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Prophylaxis of uric acid and cystine stones

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Summary. Although they are two very distinct entities, uric acid and cystine stone disease share a common physico-chemical background, i.e. urinary supersaturation with respect to a compound that is poorly soluble in an acid milieu. Therefore, high-fluid intake and urine alkalinization, preferably by potassium citrate, are of utmost importance for prophylaxis. Urinary excretion of uric acid and cystine may be reduced by dietary measures as well as by drug therapy (allopurinol and thiols, respectively).

Key words: Uric acid and cystine stones – High-fluid intake – Urinary alkalinization – Dietary regimens – Drug therapy

Although uric acid and cystine stone disease are metabolically very distinct diseases, they share a common physico-chemical background for kidney stone formation: in both diseases, urine is highly supersaturated with a compound that is poorly soluble in acid urine, i.e. undissociated uric acid and cystine. The aim of prophylaxis is mainly to reduce urinary supersaturation, which is principally achieved in three ways (Fig. 1): solubility of the poorly soluble compound is increased by urinary alkalinization and by the formation of more soluble complexes with other compounds, or the concentration of stone components is lowered by high-fluid intake and dietary measures.

Uric acid stones

For lowering urinary supersaturation and preventing massive uric acid crystallization with subsequent stone formation, three measures are feasible: (1) uric acid *solubility* may be enhanced by increasing urinary pH; (2) uric acid *excretion* can be reduced by an adequate diet or by allopurinol; and (3) an increase in urinary volume lowers urinary uric acid *concentration* [24].

Urinary alkalinization

Urinary alkalinization is by far the most important measure in the treatment and prophylaxis of uric acid stone patients [24]. At low urinary pH values, highly characteristic of uric acid stone-formers [18, 28], the majority of urinary uric acid is excreted as *undissociated* uric acid (UUA). Its low solubility of only 0.54 mmol/l [5] increases strongly with increasing pH [5, 28]. In urine, the pK value, at which 50% of total uric acid (TUA) occurs in the form of the more soluble sodium urate, is 5.35 [5]. Using the formula

$$[UUA] = [TUA]/(1 + 10^{pH-pK}),$$

the concentration of urinary UUA can be derived from measured TUA [5].

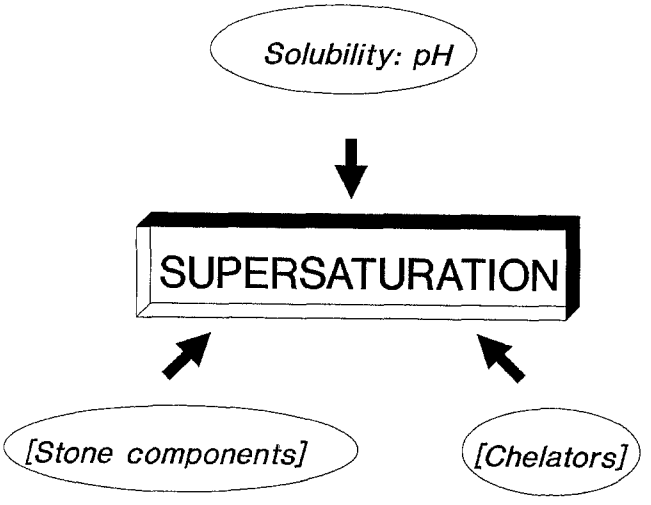

Fig. 1. Factors influencing urinary supersaturation

Table 1. Prophylaxis of uric acid stone formation

1. High-fluid intake: urinary output of > 2,500 ml/day
   Beer: rich in guanosine → *uricosuria* ↑
2. Avoid overconsumption of purine-rich foods
3. Urinary alkalinization: *potassium citrate*
   ⇒ urinary pH of 6.5–7

▶ If levels of urinary [uric acid] are *persistently* high:

4. Allopurinol 300 mg/day

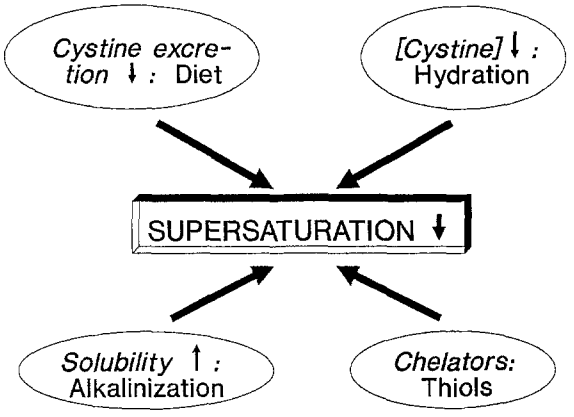

Fig. 2. Possibilities of reducing urinary supersaturation with respect to cystine

Sodium citrate. Although it increases urinary pH very reliably, this compound has been found to have some disadvantages [26]: (1) more alkaline urine facilitates calcium phosphate precipitation, since more phosphate is dissociated in the presence of unchanged calciuria [26]; and (2) the sodium load increases monosodium urate saturation, which may attenuate urinary macromolecular inhibitors of calcium oxalate crystal growth, thereby promoting hyperuricosuric calcium lithiasis [30].

Potassium citrate. At an average dose of 60 mEq/day (in 3 doses), potassium citrate produced a sustained increase in urinary pH over 24 months [22]; simultaneously, mean UUA concentration fell below the solubility limit. Due to the chelating properties of citrate, calcium oxalate supersaturation was reduced [22]. Adverse side effects (diarrhea, nausea, burning, indigestion) were rather frequent (27%) when potassium citrate was taken in liquid form, but their incidence fell to 9% with the solid form [21].

Reducing urinary uric acid excretion

Dietary purine intake. As demonstrated earlier by Coe et al. [4], there is a positive linear correlation between dietary purine intake und daily urinary uric acid excretion. Therefore, massive consumption of purine-rich foods such as liver, steak, veal chops and some kinds of fish [4] should necessarily be avoided.

Allopurinol. This substance successfully lowers uric acid excretion; however, urinary concentrations of UUA may stay elevated if the urine is not alkalized. The incidence of adverse reactions (skin rash, gastrointestinal discomfort, fatigue), although said to be minimal [24], may be as high as 8% [11]. Furthermore, one should watch for an acute gouty attack in hyperuricemic patients immediately after the start of allopurinol treatment [24]. In combination with a high-fluid intake and potassium citrate, allopurinol was highly successful, dissolving preexisting uric acid stones in 75% [14] and 71% [10] of patients, respectively.

Conclusions

Recommendations for uric acid stone prophylaxis are summarized in Table 1. High-fluid intake, regularly distributed over 24 h, and avoidance of overconsumption of purine-rich foods are self-evident measures. Patients should bear in mind that beer contains guanosine, which is metabolized to uric acid; therefore, heavy beer drinkers may increase their daily urinary uric acid excretion by 3–6 mmol as compared with non-beer drinkers [25].

The crucial measure in most patients with pure uric acid stone disease is *urinary alkalinization*, preferably by potassium citrate. Urinary pH should be kept between 6.5 and 7 and should be monitored regularly. Allopurinol may be given only if the aforementioned strategies (consequently applied) fail or in cases of hyperuricemia with gouty attacks.

Cystine stones

As demonstrated in Fig. 2, supersaturation with respect to cystine can be lowered in four ways [7, 20, 29]: urinary cystine concentration is reduced by high-fluid intake, dietary measures may lower cystine excretion, urinary alkalinization increases the solubility of cystine, and drugs such as thiols form more soluble cysteine-thiol-disulfides.

High-fluid-intake

At pH values between 5 and 7, the solubility of cystine in urine is about 300 mg, or 1.25 mmol/l [8]. Since cystinurics may excrete as much as 1 g cystine daily [8], urinary output (regularly distributed over 24 h) may reach 3.5 l in some cases. A constant urinary flow of > 2 ml/min, obtained by the administration of 500 ml fluid/4 h during the day and 750 ml/4 h at night, lowers urinary cystine concentration below solubility throughout a 24-h period [8].

Urinary alkalinization

Above a pH of 7, the solubility of cystine in urine rises exponentially, reaching 1,000 mg/l at pH 8 [8]. *Sodium bicarbonate*, which was not successful at doses of 5–10 g/day, sufficiently raised pH only at doses as high as 30 g/day, which is unacceptable for many patients because of

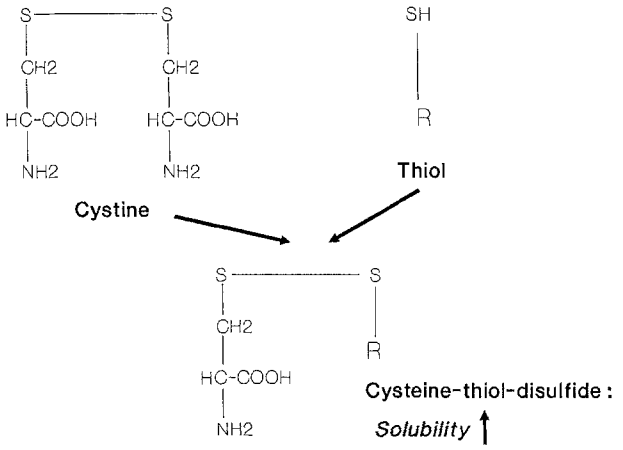

Fig. 3. Formation of more soluble disulfides by thiols

sodium overload with hypertension and thirst as well as abdominal pain, diarrhea and symptoms of alkalosis [9, 12, 20]. A reduced dose of sodium bicarbonate (3×1 g/day) combined with acetazolamide (3×250 mg) seems to increase bicarbonaturia as well [12].

Chronically increased urinary pH raises supersaturation with respect to calcium phosphate [3]. Furthermore, extrapolating from the studies of Jaeger et al. [15], the additional sodium load given with sodium bicarbonate might increase cystine excretion. As a chelator of calcium ions [21], citrate in the form of *potassium citrate* seems to be the alkalizing agent of choice without creating obvious risks of increasing urinary supersaturation with respect to cystine and calcium phosphate.

Dietary regimens

A regimen extremely *low in protein* (20 g/day) has been found to lower cystine excretion by 34% [8] but is possibly harmful and certainly not well accepted by patients [7]. Evidence from several case reports [6, 7, 16] suggests that a diet *low in methionine and cysteine*, maintained for >3 weeks may lower cystine excretion by as much as 25% but rarely to levels below 150 mg/day. One extreme case involved a patient with an initial cystine output as high as 3,600 mg/day, who rigorously maintained his low-methionine diet for 10 years, becoming stone-free; cystine was no longer detectable in his urine by the nitroprusside test [16].

It was recently demonstrated that a *low-sodium diet* reduces cystine excretion, in that lowering sodium intake by 150 mmol/day decreases daily cystine excretion by about 650 µmol, or 156 mg [15]. Thus, highly cystinuric patients with a moderate sodium intake would have to reduce their dietary sodium content to extremely low levels for their cystine excretion to lower significantly. In the same study it was demonstrated that the controversy about the anticystinuric effect of glutamine was due to differences in sodium intake: only cystine excretion was lowered when glutamine was given together with high-sodium intake. Therefore, the authors concluded that glutamine was not a practical treatment for cystinuria [15].

Thiols

The mechanism by which thiols raise cystine solubility is illustrated in Fig. 3. The level of "free" cystine is reduced by the formation of a much more soluble, new mixed disulfide, cysteine-thiol-disulfide. Three such thiols are being used clinically.

D-penicillamine. As a rule of thumb, 1 g D-penicillamine solubilizes 300 mg urinary cystine [3]. Penicillamine-cysteine is about 50 times more soluble than cystine [20]. The daily dose that has been given varies considerably, reaching 3 g in some cases [29]. Toxicity is a major problem: in one study, 69.4% of patients were forced to discontinue the treatment because of adverse reactions [23]. The most frequent adverse reactions are skin rash (30%–50%), nausea and emesis (29%–37%), reversible loss of taste (35%) and proteinuria/nephrotic syndrome (25%) [20, 23, 29]. There is some controversy as to whether a gradual increase in the daily dose might reduce the frequency of adverse reactions [7] or not affect it [29].

Alpha-mercaptopropionylglycine. On a weight-for-weight basis, this compound was found to be 1.5 times as potent as D-penicillamine [13]. A wide range of daily doses, 100–2,000 mg, has been applied [7, 23]. As compared with D-penicillamine, alpha-mercaptopropionylglycine induced a higher rate of remission and fewer recurrences [23]. Its adverse effects seem to be similar to those caused by D-penicillamine, albeit less frequent: diarrhea/soft stools, 14% (74% in 1 study); nausea, 25%; rash, 14%; and proteinuria, 12% [23]. Treatment had to be stopped in 31% of cases because of toxicity [23].

Captopril. In 1987, Sloand and Izzo [27] found that captopril forms a mixed disulfide captopril-cysteine that is 200 times more soluble than cystine. These authors successfully treated 2 patients over 26 and 9 weeks, lowering their cystine excretions by 70% and 93%, respectively. Daily doses were 75 and 150 mg, respectively, and no side effects were reported [27]. This interesting new treatment approach certainly needs further confirmation by controlled studies.

Ascorbic acid

In the late 1970s, Asper and Schmucki [1] hypothesized that the redox-equilibrium cystine-cysteine might be shifted towards the much more soluble cysteine by a reduction in the ascorbic acid excreted in urine. In their patients, treatment with 5 g ascorbic acid/day lowered cystine excretion by 40%. Another study also reported the complete absence of stone recurrence and reduced urinary cystine concentrations in 4 patients treated with ascorbic acid for 19–30 months [17]. In both studies, however, ascorbic acid was given in the form of effervescents containing sodium bicarbonate that alone may have been beneficial because they increased the urinary pH. In addition, one study initiated a high-fluid regimen simultaneously with ascorbic acid therapy [17], which made it

Table 2. Prophylaxis of cystine stone formation

1. Hydration
   Urinary output > 3 l/day
2. Urinary alkalinization
   Potassium citrate 3 × 30 mEq/day
3. Reduce cystine excretion: diet
   Sodium intake ↓ < 50 mmol/day: trial for 3 weeks
   Low-methionine/low-cysteine diet
4. Chelators: thiols
   1) Captopril 3 × 25 or 3 × 50 mg/day
   2) α-mercaptopropionylglycine 5 × 100 mg/day
   3) D-penicillamine 4 × 150 mg/day

almost impossible to disentangle the effects of the various treatment modalities.

A more recent study [2] failed to confirm the previous results: 29% of patients had to discontinue the treatment because of stone recurrence or unchanged cystine excretion. In accordance with previous investigations [19], high-dose ascorbic acid therapy acidified the urine, and additional alkali had to be given [2]. In summary, there is *no convincing evidence* for successful treatment of cystinuria with high-dose ascorbic acid.

Conclusions

As summarized in Table 2, metaphylaxis of cystine stone disease begins with a *high-fluid regimen* and urinary *alkalinization*, preferably with potassium citrate. If these measures, consequently applied, prove to be insufficient, a trial using a low-sodium and/or a low-methionine/low-cysteine *diet* might be recommended. Because of the high rate of adverse effects, the use of *thiols* remains a last additional step; this may change as more experience with less toxic compounds such as captopril is gained.

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