crystal deposition. The KDIGO (Kidney Disease: Improving Global Outcomes) classification system was used to stage CKD[14]. Available Scr values were used to identify episodes of AKI, defined according to the KDIGO criteria as increase in Scr of ≥26.5 μmol/L (≥0.3 mg/dL) within 48 hours or ≥1.5 times baseline within 7 days.[15]

Statistical Analysis

Statistical analyses were performed using SPSS (IBM SPSS Statistics version 21.0, 2012, Armonk, NY, USA). Data are presented as number, percentage and median (range). Chi-square analysis was used to compare the prevalence of CKD in Icelandic patients and those

from other countries. Slopes of eGFR and staging of CKD were based on annual eGFR values derived from the lowest available Scr measurement in each calendar year, excluding all Scr values obtained during episodes of AKI; patients receiving RRT were assigned an eGFR of 10 mL/min/1.73 m^2. Comparison of eGFR slopes of patients receiving XDH inhibitor treatment and those who were untreated prior to the development of end-stage kidney failure were compared using the Mann-Whitney U test. The Wilcoxon signed-rank test was used to compare eGFR slopes of patients before and after the initiation of pharmacotherapy. A $P < 0.05$ was considered statistically significant.

Results

Clinical Characteristics

The 53 patients belonged to 42 families. Fifty patients were white; one, African American; one, Indian; and one, of Japanese descent. Thirty patients (57%) were female. The median age at diagnosis was 37.0 (range, 0.6–67.9) years and the age of symptomatic and asymptomatic patients was 40.6 (range, 0.6–67.9) and 25.7 (range, 3.6–39.2) years, respectively. The median duration of follow-up after diagnosis was 10.3 (range, 0.0–31.5) years and the median age at last follow-up was 43.2 (range, 2.7–75.0) years. The median number of Scr values per patient was 10 (range, 2–130). Clinical characteristics of the 53 patients at the time of diagnosis are presented in Table 1. The most frequently noted clinical manifestation was nephrolithiasis (n=29); 20 patients had CKD stages 3–5, which occurred in 9 patients without a history of kidney stones, and 16 patients had AKI or a history of the condition. Five asymptomatic individuals, identified by the detection of 2,8-DHA crystals on urine microscopy, were diagnosed in childhood or early adulthood. Kidney stones were a more frequent presentation than CKD stages 3–5 in childhood, while advanced CKD was more commonly observed in adults (Figure 2).

Table 2 outlines the clinical course and management of all 33 patients who eventually developed kidney stones. Twenty-nine had had 80 symptomatic stone events at the time of diagnosis. In 20 of those patients, stones were first detected a median of 10.5 (range, 0.8–47.9) years before the diagnosis of APRT deficiency but in 9 patients the disorder was diagnosed during the initial stone event.

Two of the 16 patients who had AKI prior to diagnosis required transient hemodialysis, while 2 additional patients who developed AKI at a later stage responded well to conservative treatment. The causes of AKI included biopsy-proven crystal nephropathy in 7 patients, urinary tract obstruction from stones in 9 and volume depletion in 2. Ten of the 18 patients with AKI developed CKD stages 3–5 at a median of 1.6 (range, 0.3–29.5) years after the AKI event.

Stages of CKD and the requirement for RRT are presented in Table 3. The median age of the 20 patients who had developed CKD stages 3–5 at diagnosis was 44.5 (range, 11.9–67.9) years. Two additional patients had CKD stages 3–5 during follow-up. Six patients had initiated RRT a median of 3.8 (range, 1.1–7.4) years prior to the diagnosis of APRT deficiency, including 4 with recurrent 2,8-DHA allograft nephropathy. In addition, one Icelandic patient died from complications of kidney failure in 1967, before APRT deficiency

was first described. Of 14 patients with CKD stage 5 at latest follow-up, 12 had initiated RRT, of whom 11 had undergone kidney transplantation and received a total of 15 allografts. Three patients died with a functioning graft at a median age of 43.2 (range, 36.7–51.9) years.

Thirteen of the 20 patients (65%) from countries other than Iceland had developed CKD stages 3–5 at diagnosis compared with only 7 of the 33 (21%) Icelandic patients (p=0.001; Figure 3). Eight non-Icelandic patients had already initiated RRT at diagnosis, compared with no Icelandic patient.

Diagnosis of APRT Deficiency

The diagnosis of APRT deficiency was initially suggested by detection of urinary 2,8-DHA crystals in 34 cases, by histological findings of crystal nephropathy in 9, and kidney stone analysis in 8 cases. Two cases were diagnosed post-mortem by review of autopsy findings which were consistent with 2,8-DHA crystal nephropathy. In all cases, the diagnosis of APRT deficiency was confirmed by genetic testing (n=46) and/or absence of APRT enzyme activity in red cell lysates (n=11). A total of 10 different pathogenic variants in the *APRT* gene were identified, including one novel mutation. All 33 Icelandic patients were homozygous for the missense variant c.194A>T (p.Asp65Val; ie, an adenine to thymine change at nucleotide 194 of the complementary DNA, leading to a aspartate to valine substitution at amino acid 65) and 4 American and one Indian patients were found to be homozygous for c.400+2dup (IVS4+2insT; ie, a duplication of the thymine found at nucleotide 2 of the fourth intervening sequence of the *APRT* complementary DNA) which results in aberrant splicing and deletion of exon 4.

A median delay in diagnosis of 7.5 (range, 0.4–47.9) years occurred in 37 patients following their first symptomatic stone event or detection of elevated Scr. Misidentification of radiolucent kidney stones as uric acid calculi in 4 patients and confusion of renal histopathological findings with other forms of crystal nephropathy in 6 patients contributed to the diagnostic delay, whereas urinary 2,8-DHA crystals were not correctly identified in 17 cases.

Pharmacologic Treatment

While 52 of the 53 patients were prescribed therapy with allopurinol at some point, none of the 11 patients who had developed CKD stage 5 by the time of diagnosis had received XDH inhibitor therapy. The clinical features of patients who received allopurinol treatment prior to initiation of RRT and those who did not are presented in Figure 4. Thirty-eight adult patients initiated allopurinol treatment, at a median age of 42.2 (range, 20.5–62.8) years with a daily dose of 100 mg (n=7), 150 mg (n=3), 200 mg (n=21) or 300 mg (n=7). In 14 children, allopurinol therapy was begun at a median age of 3.3 (range, 0.6–16.6) years at a median daily dose of 8 (range, 3–11) mg/kg or total dose of 100 (range, 25–200) mg. The prescribed dose of allopurinol increased over time and, at latest follow-up, 13 adult patients were receiving doses as high as 400–600 mg/d, regardless of kidney function. Allopurinol was discontinued in 7 patients after a median 7.1 (range, 0.4–16.4) years of treatment due to presumed adverse reactions that included itching, hair loss and severe ocular symptoms,

such as pain and photosensitivity and blurred vision. These patients were taking a median of 300 (range, 100–600) mg of allopurinol daily. All 7 of these patients were subsequently prescribed febuxostat, 80 mg daily, once the drug became available. Febuxostat use was discontinued in 2 patients due to severely blurred vision and punctate keratitis in one patient and ocular dryness in the other. Of 12 minimally symptomatic patients who began XDH inhibitor therapy at a median age of 7.5 (range, 1.0–39.2) years, none subsequently developed kidney stones, AKI or CKD stages 3–5. Absence of urinary 2,8-DHA crystals was generally considered indicative of adequate drug dosing. However, quantitative assessment of crystalluria was not systematically performed.

Eighteen patients (34%) had 35 clinical stone events while receiving allopurinol treatment (Table 2), most frequently at a daily dose of 300 mg (n=8). One patient with CKD stage 3b, one with stage 4 and another with stage 5 had temporary improvement in kidney function after initiation of XDH inhibitor treatment. Nevertheless, 2 additional patients developed CKD stage 3–5 (Table 3).

Evolution of Kidney Function in Patients With APRT Deficiency

The median eGFR in the 53 patients was 68 (range, 3–165) mL/min/1.73 m^2 at diagnosis, which included several patients with AKI, and 73 (range, 10–163) mL/min/1.73 m^2 at latest follow-up. A boxplot of eGFR in different age groups demonstrated a relatively low median eGFR, particularly after age 40 years (Figure 5). The median eGFR slope was −0.38 (range, −21.99 to 1.42) mL/min/1.73 m2 per year in patients receiving pharmacotherapy and −5.74 (range, −75.8 to −0.10) mL/min/1.73 m2 per year in those not treated prior to the development of CKD stage 5 (p=0.001). In 7 patients who had serial Scr measurements available before and after the initiation of XDH inhibitor therapy, the median eGFR slopes were −3.01 (range, −14.43 to 0.92) and 1.76 (range, −0.7 to 13.50) mL/min/1.73 m2 per year, respectively (p=0.04). Finally, the median eGFR slope was 1.88 (range, −4.16 to 5.12) mL/min/1.73 m2 per year in 9 patients with CKD stage 3 or 4 when pharmacotherapy was initiated.

Discussion

Our findings demonstrate a highly variable clinical presentation and course of kidney disease in patients with APRT deficiency. The most commonly observed clinical manifestations were nephrolithiasis, episodes of AKI, and progressive CKD, eventually requiring dialysis or kidney transplantation in a significant proportion of patients. Interestingly, a considerable number of patients with advanced CKD had no history of kidney stones. Patients who progressed to kidney failure almost invariably had not received XDH inhibitor treatment, whereas timely pharmacotherapy retarded or prevented CKD progression. Lack of awareness of APRT deficiency appears to have resulted in marked treatment delay, particularly in non-Icelandic patients.

Approximately half of the patients in our study had developed kidney stones by the time of diagnosis. This is substantially less than in the largest previously reported series from France[5], in which 90% of the 40 patients with available clinical data had had kidney stones at diagnosis. Interestingly, recurrent stone events were observed more frequently in our

patients, despite the use of similar doses of allopurinol.[5, 8] The reasons for this observed difference in stone recurrence may include the longer median observation period and the relative completeness and quality of data obtained at scheduled annual follow-up visits for a large proportion of our cohort, reducing the likelihood that stone events were missed. Difference in adherence to allopurinol therapy may also have played a role.

One-third of our patients had episodes of AKI, which previously has only rarely been reported for APRT deficiency. In the aforementioned French cohort[5], only a single case of AKI was noted. A likely explanation for the relatively high frequency of AKI in our study is the availability of numerous Scr values over many years for most of the patients, allowing more sensitive detection of AKI. While recovery of kidney function occurred in all these patients, our findings suggest that AKI may contribute to disease progression.

The proportion of patients with CKD stages 3–5 in our cohort was similar to that observed in the French study.[5] However, the absence of nephrolithiasis in many of our patients with CKD stages 3–5 is striking because stone disease has generally been considered the characteristic feature of APRT deficiency. Another noteworthy finding of our study is the much lower prevalence of advanced CKD or kidney failure in the Icelandic patients compared with those from other countries. This observation together with the relatively low number of reported cases in these countries suggests lack of awareness of APRT deficiency as a cause of CKD and crystal nephropathy among nephrologists and renal pathologists. In fact, misinterpretation of kidney biopsy findings contributed to diagnostic delay in at least 6 patients in our study. When the histological examination of a renal tissue reveals a crystal-associated tubulointerstitial lesion, 2,8-DHA nephropathy should always be considered.[2, 7, 16] Polarized light microscopy facilitates the identification of renal parenchymal crystal deposits, but caution must be exercised to avoid confusion of 2,8-DHA with oxalate.[2, 7] While crystal nephropathies are associated with inflammation and fibrosis leading to progressive kidney damage, the pathogenesis of crystal-induced injury in humans remains elusive. The best characterized mediator of crystal-induced inflammation is the intracellular NLRP3 inflammasome, which has been shown to cause direct injury to tubular cells, tubulointerstitial inflammation and kidney failure in oxalate nephropathy.[17, 18]

Earlier studies[5, 8] have described improvement in eGFR following onset of allopurinol therapy. When we included acutely elevated Scr measurements obtained at the time of diagnosis, we observed a similar improvement in eGFR, which may in part reflect the effect of pharmacologic therapy. In contrast, we carefully excluded episodes of AKI when characterizing the course of kidney function. As previously reported,[1, 5] treatment with an XDH inhibitor, primarily allopurinol, clearly stabilized or improved kidney function in our cohort, whereas eGFR invariably declined in untreated cases. Indeed, allopurinol treatment preserved kidney function and prevented stone formation for decades in a subgroup of patients with minimal or no symptoms at diagnosis. The frequent development of advanced CKD and end-stage kidney failure in patients not receiving XDH inhibitor treatment underscores the importance of timely diagnosis and pharmacotherapy.

Presumed adverse reactions precluded the use of allopurinol or febuxostat in several patients in our study.[19] However, the eye symptoms that led to discontinuation of XDH inhibitor

therapy have not been previously reported for these drugs except as a part of allopurinol hypersensitivity syndrome.[20, 21] While APRT deficiency has not been clearly demonstrated to affect other organ systems than the kidneys and urinary tract, 2 cases of corneal dystrophy were reported in Belgium in 1986 and the authors concluded that corneal crystal deposition was a probable cause, although this was not histologically confirmed.[22] No other reports of ocular manifestations in patients with APRT deficiency exist. Nevertheless, the frequently reported eye symptoms by the patients in our study warrant further investigation to determine whether corneal 2,8-DHA crystal deposits do occur.

The dose of XDH inhibitors required to adequately reduce urinary 2,8-DHA excretion has not been defined. The adverse outcomes observed in our cohort, particularly progressive allograft dysfunction, suggest a need for higher doses of allopurinol than have generally been used, perhaps in the range of 600–800 mg daily. In the past, it has been recommended to avoid using allopurinol doses above 200–300 mg per day in patients with CKD based on a report of increased risk of allopurinol hypersensitivity syndrome.[23] Later studies have contradicted this notion.[24] However, it is recommended to begin with a low dose as recent work has shown that higher starting doses of allopurinol may increase the risk of allopurinol hypersensitivity syndrome.[25] The response to therapy has generally been monitored by assessment of 2,8-DHA crystals in the urine sediment, which may not be accurate enough to guide drug treatment. Therefore, reliable methods for the measurement of urinary 2,8-DHA are needed. An assay using ultra high-performance liquid chromatography-tandem mass spectrometry for measurement of urinary 2,8-DHA is currently being developed by our group.

The reason for the relatively high number of APRT deficiency cases reported in Japan, France and Iceland compared to in the United States is not clear. Based on reported heterozygote frequency rates of 0.4%–1.2%,[4, 26] one might expect 3,000–6,000 cases of APRT deficiency in the United States. However, a recent report of kidney stone composition from 43,545 US patients did not reveal a single 2,8-DHA stone, which would suggest a lower prevalence.[27] Because APRT deficiency is a preventable cause of CKD, strategies to increase awareness among clinicians and pathologists are important. The disorder should be considered in the differential diagnosis of radiolucent kidney stones and unexplained CKD, and in cases of kidney allograft dysfunction of unclear etiology.

Absence of APRT enzyme activity in red cell lysates and the identification of functionally significant mutations in both copies of the *APRT* gene are the only reliable methods for the diagnosis of APRT deficiency.[2] Based on reports in the literature and our own experience, urine microscopy has not proved to be reliable enough as the sole method for diagnosis of APRT deficiency. The 2,8-DHA crystals have frequently either been overlooked or not recognized or misidentified. Infrared spectroscopy, which is considered the gold standard technique for stone analysis, has, in experienced hands, been shown to be a reliable test for detecting 2,8-DHA in stone materials. However, the 2,8-DHA spectrum can be confused with uric acid as is illustrated by 3 cases recently referred to us. Hence, identification of 2,8-DHA in stones with the infrared technique cannot be considered diagnostic of APRT deficiency.

Strengths of the current study include the abundance of data entered into the APRT Deficiency Registry of the Rare Kidney Stone Consortium, which contains over 950 patient-years of clinical information, making this the largest patient cohort with complete clinical data and the longest observation time reported to date. Furthermore, the availability of multiple Scr values for most patients facilitated accurate ascertainment of AKI, CKD staging and characterization of the course of kidney function.

Limitations of the study include a small sample size, as is expected for any rare disease, and the use of observational registry data. As a result, the duration of observation varied as did the scope of laboratory evaluation. Moreover, the large proportion of patients from Iceland, where the awareness of APRT deficiency appears high, may limit the conclusions that can be drawn regarding variability in clinical presentation and outcomes between countries. However, factors such as the rate of 2,8-DHA production may influence clinical expression and warrant further investigation.

In conclusion, our study indicates that the clinical presentation of APRT deficiency may be more variable than previously suggested. Both AKI and progressive CKD have emerged as major features of APRT deficiency, while nephrolithiasis remains the most common presenting manifestation. Timely pharmacologic therapy appears to slow the progression of CKD, even in severely affected individuals. The relatively frequent occurrence of advanced CKD and even kidney failure at diagnosis is concerning and suggests a lack of familiarity with this treatable condition. This underscores the importance of a kidney biopsy in younger patients with unexplained CKD.

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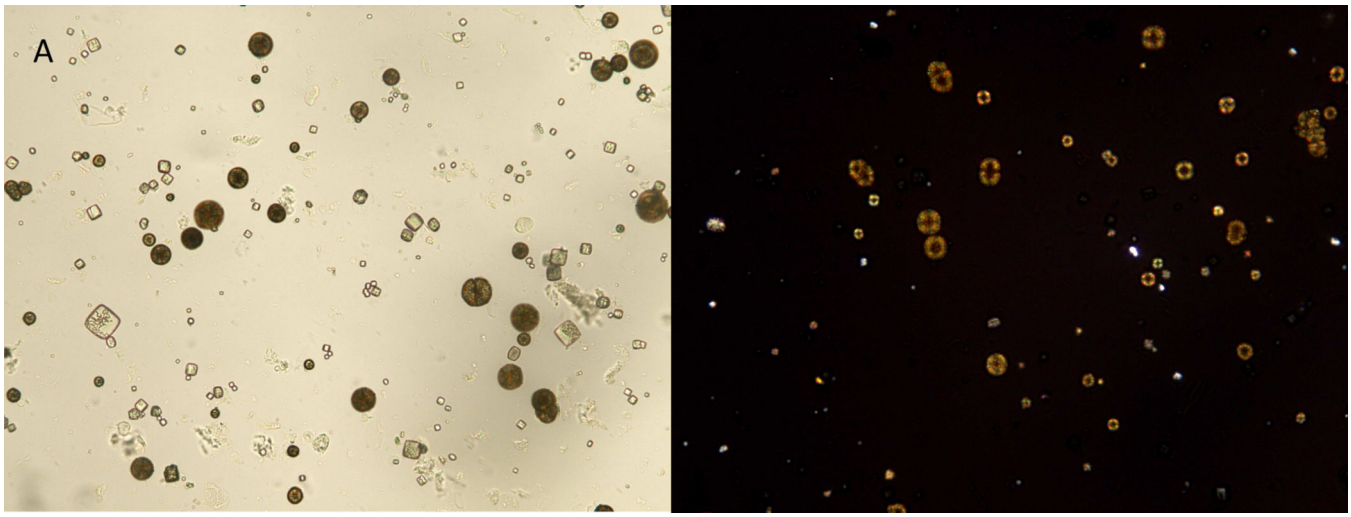
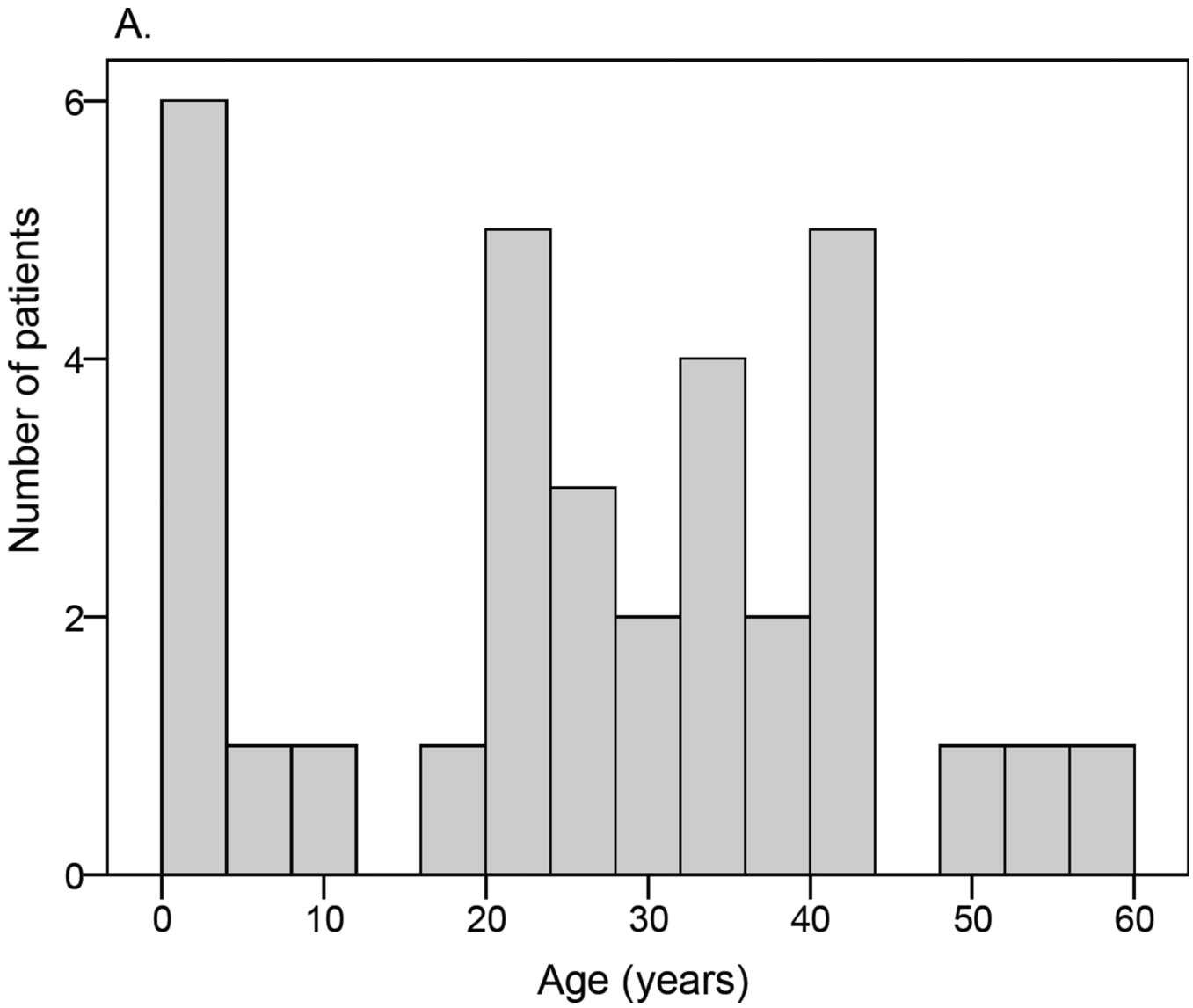


Figure 1.

Urinary 2,8-dihydroxyadenine crystals. (A) The characeristic medium-sized crystals are brown with a dark outline and central spicules. (Original magnification, ×400). (B) The same field viewed with polarized light microscopy shows that the small- and medium-sized crystals appear yellow in color and produce a central Maltese cross pattern. (Original magnification, ×400)



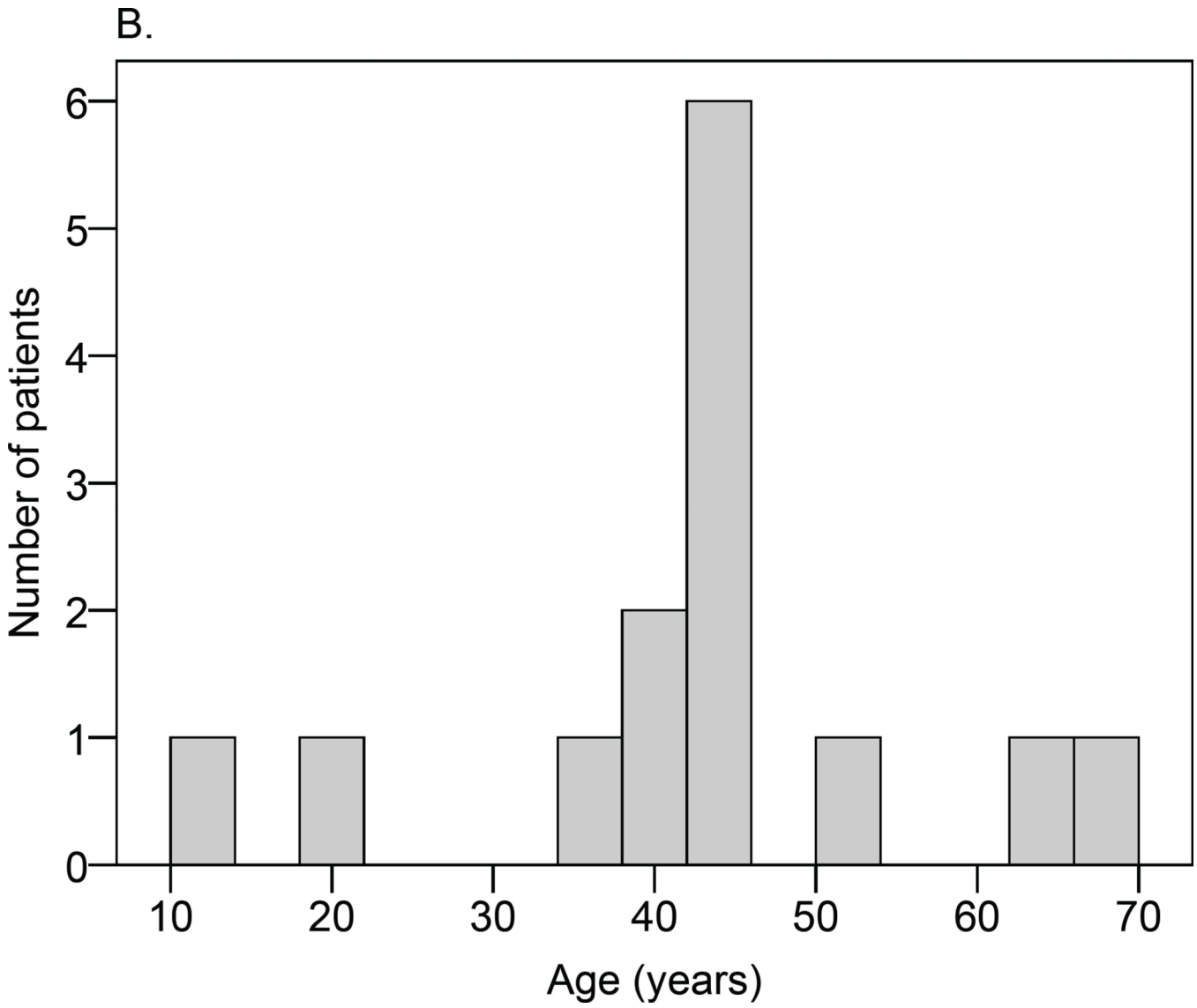


Figure 2.

Age distribution (A) at the occurrence of first kidney stone event and (B) at the detection of CKD stage 5 in patients with adenine phosphoribosyltransferase deficiency.

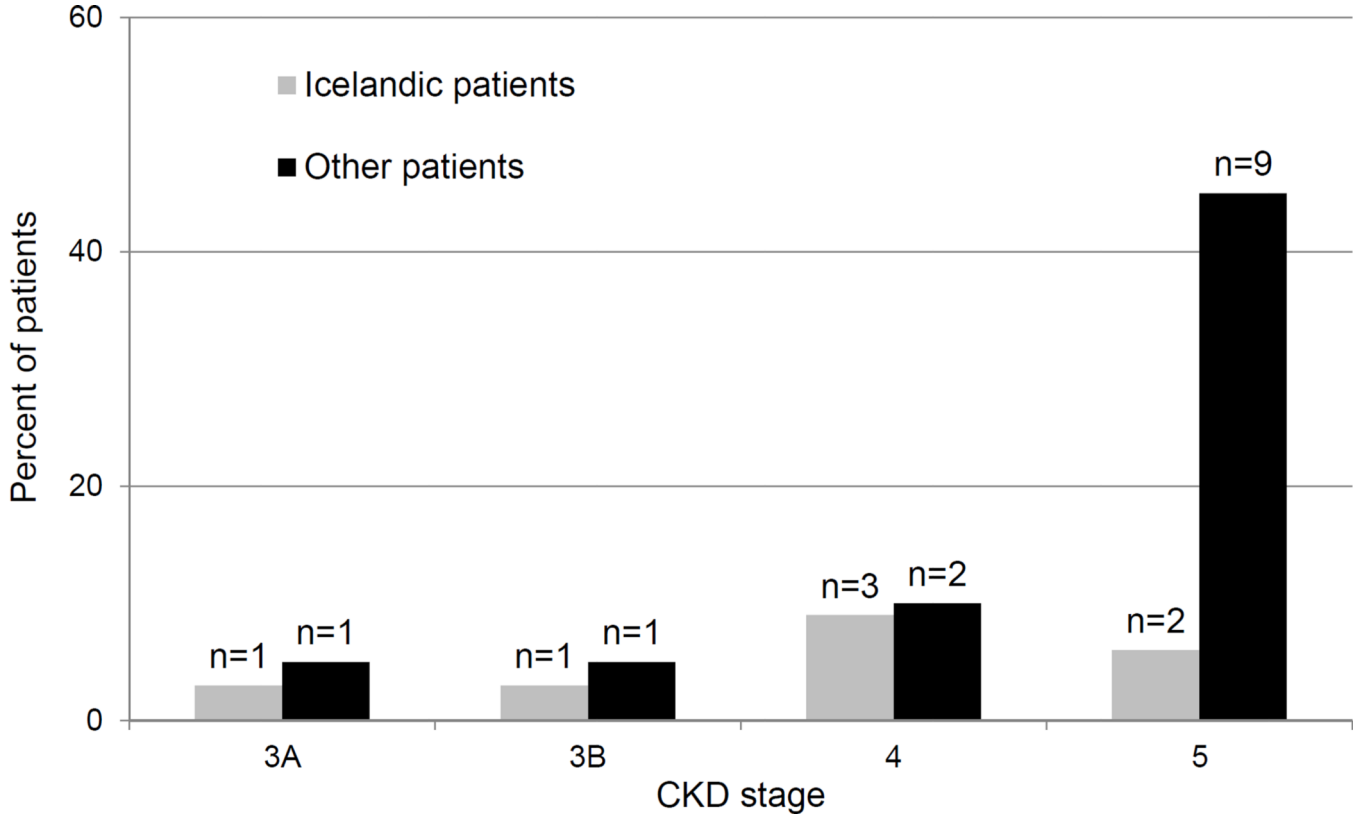


Figure 3.

Chronic kidney disease stages 3–5 in patients with adenine phosphoribosyltransferase deficiency from Iceland and other countries at the time of diagnosis. Abbreviations: CKD, chronic kidney disease.

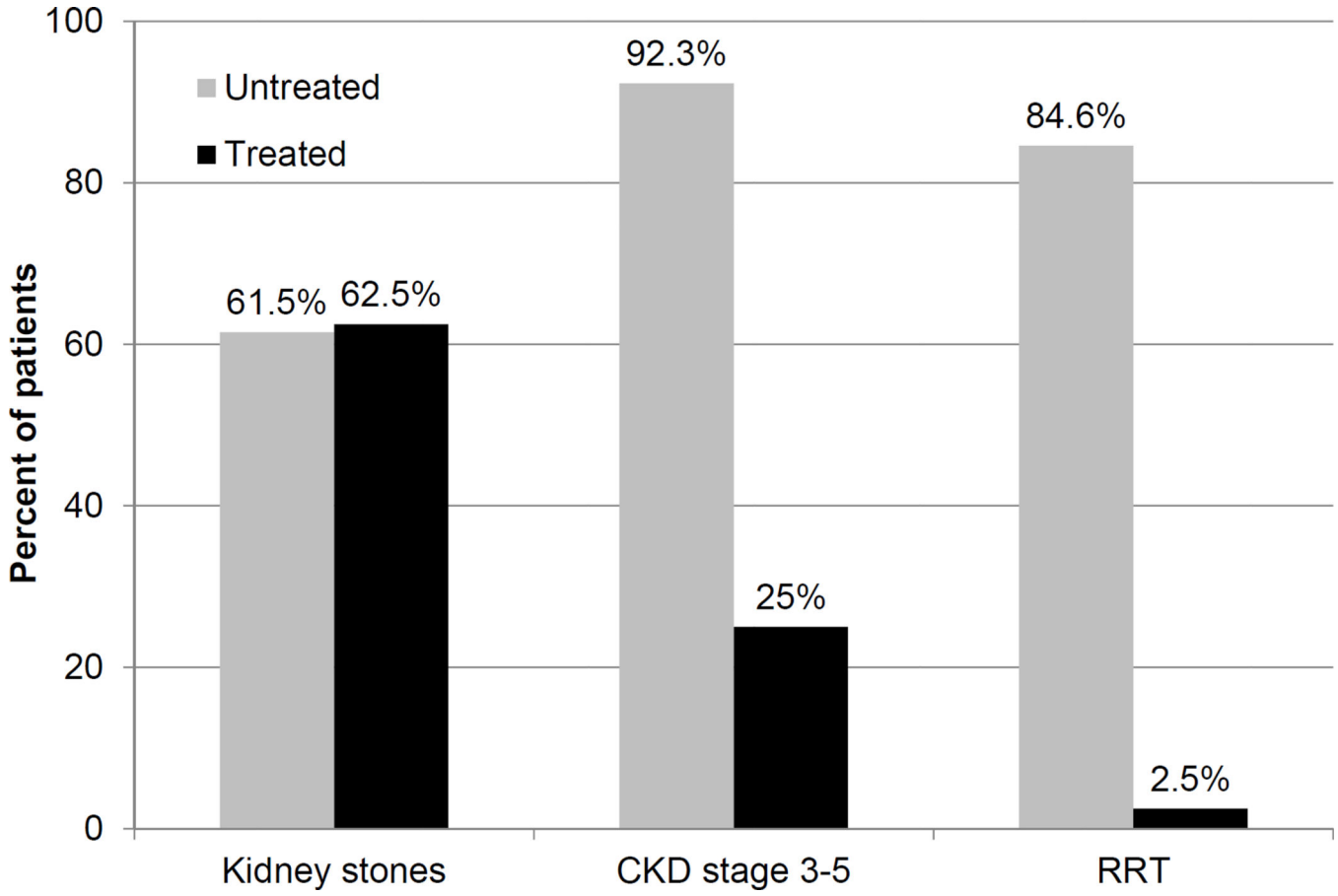


Figure 4.

Kidney stones, chronic kidney disease stages 3–5 and initiation of renal replacement therapy in patients with adenine phosphoribosyltransferase deficiency who received xanthine dehydrogenase inhibitor treatment and those who did not. Abbreviations: KS, kidney stones; CKD, chronic kidney disease; RRT, renal replacement therapy.

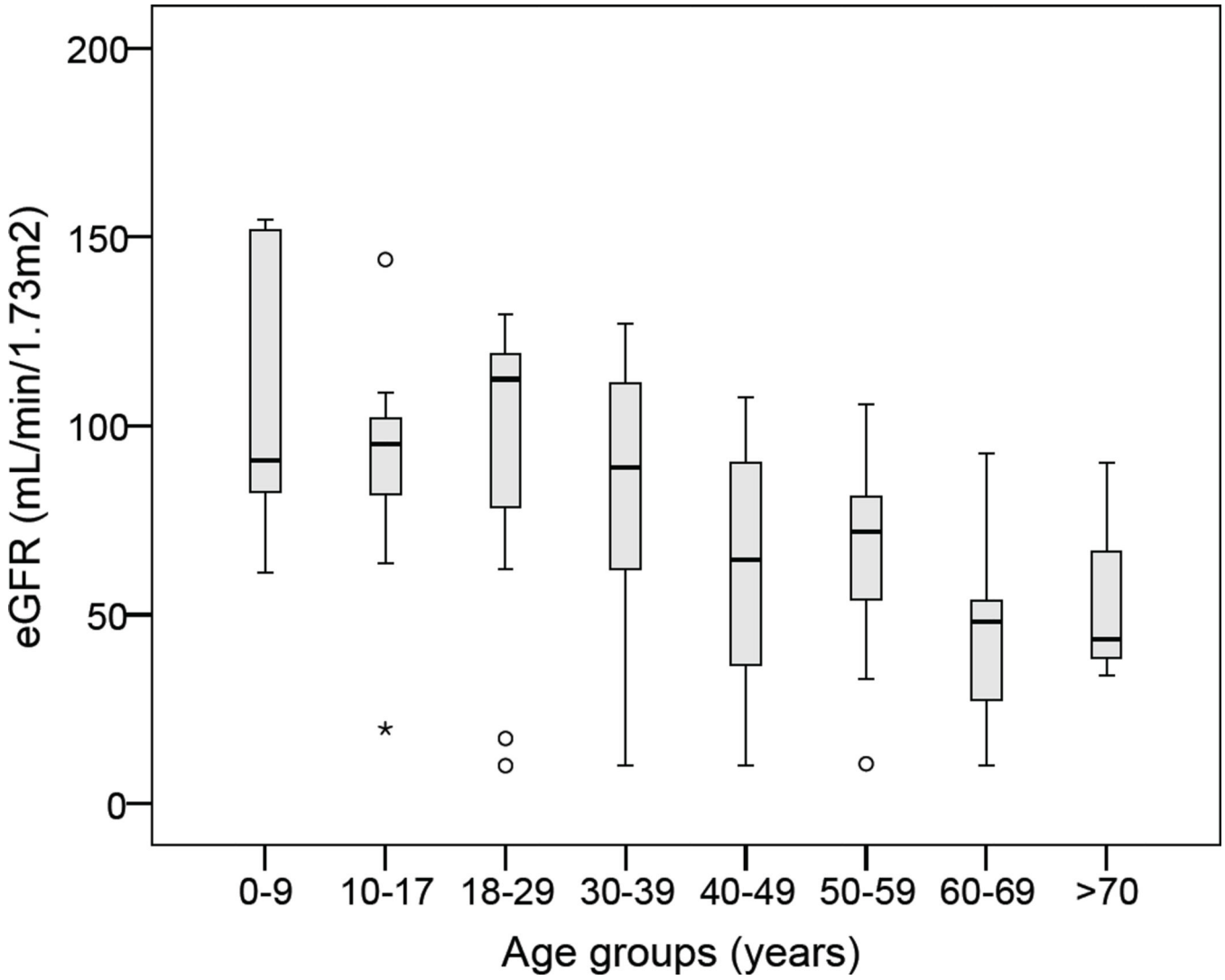


Figure 5.

Boxplot of estimated glomerular filtration rate in different age groups of patients with adenine phosphoribosyltransferase deficiency. Patients contributed data to every age group for which they had serum creatinine value available and for each individual the mean of all eGFR values in any given age group was used. Patients receiving renal replacement therapy were assigned an eGFR of 10 mL/min/1.73m^2. Abbreviations: eGFR, estimated glomerular filtration rate.

Table 1

Clinical characteristics at diagnosis of APRT deficiency

Characteristic	Value
Female sex	30 (57)
Age	
Median (range), y	37.0 (0.6–67.9)
<18 y	14 (26)
≥18 y	39 (74)
Kidney stones	29 (55)
Chronic kidney disease stages 3–5	20 (38)
Renal replacement therapy	8 (15)
Acute kidney injury	16 (30)
Lower urinary tract symptoms	15 (28)
Reddish-brown diaper stain in infancy	11 (21)
2,8-DHA crystalluria	34 (64)
Asymptomatic	5 (9)
Family screening	3
Incidental finding	2

Note: N=53. Unless otherwise indicated, values are given as number or number (percentage).

Abbreviations: APRT, adenine phosphoribosyltransferase; DHA, dihydroxyadenine.

Table 2

Kidney stones in patients with APRT deficiency

Variable	Value
Total no. of patients with kidney stones	33 (62)
At time of diagnosis	29 (55)
During follow-up	4 (8)
Age	
At first kidney stone event, y	26.4 (0.3–56.4)
≥18 y at first episode	26 (49)
Kidney stones before diagnosis of APRT deficiency	20 (38)
Delay from first clinical stone event to diagnosis, y	10.5 (0.8–47.9)
Kidney stone recurrence	18 (34)
Off XDH inhibitor treatment	2 (4)
On XDH inhibitor treatment	16 (30)
Allopurinol dosage, mg	200 (100–600)
Kidney stone events	
1	14 at diagnosis; 7 during f/u
2–3	10 at diagnosis; 8 during f; u
4–5	1 at diagnosis; 2 during f; u
>5	3 at diagnosis; 0 during f; u
Asymptomatic stones	5 at diagnosis; 2 during f; u
Urologic procedures	
extracorporeal shockwave lithotripsy	4 at diagnosis; 6 during f; u
Endoscopic surgery	6 at diagnosis; 9 during f; u
Open or percutaneous surgery	4 at diagnosis; 3 during f; u

Note: Unless otherwise indicated, values are given as number (percentage) or median (range).

Abbreviations: APRT, adenine phosphoribosyltransferase; XDH, xanthine dehydrogenase.

Table 3

Stages of CKD and RRT in patients with APRT deficiency

	At diagnosis	At last follow-up
CKD stage		
1	19	19
2	14	12
3A	2	2
3B	2	3
4	5	3
5	11	14
RRT		
Functioning allograft	3	7
Dialysis	5	2

Note: Values are given as number of patients.

Abbreviations: CKD, chronic kidney disease; RRT, renal replacement therapy; APRT, adenine phosphoribosyltransferase.