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REVIEW

Cystinuria: an update on pathophysiology, genetics, and clinical management

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Abstract

Cystinuria is the most common genetic cause of nephrolithiasis in children. It is considered a heritable aminoaciduria as the genetic defect affects the reabsorption of cystine and three other amino acids (ornithine, lysine, and arginine) in the renal proximal tubule. Patients affected by this condition have elevated excretion of cystine in the urine, and because of this amino acid's low solubility at normal urine pH, patients tend to form cystine calculi. To date, two genes have been identified as disease-causative: *SLC3A1* and *SLC7A9*, encoding for the two subunits of the heterodimeric transporter. The clinical features of this condition are solely related to nephrolithiasis. The diagnosis is usually made during infancy or adolescence, but cases of late diagnosis are common. The goal of therapy is to reduce excretion and increase the solubility of cystine, through both modifications of dietary habits and pharmacological treatment. However, therapeutic interventions are not always sufficient, and patients often have to undergo several surgical procedures during their lives to treat recurrent nephrolithiasis. The goal of this literature review is to synthesize the available evidence on diagnosis and management of patients affected by cystinuria in order to provide physicians with a practical tool that can be used in daily clinical practice. This review also aims to shed some light on new therapy directions with the aim of ameliorating kidney outcomes while improving adherence to treatment and quality of life of cystinuric patients.

Keywords Cystinuria · Nephrolithiasis · Genetics · Chronic kidney disease

Introduction

Cystinuria is an autosomal recessive disorder characterized by cystine and other amino acids' tubular reabsorption dysfunction in the proximal tubule that eventually leads to nephrolithiasis. It is the most common genetic cause of nephrolithiasis in children, although cases of diagnosis in adulthood are not rare.

The overall prevalence of cystinuria is believed to be approximately 1:7,000 in neonates; however, it may vary by geography [1]. The rate of stone formation appears to be one stone every 1 to 2 years for untreated cystinuric stone formers, and they usually undergo several surgical procedures [2]. It has been estimated that patients affected by cystinuria may undergo up to 7 surgical procedures by middle age [3]. However, it should be noted that these calculations are only estimates and do not apply necessarily to all patients, as cystinuria's presentation has a high interindividual variability. This inevitably leads to increased risk of kidney injury and chronic kidney disease (CKD) (up to 70% for cystinuric

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stone formers), although kidney failure remains uncommon (overall risk less than 5%) [4].

Pathophysiology

Cystine is a sulfur-containing homodimer amino acid composed of two cysteine molecules linked via a disulfide bond. Under physiological conditions, cystine is freely filtered by the renal glomerulus and reabsorbed by the proximal tubule by a transport mechanism that is not completely understood. The protein responsible for this transport is a heterodimeric complex composed of $b^{0,+}$AT, encoded by *SCL7A9*, that is the actual amino acid transporting subunit [5], and the glycoprotein rBAT, encoded by *SLC3A1* that guarantees the correct location of $b^{0,+}$AT in the apical membrane of the cells [6]. Mutations in one of the two proteins lead to a deficient reabsorption of cystine and other amino acids (ornithine, arginine, and lysine) and to abnormal excretion of the aforementioned amino acids in the renal tubular lumen. Because of its low solubility at physiologic urine pH, elevated cystine excretion causes supersaturation of the urine and cystine precipitation leading to nephrolithiasis, while the other amino acids are more soluble and their increased excretion does not have any clinical consequences [7]. Since the distal tubule plays a central role in urinary acidification and cystine has low solubility at acidic urinary pH, cystine crystal precipitation takes place mainly in the distal tubule (Fig. 1). Although in most cystinuric patients stones are made of pure cystine, in a significant percentage (up to 40%) of patients, calculi may also contain calcium oxalate, calcium phosphate, and struvite [8]. Cystine solubility is < 250 mg/L (1.05 mmol/L) at a pH < 6, but it increases to 500 mg/L (2.1 mmol/L) at a pH > 7.5. Patients affected by cystinuria typically excrete more than 400 mg (1.6 mmol) of cystine per day (600–1,400 mg/24 h or 2.5–6 mmol/24 h), whereas the normal excretion would not exceed 50 mg/24 h (0.2 mmol/24 h) [9]. Cystine excretion does not generally exceed 250 mg/24 h in heterozygotes for cystinuria and patients affected by Fanconi syndrome. Intestinal cystine absorption appears to be altered as well, although its clinical relevance is uncertain [10].

Genetics and classification

Cystinuria is an autosomal recessive hereditary disorder. Traditionally, cystinuria has been classified according to the amount of cystine excreted in the urine in the obligate heterozygous parents of an affected patient [11]. Patients were

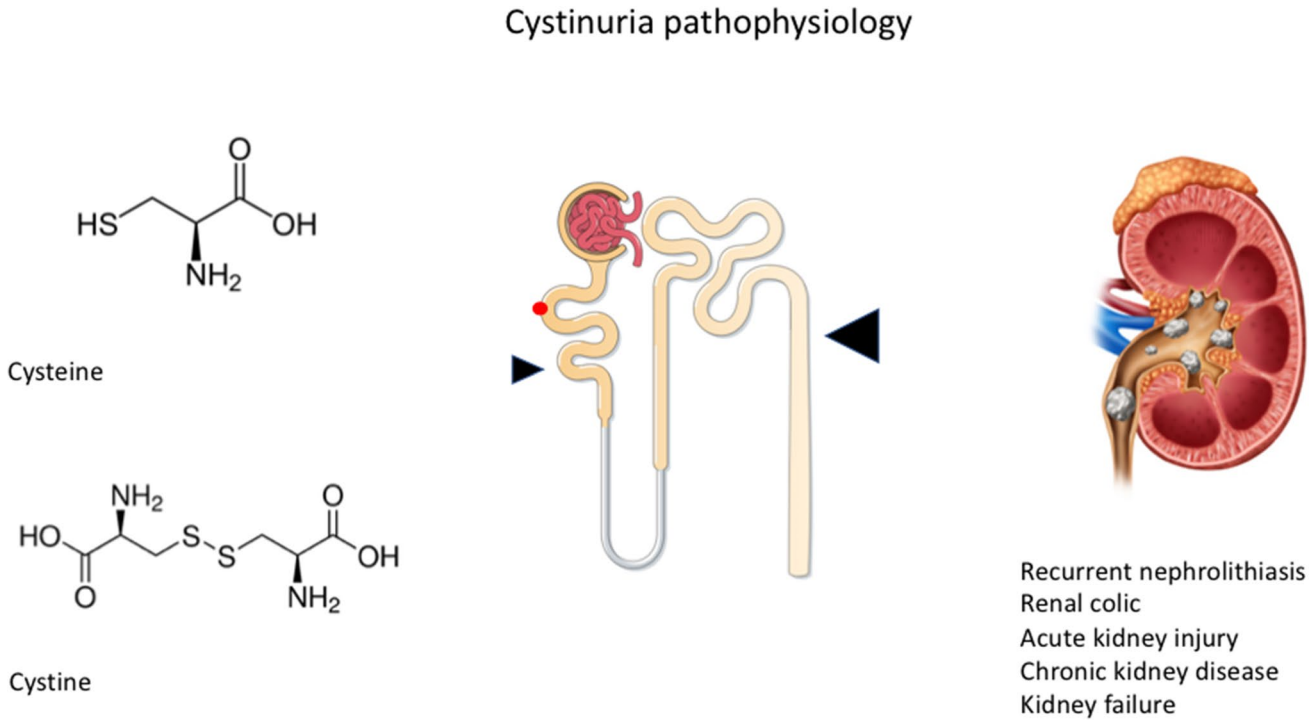

Fig. 1 Cystine is an amino acid composed of two cysteine molecules linked via a disulfide bond. Under physiological conditions, cystine is freely filtered by the glomerulus and then reabsorbed in the proximal tubule (small black arrow head) by the $b^{0,+}$AT-rBAT complex (red dot). Dysfunctions of the transporter cause high urinary cystine excretion and supersaturation that, in the distal tubule (big black arrow head), leads to cystine precipitation and calculi formation with damaging consequences for the kidney

classified as having type I cystinuria if their parents had normal cystine excretion, type II if cystine excretion was greatly increased or type III if it was only moderately increased (in both type II and type III cystinuria, parents rarely form stones, but their risk is increased if certain dietary habits are present such as low fluid or high animal protein intake). More recently, this phenotypic classification has been replaced by a genotypic one, due to the identification of two responsible genes: *SLC3A1* and *SLC7A9* [12]. *SLC3A1* is located on chromosome 2p16.3-p21 [5] and encodes for the heavy chain subunit rBAT, while *SLC7A9* is located on chromosome 19q12-13.1 and encodes for the transporting unit of the heterodimeric complex [13]. In the new classification, patients who have biallelic mutations in *SLC3A1* are referred to as having type A cystinuria (type I in the phenotypic classification); conversely, patients who have biallelic mutations in *SLC7A9* are classified as type B cystinuria (previous type II and type III). The fact that the parents of patients with type B cystinuria do not form stones but still have increased cystine excretion led to the consideration that this subtype should be considered an autosomal dominant disorder with incomplete penetrance for nephrolithiasis [14]. This is not only true for *SLC7A9* (86% of heterozygotes patients for *SLC7A9* in a UK cohort), but also for specific mutations in *SLC3A1* (duplication of exons 5–9) [15]. Cystinuria can be caused by multiple genetic defects in both *SLC7A9* and *SLC3A1*, two of the most common being large deletions and duplications, that can be identified by performing Multiplex Ligation-dependent Probe Amplification (MLPA) assay and Copy Number Variations (CNV) assay. A small percentage of patients have digenic inheritance of both *SLC3A1* and *SLC7A9*; these mixed heterozygotic patients do not form stones unless mutations in both alleles of at least one of the two genes are present [AB(B) or AB(A)]. To date, both the phenotypic and genotypic classifications are not considered to have an impact in terms of prognosis and clinical course of the disease. *SLC3A1* and *SLC7A9* are the only known genes responsible for cystinuria so far, although they only explain 90% of the cases of the disease. As a matter of fact, in 10% of patients, the disease-causing genetic mutations have not yet been identified. Some cases of cystine stones in the context of multigenic syndromes have been described in the literature: hypotonia-cystinuria syndrome and 2p21 deletion syndrome [16].

Clinical features

The most common clinical features of cystinuria are those related to recurrent nephrolithiasis. The initial presentation is usually related to stone passage and it is characterized by acute flank pain that radiates towards the groin, microscopic or gross hematuria (although 15% of patients may not have microhematuria), urinary tract infections and variable nausea and vomiting [4]. Stone formation usually starts in the first two decades of life [17]. About 75% of cystinuric patients have bilateral stones and the average age of first stone detection is about 12–13 years [12]. Cystinuria should therefore be suspected in patients presenting with the first stone during infancy or adolescence, in patients with staghorn calculi involving the calyces or bilateral stones and a positive family history for kidney stones [15], or in young children presenting with obstructive acute kidney injury [18]. For yet unknown reasons, in some, but not all, series males appear to be more severely affected than females [19]. Besides these clinical features that appear to be prevalent in both children and adults, neonates can present with hypotonia, growth disorders, polyphagia, and eventually childhood obesity [20]. Patients affected by cystinuria have increased risk of developing CKD and kidney failure compared not only to the general population but also to other stone formers. It has been estimated that up to 70% of cystinuric patients may develop such comorbidities [3, 15]. The high prevalence of CKD in cystinuria was confirmed in a large French cohort of 442 patients of whom 314 were older than 16 years of age with cystinuria. Among these, 26.7% had eGFR < 60 ml/min/1.73 m^2 (only 5 had CKD stage 5), and 31 patients underwent unilateral nephrectomy [21]. In an American case population of 95 cystinuric patients, the prevalence of nephrectomy was higher than in calcium oxalate stone patients [22]. A history of staghorn stones and of multiple open urological procedures was a risk factor for CKD and nephrectomy [23]. The elevated risk for CKD may be ascribed to the recurrent nature of cystine stones, the need for several urological procedures or direct intratubular obstruction. The prevalence of hypertension in cystinuria ranges from 29 to 51% in adults and is mostly associated with CKD [21, 24]. Cystinuria has a highly variable phenotypic presentation, even in families with the same mutation, suggesting a possible interference of modifying genes, epigenetic mechanisms, and environmental factors such as diet. To date no genotype–phenotype correlation has been identified that could explain this phenotypic variability.

Diagnosis

The diagnosis of cystinuria can be made by stone composition analysis, urinary sediment analysis, or 24-h urinary excretion of cystine. Stone composition analysis is generally performed through infrared spectroscopy or X-ray diffraction, but cystine stones can also be recognized microscopically. Cystine stones of untreated patients appear yellow–brown with a granular surface and radial structure. Urinary sediment analysis is also a practical tool with high specificity for the diagnosis of cystinuria. Microscopic

examination reveals pathognomonic flat hexagonal crystals in two-thirds of patients, and it can be performed both on first morning or on a random urine sample. The presence of crystalluria in random urine samples has indeed been positively correlated to the presence of stones in cystinuric patients [25]. Although these tests have high specificity and sensitivity, the diagnosis of cystinuria should be confirmed by assessing the 24-h urinary excretion of cystinuria. This test is of limited feasibility in children; therefore, urinary cystine concentration can be assessed by cystine-to-creatinine ratio over the first or second morning urine. The normal urinary excretion of cystine may vary according to age (Table 1) [26], and affected AA or BB patients generally excrete > 400 mg/24 h (1.7 mmol/24 h).

Stone formation is rare in these patients as cystine solubility is preserved; however, occasional kidney calculi can occur probably due to variations of urine pH, urine volume, and dietary acid load during the day, suggesting a role for fractionated urine collection [27]. Genetic testing is not mandatory for diagnosis to date, but it may be useful in cases of atypical presentation, familial genetic counseling, and research purposes [9]. The qualitative sodium cyanide-nitroprusside test has been proposed as a screening method for cystinuria, although currently considered outdated [28]. The test is usually positive for cystine levels above 75 mg/g creatinine. Attenuated total reflection-Fourier transform infrared spectroscopy (ATR-FTIR) has recently been evaluated as a cost- and time-effective screening test for cystinuria with high specificity and sensitivity [29]. If the screening test is positive, then a quantitative test should be performed, such as high-performance liquid chromatography with fluorometric detection (HPLC-FL). In terms of imaging, the "gold standard" for the detection of cystine stones and stones in general remains the non-contrast computed tomography of kidneys, ureters, and bladder (CT KUB) due to its high sensitivity and specificity [30]. Recent data suggest that CT KUB may be useful not only to detect the size and location of stones, but also their composition through non-invasive assessment of their density (expressed in Hounsfield Units, HU) in order to choose the most appropriate urological treatment (percutaneous nephrolithotomy vs. less invasive procedures) [31]. Abdomen ultrasound (US) however remains the first-line imaging performed in clinical practice, both for first assessment and follow-up [32]. This is especially true for recurrent stone formers who need frequent reassessment and for children in order to reduce radiation exposure. Plain abdomen X-ray is not routinely performed due to it being inferior to CT KUB and ultrasound. Prenatal diagnosis is possible by performing an ultrasound before 36 weeks of gestation, as fetuses may present with hyperechoic colon. This exam has high positive predictive value (89%) [33]. The diagnosis should nonetheless be confirmed after birth. Since the disease may be asymptomatic, siblings of patients should also be investigated by a qualitative test such as the cyanide-nitroprusside test or ATR-FTIR.

Table 1 Normal cystine excretion according to age

Cystine/24 h	
< 10 years	≥ 10 years
< 13 mg/1.73 m^2/24 h	< 48 mg/1.73 m^2/24 h
< 55 µmol/1.73 m^2/24 h	< 200 µmol/1.73 m^2/24 h

Treatment and follow-up

Medical preventive treatment for cystinuria is targeted to increase cystine solubility by urine volume expansion and urine alkalinization. The three cornerstones of conservative treatment are as follows: (1) adequate urine volume, (2) urinary alkalinization, and (3) low-sodium and low methionine diet. Adequate urinary output of at least 2.5 L/day (2 L/1.73 m^2 in children) can be monitored with a 24-h urine collection and should be preserved with the aim to maintain cystine excretion below 243 mg/L (1 mmol/L) and cystine supersaturation below 1 (at a urine pH above 7.5). For urinary alkalinization, the goal is to maintain urinary pH above 7.5 in order to increase cystine solubility; it can be achieved by potassium citrate or potassium bicarbonate administered orally. Oral alkaline therapy should be divided into three or four doses in order to guarantee 24-h urinary alkalinization [34] (Table 2). Decreasing urine specific gravity below 1.005 and increasing pH above 7.5 have been reported to significantly reduce the risk of cystine crystalluria. However, the risk of calcium-phosphate crystal precipitation in the urine should be considered and carefully investigated at high pH value [35]. Home monitoring of the urine pH is suggested because of the possibility to self-adjust alkaline treatment avoiding too high urine pH while keeping it on target [36]. Dietary recommendations represent an important therapeutic strategy and should include a low daily sodium intake and methionine-rich food restriction rather than general protein restriction to respectively lower cystine excretion and production. Restriction of methionine-rich protein intake also reduces net acid excretion, leading to higher urine pH and the need for lower doses of alkali. The relationship between the excretion of urinary sodium and cystine has been demonstrated, although the physiologic basis for it has not been explained [37]. This evidence justifies the adoption of a daily sodium intake of 100 mEq/day for adults (1–1.5 mEq/kg/day for children). Protein restriction is not recommended in children for growth concern and methionine-rich foods should be reduced, but not avoided. In those in whom stones continue to form and/or grow despite high urinary output and alkalinization, it is advised to use sulfhydryl agents

Table 2 Treatment recommendations for adults and children affected by cystinuria

Treatment	Dosage	
	Adults	Children
Fluid intake	Enough to guarantee a urinary output of at least 2.5 L/day	Enough to guarantee a urinary output of at least 2 L/day
Potassium citrate	60–80 mEq/day in three to four doses	60–80 mEq/1.73 m^2 in three to four doses
Sodium restriction	100 mEq/day or 6 g of NaCl	1–1.5 mEq/kg/day
Protein restriction	1 g/kg of ideal weight	Not recommended
Methionine restriction	1,200–1,400 mg/day	
Cystine binding drugs		
Tiopronin	800–1,500 mg/day in three doses	15–40 mg/kg/day in three doses
D-penicillamine	1–4 g in four doses	20–30 mg/kg/day in four doses (maximum dose 1.2 g/day)

named cystine binding drugs (CBD), D-penicillamine and tiopronin, effective in reducing free cystine levels [38, 39] (Table 2). These agents cleave cystine into two cysteines to form the more soluble complex cysteine-penicillamine and cysteine-tiopronin, respectively [40]. In patients prescribed thiol-containing drugs, potential adverse effects (AE) should be monitored according to the drug used. These drugs can indeed be associated with severe adverse events like mucocutaneus lesions, alteration in taste, neutropenia and thrombocytopenia, gastrointestinal and liver disorders and proteinuria. Patients treated with thiol agents should be regularly monitored for increase of liver enzymes, new onset proteinuria, and alteration of blood cell count. Tiopronin has indeed been associated, although rarely, with membranous nephropathy and minimal change disease [41]; therefore, a spot measurement of urine protein/creatinine ratio should be performed at baseline and during follow-up [42]. D-penicillamine seems to be associated with a higher incidence of adverse effects, ranging from mild symptoms such as fever and rash to leukopenia, aplastic anemia, hepatotoxicity, and vitamin B6 deficiency. Just as for tiopronin, cases of membranous nephropathy presenting with proteinuria have been described in patients prescribed D-penicillamine [43] as well as rapidly progressive glomerulonephritis [44]. When nephrotic syndrome occurs, it will generally resolve with drug cessation, albeit after several months. Patients should initially be monitored every 3 to 6 months until they are stable on therapy. Surgical management of cystine stones in children does not differ substantially from that of adults. Extracorporeal shockwave lithotripsy (ESWL) is considered an option in patients already treated successfully or patients that require less invasive procedures including children. However, it has some limitations: cystine calculi are often more resistant to ESWL [45] and in children it may require general anesthesia. EWSL is also considered an option in combination with percutaneous nephrostolithotomy (PCNL) in staghorn calculi. For ureteral and kidney stones < 20 mm, flexible ureteroscopy (URS) should be preferred [46]; while for stones greater than 15–20 mm, PCNL is recommended [35]. Open surgery should be limited to cases of anomalies of congenital anomalies of the kidney and urinary tract (CAKUT). Cystine stones are difficult to manage from a medical and surgical point of view, especially when considering that poor patient compliance and quality of life are limiting factors for successful treatment. Therefore, there is the need for new diagnostic and therapeutic tools to optimize the management of affected patients. Follow-up time can be increased up to 1 year if the patient is compliant and has no biochemical, clinical, and radiological evidence of new stone formation. Stone activity is generally monitored radiologically with periodic non-contrast CT KUB or ultrasound if the patient requires more frequent radiological assessment.

Future directions

Inhibitors of crystal growth are currently under investigation and results on mice are promising. Ward et al. proposed a model of cystine mimics (such as cystine dimethyl ester, CDME) that slows down crystal growth by binding specific sites on crystal surfaces in vitro [47]. Sahota et al. used the same model on a *Slc3a1* knockout mouse, with promising clinical results [48]. That work led Hu et al. to propose a cystine diamide (LH708) with greater stability and bioavailability compared to CDME that appears to be effective in *Slc3a1* knockout mice [49]. Alpha-lipoic acid, a pro-antioxidant compound, has demonstrated effective inhibition of cystine stone formation in a *Slc3a1* knockout mouse model [50]. A phase 2, placebo-controlled, randomized interventional clinical trial investigating the effect of lipoic acid natural supplement on cystine stone formation is currently active (NCT02910531). Another trial that deserves to be mentioned is NCT04147871, whose aim is to evaluate the effect of ADV7103 (potassium citrate + potassium bicarbonate) on around-the-clock urinary pH in cystinuric patients. With the aim of increasing urinary output and therefore decreasing

urinary cystine supersaturation, tolvaptan, an arginine vasopressin receptor antagonist, was proposed as a possible treatment for cystinuric patients. Indeed, a study conducted on cystinuric patients taking 15 mg of tolvaptan for 5 days, revealed an increase in urinary output and a decrease in cystine concentration [51]. Additionally, tolvaptan showed its effectiveness in delaying stone growth in a mouse model [52]. However, it is still very expensive and not a practical therapy as it requires a very large amount of fluid intake and it causes side effects such as polyuria, nocturia, thirst, and polydipsia that may worsen the quality of life of cystinuric patients. Besides the need to find more tolerable and effective therapies for cystinuric patients, future research should also focus on establishing a genotype–phenotype correlation that both clinicians and patients may benefit from in terms of genetic counseling and prognosis.

In conclusion, cystine stones are difficult to manage from a medical and surgical point of view, especially when considering that poor patient compliance and quality of life are limiting factors for successful treatment. Therefore, there is the need for new diagnostic and therapeutic tools to optimize the management of affected patients. Lastly, this review aims to give an overview on cystinuria and to summarize some important aspects of cystinuric patient management, from clinical suspicion, diagnosis, and management to follow-up. Finding more tolerable and effective therapies is the mainstay of the ongoing research in this field, as this last section demonstrates.

Author contribution All authors contributed to the conception and design of the review. VDA and PMF devised the literature search strategy, VDA and GC wrote the first draft of the manuscript, PMF reviewed and modified the first draft, and DG and GG reviewed and modified the second draft. All authors read and approved the final manuscript.

Declarations

Conflict of interest PMF received consultant fees/grant support from Allena Pharmaceuticals, Alnylam, AstraZeneca, BioHealth Italia, Vifor Fresenius and author royalties from UpToDate. All of the other authors have no potential conflicts of interest to disclose. VDA, GC, and PMF are members of the European Reference Network for Rare Kidney Diseases (ERKNet) – Project ID No 739532.

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