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Treatment of cystinuria

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Abstract Cystine urolithiasis is the only clinical expression of cystinuria, an autosomal recessive genetic defect of the transepithelial transport of cystine and other dibasic amino acids in the kidney. Stones form due to the increased excretion of cystine, which is poorly soluble at normal urine pH. Cystine stones are often resistent to extracorporeal shock wave lithotripsy, so that percutaneous surgery or ureteroscopy are the preferred techniques of stone extraction. Medical preventative treatment is based on high diuresis (≥1.5 l/m^2 per day) well distributed throughout the day and night, and urine alkalinization up to pH 7.5 by means of sodium bicarbonate and/or potassium citrate. When these basal measures are ineffective at preventing stone recurrence or dissolving pre-existing stones, sulfhydryl agents such as D-penicillamine or tiopronin, which form highly soluble mixed disulfides with cystine moieties, are to be added to urine dilution and alkalinization, especially when cystine excretion is in excess of 750 mg/day (3 mmol/day). Frequent clinical and ultrasound follow-up is needed to encourage patient compliance and assess efficacy and tolerance of treatment.

Key words Cystine urolithiasis · Cystinuria · D-Penicillamine · Tiopronin

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Introduction

Formation of cystine stones is the only clinical expression of cystinuria, an autosomal recessive genetic defect of transepithelial transport of dibasic amino acids in the kidney and intestine. The increased urinary excretion of cystine, the least soluble of all amino acids, results in cystine crystallization and formation of stones. Cystinuria is the cause of 1%–2% of stones observed in adults and about 10% of those occurring in children. As the genetic transport defect exists from birth, stone formation begins in the first decades of life and continues life long, and as cystine stones are poorly fragmented by extracorporeal shock wave lithotripsy (ESWL), regular medical treatment is of particular importance in affected patients.

Genetic mechanisms of cystinuria

In 1966, Rosenberg et al. [1] described three types of classic cystinuria according to the urinary phenotype of obligate heterozygotes in the proband's family: type I heterozygotes show normal aminoaciduria, whereas type II and III heterozygotes show high or moderate excretion of cystine and dibasic amino acids, respectively [2]. Type III homozygotes have a nearly normal increase in plasma cystine level after oral cystine load, in contrast to type I and II homozygotes who exhibit no increase (Table 1). From the parental phenotype, some probands have been classified as double heterozygotes (e.g., I/II, I/III, or II/III genotype). Children with type I/I homozygous "classic" cystinuria often excrete cystine at levels greater than the theoretical solubility limit and may be at higher risk for nephrolithiasis than other genotypes (Table 2). Type II/normal heterozygotes may excrete more than 600 mg cystine/day (3.3 mmol/day) and are at risk for urolithiasis; identification of these individuals is useful to provide accurate genetic counselling, because dominant inheritance may be observed in such families [3, 4].

Table 1 Rosenberg's classification of cystinuria (simplified)

	Type I	Type II	Type III
Heterozygotes			
Urinary excretion of cystine and dibasic amino acids	Normal	Elevated	Moderately elevated
Homozygotes			
Plasma cystine level after oral cystine load	Not elevated	Not elevated	Elevated

Table 2 Urinary excretion of cystine among heterozygotes and homozygotes[a]

Type	Value (μmol/g of creatinine)
Heterozygotes	
I/N	81±10
II/N[b]	400–2,400
III/N	311±34
Homozygotes and compounds	
I/I[b]	1,215±285
I/III[b]	1,420±423
III/III[b]	1,354±328

[a] Data from refs. [3] and [8]
[b] Risk of urolithiasis

In 1994, a linkage analysis and a candidate gene strategy found an amino acid transporter gene on chromosome 2p, *SLC3A1* (formerly *rBAT*), to be the type I cystinuria gene [5, 6]. Mutational and linkage analysis proved genetic heterogeneity, since the *SLC3A1* gene was not responsible for type II or type III cystinuria [7, 8]. More recently, the identification of the cystinuria type III locus on the long arm of chromosome 19 (19q13.1) was reported, and preliminary data suggest that type II families could share the same locus [9, 10]. Identification of cystinuria genes has no impact on the clinical management of the cystinuric patient; however these advances will certainly help clarify the physiology of cystine reabsorption, a process not yet completely understood [11]. This process could involve two transport systems located at the brush border membrane of the proximal tubular epithelial cells, one with high affinity for dibasic amino acids and one with low affinity for cystine alone [12–14]. Molecular composition and sodium sensitivity of these transporters remain to be determined.

Factors of cystine stone formation

The major lithogenic factor in cystinuric patients is the high concentration of cystine in urine, because cystine is poorly soluble in aqueous solutions at the usual urine pH. The solubility of cystine (molecular weight 240 daltons) in urine is about 250 mg/l (1 mmol/l) up to pH 7, but sharply rises with higher pH, up to 500 mg/l (2 mmol/l) or more above pH 7.5 [15].

Normal subjects excrete less than 10 μmol/mmol creatinine (20 mg/g) or less than 30 mg/day (0.13 mmol/day). Homozygous patients excrete more than 400 mg/day (1.7 mmol/day), or more than 250 mg/g creatinine (0.12 mmol/mmol creatinine), and some excrete as much as 3,600 mg/day (15 mmol/day). Generally, cystine excretion in homozygous patients is 600–1,400 mg/day (2.5–5.8 mmol/day). Heterozygotes in types I and III excrete less than 200 mg/day (0.8 mmol/day) and do not form stones, whereas in type II they excrete up to 200–400 mg cystine/day and may form stones (Table 2). The probability of stone formation rises with higher rates of urinary cystine excretion, although there is no close correlation between daily urinary cystine excretion and the rate of stone formation. However, Lindell et al. [16] observed a marked rise in the incidence of stone formation when urinary cystine concentration was in excess of 700 μmol/l (170 mg/l). Sakhaee et al. [17] observed that hypercalciuria, hyperuricosuria, and/or hypocitraturia may accompany cystinuria, thus contributing to the formation of mixed stones. Hyperdiuresis, which decreases cystine concentration, and urine alkalinization up to pH 7.5 are the only means of increasing the solubility and preventing the crystallization of the free cystine present in the urine, because no inhibitor of cystine crystallization is known [18].

There is no clear explanation why some patients begin forming stones in the earlier years of life, whereas the disease first manifests much later, up to the 6th decade, in others. The permanent excretion of excessive amounts of cystine is spontaneously associated with the relentless formation of stones, which can have a staghorn development. Recurrent obstructive episodes, especially when urinary tract superinfection occurs, alter renal function, may require nephrectomy, and ultimately result in end-stage renal failure and need for supportive treatment [18]. The risk of recurrent stone episodes and loss of renal function justifies a regular follow-up of all cystinuric patients, with integrated urological and medical treatment [18–22]. As expected, no recurrence of cystinuria occurs following kidney transplantation [23].

Urological management

Cystine stones often require urological intervention when they cause symptoms or obstruction, or when they increase in size on serial radiological studies. Physicochemical properties of cystine stones make them relatively resistant to shock wave lithotripsy and initial results of such treatment were discouraging, with a need for repeated procedures and a low rate of stone-free patients [24, 25]. Recent convincing results show that a single session of ESWL monotherapy may be sufficient for pyelocaliceal or upper ureteral stones if the largest individual stone is smaller than 1.5 cm [26, 27]. For large pyelocaliceal stones (above 1.5 cm), percutaneous nephrolithotomy coupled with intracorporeal ultrasonic stone fragmentation is the preferred treatment, since cal-

culi fragment more easily and become accessible for endoscopic removal; a secondary intervention (often with flexible endoscopy) can help remove residual stones in some cases, to reach an overall high percentage (>80%) of stone-free patients [28].

When large and extensively branched cystine stones are present, a combination of percutaneous nephrolithotomy/ESWL/second-look nephroscopy (termed "sandwich therapy") most often now precludes the need for renal open surgery, with 50% of patients becoming stone free. Lower ureteral cystine stones are best treated with ureteroscopy; the holmium laser now allows easy retrograde endoscopy (with flexible device) and intraureteral lithotripsy when required [28]. Thus, most cystine stones can be treated with contemporary minimally invasive techniques with excellent immediate efficacy. The type of urological intervention or the presence of residual calculi do not influence the rate of recurrence of cystine stones at 1 and 5 years, but time to recurrence is longer for stone-free patients [28]. However, as many patients will suffer recurrence of stone within a few years and need repeated urological intervention, minimally invasive procedures should be preferred to open surgery whenever possible. Minimally invasive procedures have been mainly used in adults and adolescents; their application to young children is theoretically possible, but would deserve proper validation in a large pediatric series.

Principles of medical treatment

The management of cystinuria is not different in children and in adults. The goal of treatment is to obtain solubilization of cystine excreted in urine. This can be accomplished in three ways: (1) dietary measures allowing reduction of cystine production (by decreasing methionine intake) and/or urinary excretion (by low sodium intake); (2) conservative measures directed at decreasing cystine concentration (by hyperdiuresis) and/or at increasing its solubility (by alkalinization); (3) treatment with chelating agents (sulfhydryl compounds) that convert cystine to a more-soluble disulfide, thus reducing excretion of the poorly soluble free cystine. Several of these measures are often to be combined in order to achieve an effective prevention of stone formation [21, 29]. The risk of recurrence of cystine stone formation has to be decreased as much as possible with appropriate therapeutic medical measures before planning invasive procedures.

Conservative management

Dietary approach

Methionine, an essential amino acid, is the precursor of cystine. Reduced methionine intake lowers cystine production, but cannot be lower than the physiological requirement, i.e., 1,200–1,400 mg/day. Such reduction can be achieved by avoidance of foods with a very high methionine content, including stockfish and eggs, and by moderating the consumption of meat, fish, poultry, and cheese (all of which contain about 500 mg methionine/100 g), whereas vegetables, fruits, and grains contain less than 200 mg/100 g. In one adult series, reduced methionine intake was easy to accept in the long term and decreased cystine production by about 500 µmol/day (120 mg/day) [30]. However, most authors believe that such dietary restriction is not advisable for children [18].

A low-sodium diet has also been proposed to reduce cystine excretion. In the study of Jaeger et al. [31], reducing sodium intake from 300 to 50 mmol/day decreased cystine excretion by 650 µmol/day (156 mg/day). A substantial decrease in cystine excretion on a low-sodium diet was also observed by Norman and Manette [32] and by Peces et al. [33] in adult patients, and by Rodriguez et al. [34] in cystinuric children. In this latter study, decreasing natriuresis from 6 to 1.5 mmol/kg per day resulted in a marked decrease in urinary cystine concentration, from 328 to 14 mg/l, while daily urine output was unchanged. Lindell et al. [35] examined the quantitative relationship between sodium and cystine excretion in 13 adult patients. The average 24-h excretion of free cystine decreased by 3.1 µmol (0.75 mg) for each 1 mmol decrease in urinary sodium, but the decrease in cystine excretion was much more marked in patients who did not receive concomitant tiopronin treatment, whereas the decrease in cystinuria was virtually negligible in patients on tiopronin therapy. From these studies, only a reduction of sodium intake to about 50 mmol/day (1 mmol/kg per day) produced a significant effect on cystine excretion, and such a low-sodium intake may be difficult to accept in the long term. On the other hand, alkalinization by sodium bicarbonate markedly increases natriuresis. Lindell et al. [35] compared cystine excretion before and after withdrawal of sodium bicarbonate while on a daily sodium intake of 50 mmol. Mean free cystine excretion with maintained sodium bicarbonate was 1,703 µmol/day, compared with 1,347 µmol/day after bicarbonate withdrawal.

Urine dilution

Maintaining a high fluid intake is essential in patients forming cystine stones. Augmented diuresis per se may, through solute dilution, maintain cystine concentration under 250 mg/l. In view of the cystine excretion in homozygous patients, 1.5–2 l/m^2 of urine per day or more should be necessary to achieve solubilization by means of dilution alone. The practical recommendation in every patient with cystine excretion ≥750 mg/day (3 mmol/day) is to maintain urine output at 3 l/day (1.5–2 l/m^2 in children) or more. The fluid intake should be distributed throughout the day and night. The patient should ingest a large quantity of water at bedtime and again during the night, taking advantage of the provoked nocturia. Fruit juices (citrus or orange) are useful as they contain citric acid and potassium, thus increasing both diuresis and alkali load. In pa-

tients with moderate cystinuria (≤500 mg/day), a high fluid intake with increased alkali intake may be sufficient [20, 21, 29].

Alkalinization

Urine dilution alone is rarely sufficient and sustained alkalinization is often required to obtain effective cystine solubilization, as proposed by Dent and Senior [15, 36]. Approximately 0.2 g/kg body weight per day (or 10–16 g/day) of sodium bicarbonate in divided doses is needed to maintain the urinary pH at about 7.5, but not in excess of 8, to avoid precipitation of calcium phosphate that would form a shell around the stones, rendering them insoluble [20]. Salt intake should be reduced to compensate for this large sodium load which, by itself, tends to increase cystine excretion, although the effects of alkalinization largely surpass the effects of higher sodium intake. Potassium citrate, 60–80 mEq/day, should be preferred as the alkalinizing agent, because it provides effective alkalinization without increasing sodium output [37]. The dose of potassium citrate, as of sodium bicarbonate, should be adapted to urinary pH. Potassium citrate should be used with care in patients with impaired renal function, in order to avoid hyperkalemia. The combination of diet, urine dilution, and alkalinization prevents cystine formation in the long term in a number of patients, provided that such conservative treatment is regularly pursued [18].

Pharmacologic treatment

If despite such measures there is recurrent stone formation, or if pre-existing stones fail to dissolve, chelating agents that transform cystine into a highly soluble mixed disulfide may be added to conservative treatment [18, 29]. The most widely used drugs are D-penicillamine (DP) and α-mercaptopropionylglycine or tiopronin (TP). Both compounds are sulfhydryls which cleave cystine into two cysteine moieties to form a mixed disulphide 50 times more soluble than cystine itself. DP (molecular weight 149 daltons) was introduced to the treatment of cystinuria in 1963 [38]. As two molecules of DP are needed to complex one molecule of cystine, 1,000 mg of DP can at best, on a stoichiometric basis, complex 400 mg of cystine (molecular weight 240 daltons). TP (molecular weight 163 daltons) was introduced some years later. On the same basis, 1,000 mg of TP can at best complex 365 mg of cystine. Actually, the rate of complex formation is probably lower, because complex formation is incomplete [39]. Based on such rationale, the daily dose of DP or TP should be adapted to lower free cystine excretion under 500 mg/day (about 2 mmol). The usual dose of either compound is about 1,000 mg/day (20 mg/kg, up to 40 mg/kg in children), given in divided doses, with half of the daily dose taken at bedtime [40], because cystine concentration in urine is maximal during the night [41]. Both sulfhydryl agents, especially DP, provoke frequent side-effects, including ageusia or dysgeusia (with DP), rash, pemphigus, thrombocytopenia, agranulocytosis, polymyositis, proteinuria, or full nephrotic syndrome [18]. In the latter case, membranous nephropathy is found on renal biopsy [42] and takes several months to reverse. One case of hyperlipemia has been reported with TP [43]. DP (but not TP) induces pyridoxine depletion, requiring pyridoxine supplementation [20, 21]. Immunoallergic reactions appear to be less frequent with TP than with DP, and patients who develop such reactions while on DP my further tolerate TP [44]. Therefore, at present, TP is often the preferred drug for complexing cystine.

Captopril (molecular weight =217 daltons), which is a sulfhydryl agent, has been proposed to complex cystine, since Sloand and Izzo [45] reported in 1987 a 70% reduction in cystine excretion in a patient treated with 150 mg/day and 93% in another patient patient receiving 75 mg/day. However, the amount of complexed cystine was in excess of the molar amount of captopril, which can not be explained solely on the basis of sulfhydryl formation, even if complete complex formation is assumed. Since this publication, conflicting experiences have been reported. Perazella and Buller [46] reported a marked decrease in cystine excretion in two patients, including a decrease from 3,050 to 166 mg/day with captopril. In nine adult patients treated with 150 mg/day, Cohen et al. [47] reported a mean decrease in cystinuria from 699 to 393 mg/day. Of note, five patients had no signifiant decrease, whereas the other four had a marked decrease from 775 to 230 mg/day, which is also largely in excess of the dose of captopril. In contrast, Coulthard et al. [48] observed only a small decrease in cystine excretion in five children. Similarly, Michelakakis et al. [49] observed a minimal (<10%) fall in cystine excretion in two children treated with 2 mg/kg per day of captopril for more than 2 years. Dahlberg and Jones [50] also failed to observe a significant effect of captopril. Our (unpublished) experience is similar. Such conflicting results suggest that captopril, if effective, should act in other ways than complex formation alone, such as interfering with amino acid metabolism or transport. The effects of captopril appear largely unpredictable, at variance with the effects of DP and TP.

A third-generation chelating agent, bucillamine (molecular weight 223 daltons), a dithiol compound, should theoretically be able to bind two cysteine moieties thus resulting in higher complex formation, and hence require a lower dose with a lower risk of side-effects [51]. Extended clinical experience with bucillamine, however, is still lacking.

Strategy and surveillance of treatment

Based on the results of recent studies of large series of (mainly adult) patients [21, 29, 46, 52] the following therapeutic scheme may be proposed (Table 3). Basal

Table 3 Strategy of medical therapy in patients with cystinuria and stones

Basal therapy
High fluid intake distributed throughout the day and night (citrus and orange juice are helpful)
Moderate salt intake
Moderation in methionine-rich foods (in adults only)
Alkalinization (preferably using potassium citrate)
In case of persistent stone formation or perioperatively
Reinforce above-mentioned measures
Add a sulfhydryl compound (D-penicillamine or tiopronin) at the needed daily dose to reduce free cystine excretion to <200 mg/l (approximately 0.8 mmol/l)
Surveillance of the cystinuric patient
Frequent clinics visits for severe forms (especially in children and adolescents)
24-h urine collections
volume (aim >1.5–2 l/m^2 per day)
free cystine excretion (aim <200 mg/l)
Urine pH monitoring (aim 7.5–8)
First-morning urine (aim disappearance of cystine crystals)
Echographic controls

treatment is indicated in every subject with cystinuria, with or without a history of stone formation: high fluid intake evenly distributed throughout day and night, a moderate- or low-sodium diet, and to a lesser degree reduction in methionine intake. Such dietary measures may be sufficient to prevent stone formation in most patients with moderate cystinuria. In patients with heavier cystinuria (≥750 mg/day or 3 mmol/day), alkalinization should be added, preferably by means of potassium citrate, with urinary pH being adjusted around 7.5.

If the sum of the preceding measures fails to prevent stone formation, or to dissolve pre-existing stones, a sulfhydryl agent should be added (while maintaining a large fluid intake and alkalinization) at a graded dose, starting with 500–600 mg/day (10 mg/kg) DP or TP and slowly increasing to the dose (not in excess of 1,500 mg/day) necessary to reduce cystine concentration to less than 250 mg/l (about 1 mmol/l).

Such drugs should be avoided in pregnant women, in view of their potential teratogenic effects, especially in the first trimester of gestation [53]. In the pregnant patient, treatment should rely only on hyperdiuresis and alkalinization [54]. Children born from a cystinuric mother are obligatory heterozygotes and should be screened for aminoaciduria and cystine excretion; primary prevention (by means of high fluid intake and alkalinization) should be discussed in cases where cystine excretion is high, as observed in type II cystinuria.

Efficacy of the treatment should be monitored by determination of urine density and pH, and by determination of 24-h free cystine excretion. Disappearance of cystine crystals in first-morning urine is an excellent index of treatment efficacy. Clinically, patients should have frequent clinic visits (every 3–4 months in severe forms) with echographic controls. Renal function should be regularly monitored, especially in patients who have already lost a kidney or have impaired renal function.

In conclusion, management of the cystinuric patient requires close co-operation between the urologist and the internist or nephrologist. Regular medical treatment is mandatory, because of the relentless tendency of cystine stones to recur despite improved urological techniques of stone removal. Such medical treatment is cumbersome, and only an informed and motivated patient may accept such long-term constraints. Compliance is especially difficult to obtain in children and adolescents, who often require psychological support. However, only a regular medical prophylaxis may prevent recurrent stone episodes and protect renal function.

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