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REVIEW

Hyperuricosuric calcium urolithiasis

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Abstract
Hyperuricosuric calcium urolithiasis is a condition of mixed calcium oxalate stones characterized by hyperuricosuria either in isolation or in conjunction with other risk factors for calcium oxalate stones such as hypercalciuria, hyperoxaluria, and hypocitraturia. There are three proposed physicochemical models of pathogenesis where urate in its crystalline phase via heterogeneous nucleation, in its colloidal phase via removal of crystallization inhibitors, and in solution via precipitation crystallization, can all increase propensity to calcium oxalate precipitation. Regardless of the model, the phenomenologic observation of urate increasing calcium oxalate precipitation appears solid. Another supporting factor are retrospective data analysis and prospective trials showing uric acid lowering reduces stones events in hyperuricosuric calcium stone formers. Due to the heterogeneity of pathogenesis of calcium oxalate stones in the unselected stone-formers, association cannot be demonstrated between uric acid excretion rate and risk of kidney stone the general population. In calcium oxalate stoners with isolated hyperuricosuria or hyperuricosuria in combination with other calcium stone risks where treatment of these traditional risks fails to reduce stone formation, urate acid lowering should be cautiously attempted. More refinement of pathogenic models and prospective controlled trials in phenotypically defined subgroups of subjects with calcium oxalate urolithiasis will be informative.

Keywords Hyperuricosuria · Calcium oxalate · Urolithiasis

The condition

Hyperuricosuric calcium urolithiasis (acronym HUCU) is a clinical condition characterized by kidney stones of mixed chemical composition of calcium oxalate, uric acid, and urate, proposed to be driven mainly by hyperuricosuria. In 1893, the celebrated London Surgeon Sir Henry Thompson (1820–1904) who removed a bladder litholith from Leopold, King of the Belgium, and was a stone former himself, first described 36 mixed calcium oxalate/uric acid (CaOx/UA) stones in 1007 kidney stone patients [1] (Fig. 1). Prien in 1947 and Prien and son 1968, also found mixed calcium oxalate/uric acid stones, in more than 10% of gouty subjects [2]. Gutman and Yü noted the co-existence of calcium and urate and ventured to propose pathogenicity of calcium oxalate possibly acting as nidus for mixed CaOx/UA stones [3]. The observation in stone composition was extended to urinary composition when Smith and coworkers pointed out the co-existence of hyperuricosuria and calcium stones [4]. Subsequently, Coe and coworkers found nearly 30% of patients with calcium urolithiasis suffered hyperuricosuria [5]. Furthermore, Dent and Sutor studied the ease of glass fiber to induce CaOx precipitation with solutions of calcium chloride and sodium oxalate in stone formers with idiopathic hypercalciuria, primary hyperparathyroidism, distal renal tubular acidosis, cystinuria, and hyperoxaluria, and concluded that lack of inhibitors in fact correlated better with mixed CaOx/UA stone formation than the pro-formation factors such as hypercalciuria or hyperoxaluria [6]. In a classic paper by Coe and Raisen [5], the paradigm was proposed for the first time that "…these patients (referring to calcium stone formers with hyperruricosuria) may represent a hitherto undescribed syndrome."

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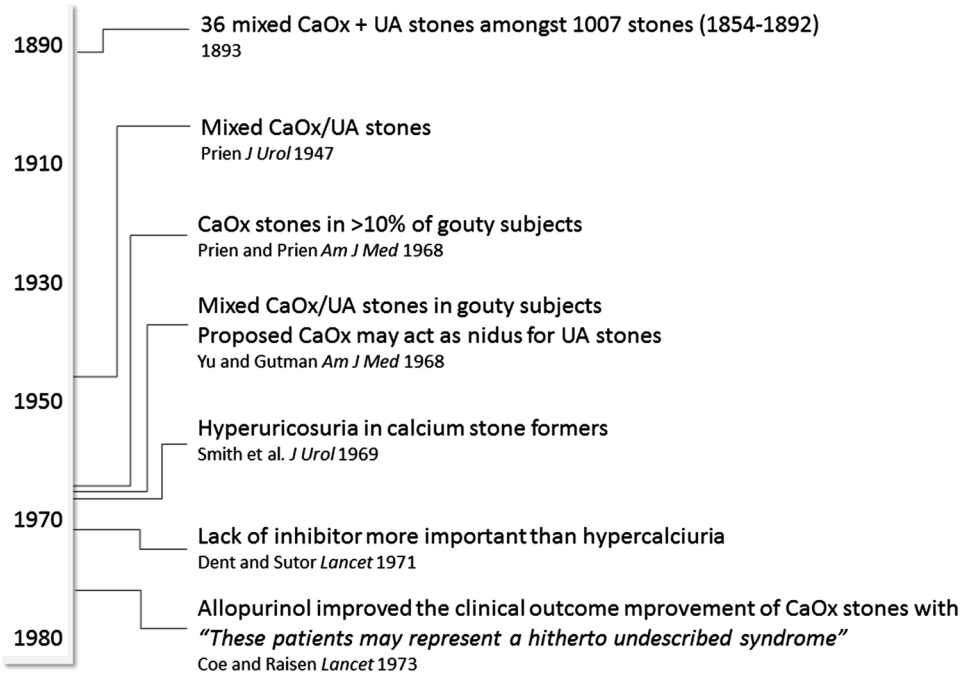

Fig. 1 Historical timeline of the discovery of the condition of hyperuricosuric calcium urolithiasis (HUCU)

One of the more compelling evidence for HUCU is the fact that treatment with urate-lowering agents decreased rate of stone recurrence rate in patients with calcium stones and hyperuricosuria [5, 7–9]. Several physicochemical models had been described to collaboratively contribute to formation of calcium stones under hyperuricosuria (Fig. 2) [10–15], and will be discussed individually. Based solely on cross-sectional epidemiologic data, some doubts were raised about whether uric acid alone promotes calcium oxalate stones [16]. In this monograph, we will review the physicochemical models on hyperuricosuric calcium stones, clinical trials, and highlight some questions that require answers.

The requisites for making the diagnosis of HUCU are mixed calcium oxalate-urate-uric acid stones and the absolute presence of hyperuricosuria. Other risk factors for calcium stones such as hypercalciuria, hypocitraturia, hyperoxaluria, and low urine volume may be concomitantly present. This creates a pathophysiologic, diagnostic, and therapeutic uncertainty because of the variable and potentially minor contribution of uric acid to lithogenesis from patient to patient, and eve in the same patient over time. Coe et al. described in 420 consecutive calcium stone formers that 15 and 12% have isolated hyperuricosuria and combined hyperuricosuria and hypercalciuria, respectively [17] amounting to about a third of calcium stone formers having hyperuricosuria, and interesting, the source of hyperuricosuria appeared to be largely dietary-related which is not that different from the hyperuricosuria of non-stone formers [18]. It is critical for the practitioner to determine whether the hyperuricosuria is pathogenic and deserves therapy.

Physicochemical models

How can urate cause crystallization of calcium oxalate? Three pathogenic models have been proposed and are presented in Fig. 2. These models are not necessarily mutually exclusive. The relative contributions of each mechanism has not be determined.

Crystalline phase: heterogeneous nucleation

The crystalline phase model, also termed as epitaxy, refers to one type of crystal growing upon the surface of another type of crystal [19] (Fig. 2). This theory was proposed for HUCU in 1975 by two groups independently in two dual publications [10, 11]. Coe et al. demonstrated precipitation of CaOx crystals at pH 5.7 when crystalline sodium urate (NaU) was added as a seed for nucleation [10] (Fig. 3). Pak et al. elaborated on the effect of NaU that caused heterogeneous nucleation of CaOx at pH 5.7 and 6.7, and of calcium phosphate (CaP) at pH 5.3, 5.7, and 6.7 from metastably supersaturated solutions in vitro [11]. In a subsequent study, Pak et al. showed stability and supersaturation of NaU in urine, reinforcing the notion that under the conditions of supersaturated urine samples from patients with hyperuricosuria and calcium stones, NaU can serve as seeds for the heterogeneous nucleation of CaOx or CaP crystals [12, 20]. In contrast, seeds of uric acid had very small or no effect [10, 11].

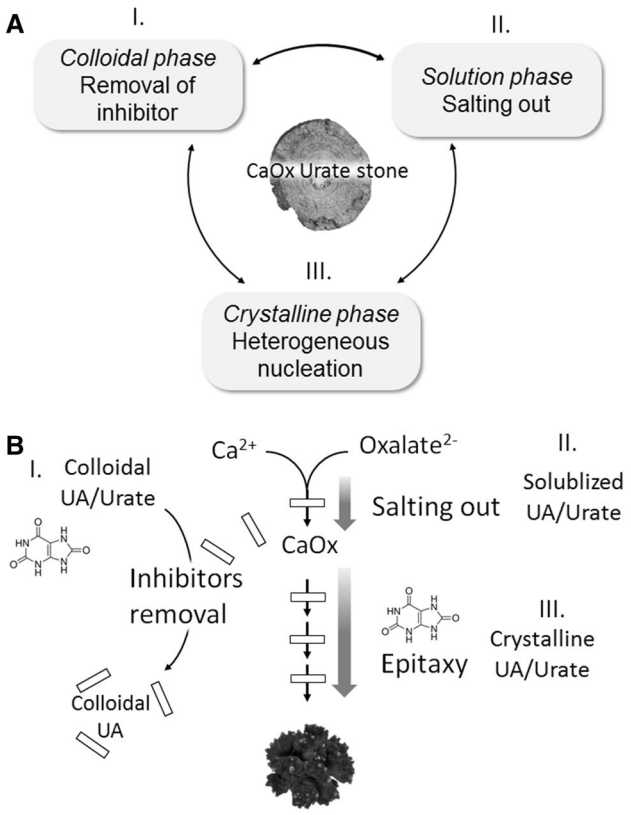

Fig. 2 Summary of the pathophysiologic mechanisms of hyperuricosuric calcium uricolithiasis. **a** Urate can enhance propensity for calcium oxalate crystallization and growth by three proposed mechanisms which are not mutually exclusive. Urate exerts its lithogenc effects while in (I) Colloidal phase (II) Solution phase, and (III) Crystalline phase. **b** (I) Colloidal uric acid can adsorb or bind various inhibitors of calcium oxalate crystallization. (II) Soluble urate salts can enhance calcium oxalate crystal formation via the chemical effect of "salting out" calcium. (III) Finally, microcrystals of Na urate can provide nidi for heterogeneous nucleation of epitaxy of calcium oxalate crystals

In vivo demonstration of this phenomenon in humans was provided by examination of the effect of oral purine load and allopurinol to increase and decrease urinary urate respectively, on calcium salts crystallization in urine. Oral purine load was associated with an increased saturation of NaU and purine deprivation and/or allopurinol therapy was found to decrease saturation with respect to Na urate [21], and the formation product ratio of CaOx (FPR; $[Ca] \times [Ox]_{crystallization}/[Ca] \times [Ox]_{initial}$, lower FPR = increased propensity to cystallization) was directly correlated with the activity product ration of NaU (Fig. 3c).

Colloidal phase: removal of inhibitor

The epitaxy model is a frequently cited model, yet caution has been raised about the extrapolation from solution chemistry to human urine in situ in the urinary space. Moreover, the formation and presence of NaU crystals were infrequently documented in human stones. It is widely accepted that urine contains large quantities of inhibitors of CaOx crystallization [22]. Pak et al. suggested that the colloidal form of urate could have promoted nucleation of CaOx by removing certain inhibitors of CaOx nucleation from urine [12].

The state of a solute in aqueous surrounding can be classified according to the size of the solute- in-solution: $< 10^{-9}$ m; colloid 10^{-6}–10^{-9} m; suspension $> 10^{-6}$ m (Fig. 3). Shade and Boden first showed the existence of colloidal NaU in urine [23]. Others subsequently succeeded in isolating the colloid with ultrafilters to make a quantitative determination and estimated up to 25% of uric acid in urine can be colloidal [24, 25]. For instance, NaU may remove mucopolysaccharides that inhibit crystal aggregation of CaOx [15, 26]. This theory is supported by more prominent CaOx aggregation in urine samples of high UA content. However, no direct experimental evidence that colloidal NaU absorbs inhibitor has yet been documented. Nevertheless, both colloidal and solid NaU may work together to formation of mixed CaOx/UA stones under hyperuricosuria.

Solution phase: salting out

A well-known phenomenon in chemistry is "salting out" (synonymous with precipitation crystallization) where certain solutes; often but not exclusively non-electrolyte organic molecules are less soluble at either very low or very high salt concentrations due mainly to the existence of an optimal window of hydration shell. It is a commonly used method of precipitating proteins and nucleic acids out of solution, followed by means to remove the salt if needed. This mechanism for calcium oxalate was proposed by Kallistratos et al. in 1970 [27], and experimentally supported by Grover et al. in 2003 [13, 14]. Various combinations of urinary calcium, oxalate, and urate were used to induce precipitation of CaOx. NaU seeds had decreased potency in promoting CaOx deposition once preincubated with human urine [13] which supports the salting out mechanism but also with adsorption of inhibitors. Importantly, they showed that the amount of oxalate required to trigger spontaneous CaOx crystal formation decreased with increases in the product of prevailing concentrations of urinary calcium and urate [14] (Fig. 3d).

Therefore, patients with hypercalciuria and hyperoxaluria would be more vulnerable to stone formation with increase in concentration of dissolved urate [14]. The study indicated that the urate's salting out effect depends upon the prevailing concentration of calcium and oxalate and that in addition to urate-lowering, steps should be taken to reduce patient's calcium and oxalate excretion.

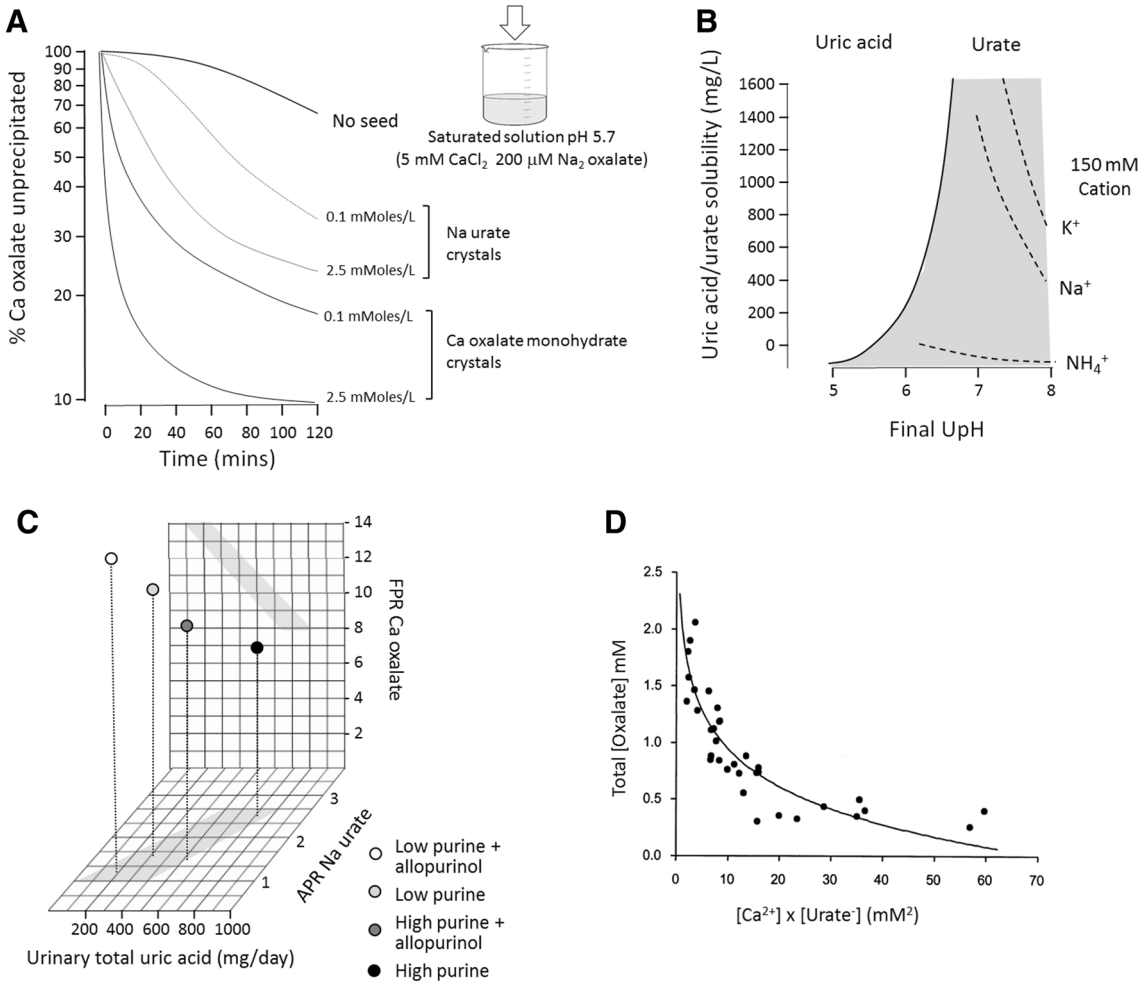

Fig. 3 Physicochemical studies of the effect of Na urate on calcium oxalate precipitation. **a** Addition of Na urate crystals in a saturated solution of Ca oxalate accelerates precipitation of Ca oxalate in a dose-dependent fashion. Ca oxalate addition is shown in comparison. Redrawn from Coe et al. [10]. **b** Distribution of total uric acid between uric acid (cation H^+) and three urate salts (K^+, Na^+, and NH_4^+) in the grey shaded region. K^+ urate has the highest, and NH_4^+ urate has the lowest solubility; with Na^+ urate being intermediate. Redrawn from Pak et al. [12]. **c** Human studies where urinary uric acid excretion manipulated by dietary purine and xanthine oxidase inhibition by Allopurinol. The three dimensional plot relates the effect of uricosuria (*x*-axis) on Na urate activity product ratio (APR, *y*-axis) and formation product ratio (FPR, *z*-axis, [Ca] $x[Ox]_{crystallization}/[Ca]x[Ox]_{initial}$, lower FPR = high propensity to crystallize) of Ca oxalate. The *x*–*y* plot shows uricosuria increases the APR of Na urate. The *y*–*z* plot shows that the increase APR Na urate is associated with decrease in FPR of Ca oxalate which signifies increased propensity to Ca oxalate crystallization. Redrawn from Pak et al. [21]. **d** Relationship between the urinary concentrations of Ca, urate, and total oxalate required to induce CaOx precipitation. *Y*-axis is the total concentrations of oxalate = sum of endogenous concentration to the addition of oxalate required to induce spontaneous CaOx precipitation [14]

Therapeutic studies

Some of the strongest evidence are derived from interventional studies with uric acid lowering agents in calcium oxalate stone formers (Table 1). These studies were all conducted from 1973 to 1986. One can identify some caveats in just about each one of these studies which are the small sample sizes, short duration, heterogeneous patient population, the lack of placebo (historical controls instead), and lack of standard treatment protocols. Nonetheless, they constitute a compelling body of literature. Four major ones will be cited here.

The first study by Coe and Raisen yielded impressive data on 21 Ca stone formers with no metabolic abnormalities other than hyperuricosuria, hyperuricemia, or both. Both hyperuricemia and hyperuricosuria responded well to allopurinol. Stone events were nearly obliterated after starting therapy with allopurinol which illustrates the unlost importance of proper selection of phenotype for therapy to reduce urinary uric acid [5]. The study of Smith was prospective and placebo-controlled [7] but no metabolic

Table 1 Therapeutic trials of uric acid lowering in stone-former

References	Subjects and design	Therapy	Results
Coe and Raisen [5]	21 Ca stone formers with hyperuricemia or hyperuricosuria but no other abnormalities. Retrospective analysis—historical control	Allopurinol vs. historical control Mean 1.9 years Range 0.5–7 years	Stones /patient-year Before Rx 0.398 After Rx 0.026
Smith [7]	92 stone formers with hyperuricemia Stone type—not reported Metabolic data- not reported	Allopurinol and $NaHCO_3$ UpH > 6.5 vs. placebo Range 0.5–5 years	% of patients who were stone free was ~60% for allopurinol ~10% for placebo
Coe [9]	Retrospective analysis- historical controls 126 hypercalciuria alone 51 hyperuricosuria alone 43 both hypercaliuria and hyperuricosuria	Hypercalciuria: thiazide Hyperuricosuria: allopurinol Mean 2.9 years Range 1–7 years	Dramatic reduction in stone events in all patients receiving tailored therapy
Ettinger et al. [8]	60 CaOx stone formers with hyperuricosuria but no hypercalciuria	Allopurinol vs. placebo 39 weeks	0.26 per patient-year for placebo 0.12 per patient-year for allopurinol

characterization of the patients were reported, and the regimen was an unusual one that combined allopurinol with urinary alkalinization to pH > 6.5 with $NaHCO_3$, which will in fact increase conversion of uric acid to urate. Coe did a more extensive analysis of 202 CaOx stone-formers with idiopathic hypercalciuria or hyperuricosuria, or both [9] were treated for an average of 2.9 years. Therapy was directed by pathophysiology so hypercalciuria was treated with thiazides, hyperuricosuria was treated with allopurinol, and when neither was present, fluid was prescribed. The reduction in stone events was no less than dramatic (Fig. 4). The study by Ettinger and coworkers was a randomized prospective placebo-controlled trial [8]. Sixty calcium stone patients with hyperuricosuria but normocalciuria were randomized to receive either allopurinol or placebo (Fig. 4). Both the Smith and Ettinger papers showed a benefit from placebo compared to no therapy, which testifies to the importance of placebo-control as mere enrollment in a clinical trial frequently improves the outcome. Part of the dramatic effect of the Coe and Raisen study may be the "clinical trial" effect.

Questions to be addressed

Basis for questioning the existence of HUCU

The argument against the condition is based on the inability to observed association between urine uric acid excretion rate and risk of being a stone former [16, 28]. One needs to exercise caution to interpret population-based data especially when the metabolic characterization of the population is unclear. The studies of Coe clearly demonstrated that only subgroups of stone formers (i.e. isolated hyperuricosuria or hyperuricosuria in conjunction with hypercalciuria) respond best to uric acid-lowering drugs [9]. Thus, the strength of hyperuricosuria as a risk factor for overall stone formation in the general population may be very difficult to demonstrate because only a small proportion of patients are actually true HUCU sufferers despite the presence of hyperuricemia and hyperuricosuria in a significant number of calcium stone formers [5]. An analogy can be with acute promyelocytic leukemia which has extremely favorable response to all-trans-retinoic therapy but a therapeutic trial of this regimen in all types of acute leukemia will not be positive [29]. While one cannot detect an association between 24 h aldosterone excretion or response to mineralocorticoid receptor antagonists in the general population of primary hypertension, in subgroups with treatment-resistant hypertension or primary hyperaldosteronism, such association and response to therapy can be detected [30, 31]. One model proposed to account for the favorable effects of allopurinol on HUCU [5, 7–9] (Table 1; Fig. 4) which is extrapolated from the beneficial effects of anti-oxidants on a rodent model of acute ethylene glycol-induced metabolic acidosis and oxalosis [32], and potential anti-oxidant effects of allopurinol, albeit admixed with the simultaneous pro-oxidant effects of allopurinol and lack of in vivo actions at human therapeutic levels [33–36].

True physicochemical pathophysiology and interaction with other stone risks

Three models were cited above and the data supporting each appears to be solid. While specific studies and investigators tend to favor one over another, there is actually no conclusive data that disproves any one of them. Figure 2 illustrates they can co-exist. It is likely that these are not static models as each stone former may differ from another in terms of relative contributions, and within a given individual, the relative contributions from each may vary over time. In addition to the fundamental philosophy of the need to understand pathogenesis of any disease, elucidation of the physicochemical pathophysiology of HUCU can potentially allow practitioners to predict the risk conferred by hyperuricosuria in a given individual. Currently, one can assess and quantify stone risk (to a certain degree), by using common urinary chemistry and entering

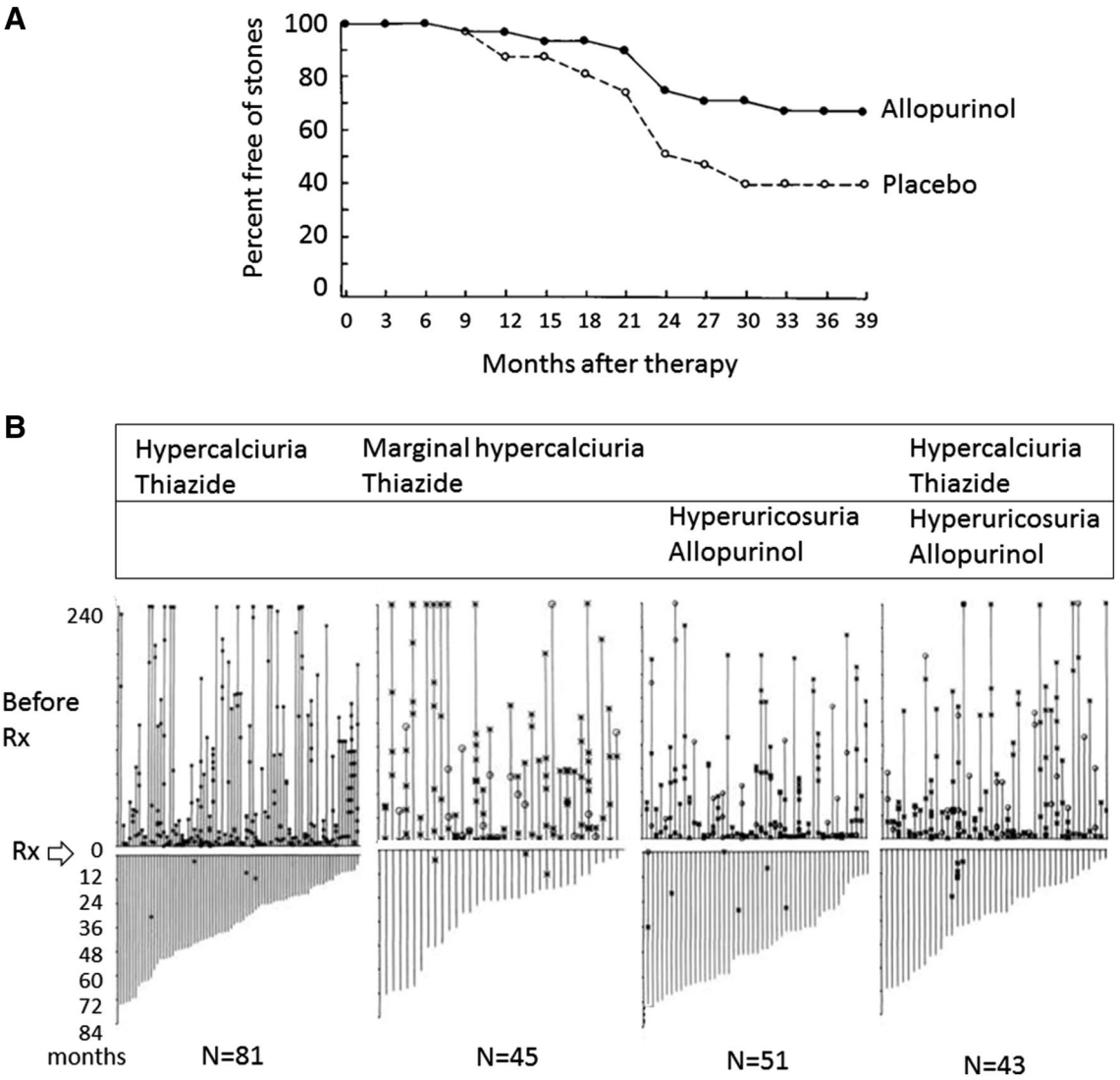

Fig. 4 Representative clinical trials. **a** Percentage of treated patient treated with allopurinol vs. placebo who are free from stones events over 39 months. **b** Stone events before and after initiation of customized therapy; each vertical line represents one patient and each stone event by one dot. Hypercalciuric patients were treated with thiazides, hyperuricosuric patients were treated with allopurinol, and those with both abnormalities were treated with both drugs

them into in silico programs such as the EQUIL2 or JESS programs [37, 38]. Currently, EQUIL2 does not have uric acid or urate as an input parameter but JESS does take into account H^+-, Na^+-, K^+-, NH_4^+-, and Ca^{2+}-urate complexes [38]. If one manually varies total urinary uric acid concentration over a 10-fold range during input into JESS, there is a < 5% resultant change in CaOx saturation index (SI, not shown). This is not unexpected because neither one of the three models described above is included in the JESS program. This will be a very challenging task indeed to mathematically model what is presented in Fig. 3. Hypothetically, if such a predictive model is achievable, one will have a way to predict how much risk hyperuricosuria is imposing on CaOx stone risk.

Hyperuricosuria: dose-relationship to stone risk, who to treat, and therapeutic target

Based on the limited but nonetheless impressive therapeutic trials cited above, lowering urine uric acid is a therapeutic option. The challenges are who to treat and how low does one need to lower the uric acid to. The obvious prerequisite is hyperuricosuria despite the fact that there is no cut-off. Based on the pathophysiologic studies [10–12, 20, 21] and therapeutic trials available [5, 7–9], one can formulate a set of recommendations based on both opinion rather than hard data. Table 2 lists some conditions that prompt the consideration of treating hyperuricosuria.

Table 2 Conditions where treatment of hyperuricosuria is considered

Mixed calcium oxalate and uric acid/Na urate stones
Hyperuricosuria
Absence or very mild degree of other risk factors for CaOx stones such as hypercalciuria, hypocitraturia, hyperoxaluria, low urine volume
Presence of both hyperuricosuria and known CaOx risk factors but not responding to conventional therapy to classical CaOx risks

If uric acid lowering therapy is attempted, there is no current clinical guideline regarding the target level of reduction. However, one can predict from knowledge of the pathophysiology that this may be a "customized" target. Pak et al. demonstrated in a human metabolic study a linear relationship between urinary total uric acid (clinically reported parameter) and the surrogate stone risk readout of FRP_{CaOx}, there is a continuous change in FRP_{CaOx} over the range of clinical uricosuria (Fig. 3c). Unless one is dealing with solitary hyperuricosuria, the levels of hypercalciuria, hypocitraturia, and hyperoxaluria will not doubt influence the target uricosuria needed to lower stone risk to acceptable values. Since physicochemical methods are not pragmatic in clinical practice and there are no available in silico methods, the eventual practical monitor of therapy must rely on clinical events and imaging studies of stone count, which are quite acceptable.

Compliance with ethical standards

Conflicts of interest The authors declare they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants performed by any of the authors.

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