




Selection and Outcomes for Dissolution Therapy in Uric Acid Stones: A Systematic Review of Literature

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Abstract

Purpose of Review The prevalence of uric acid (UA) urolithiasis contributes significantly to global disease burden, due to high rates of recurrence and diagnostic challenges. Dissolution therapy plays a valuable role in the conservative management of UA calculi, reducing the requirement for surgical intervention. This review summarises the existing evidence for the efficacy of medical dissolution of uric acid urolithiasis.

Recent Findings A systematic search was conducted of worldwide literature according to PRISMA methodology and Cochrane standards for systematic review. Studies were included if they reported outcome data for the administration of medical therapy for the dissolution of UA calculi. A total of 1075 patients were included in the systematic review. Complete or partial dissolution of UA calculi was observed in 80.5% of patients (865/1075 patients), with 61.7% (647/1048 patients) achieving complete dissolution and 19.8% (207/1048 patients) achieving partial dissolution. A discontinuation rate of 10.2% (110/1075 patients) was noted, and 15.7% (169/1075 patients) required surgical intervention.

Summary Dissolution therapy is a safe and effective method of conservatively managing uric acid stones in the short term. Despite the significant disease burden of UA calculi, current guidelines are limited by deficiencies in the existing body of research. Further research should be undertaken to develop evidence-based clinical guidelines for diagnosis, treatment, and prevention of UA urolithiasis.

Keywords Dissolution · Kidney calculi · Uric acid · Ureterscopy · Endourology · PCNL · Review

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Introduction

Contributing to 10% of urolithiasis, the prevalence of uric acid (UA) calculi is a widespread problem. Surgical intervention predominates the management of urolithiasis. However, high rates of recurrence necessitate the development of conservative medical alternatives. Advancements in the treatment of UA calculi could impact economic burden and patient morbidity on a global scale [1, 2]. With a propensity to occur as multiple radiolucent stones in bilateral kidneys, UA calculi are challenging to diagnose and treat. Medical treatment aims to dissolve urolithiasis through alkalinisation, assessed by change in urinary pH [3]. Despite the documented use of dissolution therapy over the preceding decades, standardised guidelines for treatment are limited [4, 5]. This review will focus on the efficacy of dissolution therapy for the management of UA calculi.

Methodology

Studies for inclusion in this review were selected according to the following criteria.

The inclusion criteria were as follows:

- Studies reporting on the clinical role of dissolution therapy administered through any route for the treatment/dissolution of uric acid calculi
- Articles written in the English language
- All age groups, including paediatric studies
- Studies with a minimal sample size of 8 patients

The exclusion criteria were as follows:

- Non-human studies, review articles, editorials, and guidelines
- Studies pertaining to composites of urolithiasis other than uric acid
- Studies pertaining to the prophylaxis of uric acid calculi rather than the treatment/dissolution of uric acid calculi

Search Strategy and Study Selection

The Cochrane and preferred reporting items for systematic reviews and meta-analyses (PRISMA) standards were used to conduct a systematic review. An electronic search strategy was performed on Medline, Cochrane library, EMBASE, Scopus/Science Direct, British Nursing Index, Ovid Emcare, HMIC, PsycINFO, Social Practice and Policy, and AMED to identify publications relevant to the dissolution of uric acid calculi. Boolean operators (AND, OR) were used alongside keywords including ‘dissolution’, ‘chemolysis’, ‘kidney stones’, ‘nephrolithiasis’, ‘urolithiasis’, ‘calculi’, ‘uric acid’, and ‘radiolucent’. References and individual urology journals were hand-searched and cross-checked. English articles from inception to November 2022 were included in the literature search. The studies were screened by title, then by abstract, and finally by full text according to the inclusion criteria.

Data Extraction and Outcomes of Interest

Data was extracted independently by two authors (A.O. and G.B.), and the decision to include articles was made by mutual consensus between three authors (A.O., G.B., and B.K.S.). To facilitate comparison between studies, this systematic review defined complete dissolution as the radiologically proven absence of UA calculi following intervention with dissolution therapy. Partial dissolution is defined as radiologically proven reduction in the burden of

UA calculi following dissolution therapy. Eligible studies were reviewed for patient characteristics, treatment regime, follow-up/recurrence, adjuvant investigations, secondary intervention, recurrence, side effects/discontinuation, and the effect on complete or partial dissolution of UA calculi.

Results

Three hundred ninety-two relevant articles were identified in an initial literature search; 75 were selected by title. Fifty-nine were selected from further analysis of the abstract and full text. Three in vitro studies were excluded, 11 were irrelevant, 1 was not in the English language, 1 was an animal study, 5 were systematic reviews, 23 were excluded due to sample size, and 1 article reviewing the dissolution of UA calculi in combination with extracorporeal shockwave lithotripsy (ESWL) was excluded from analysis. Fourteen articles were included for analysis (Fig. 1).

A total of 1075 patients were included in the systematic review. The mean age was 48 years old. The gender demographics were included in all but 3 of the studies, with 483 men and 351 women. Of the studies, 8 were retrospective, 5 were prospective, and 1 was a randomised controlled trial (Table 1).

Diagnostic Parameters

The studies diagnosed the presence of UA calculi by elevated serum UA levels, urine pH, varying radiological imaging modalities, and Hounsfield units (HU). Four studies reported raised serum UA levels (> 6 mg/dL) [3, 6, 7, 8•]. Initial urinary pH levels ranged from 5.17 to 6.4. End-point urinary pH levels ranged from 6.0 to 7.5 (mean pH 6.7). Computed tomography (CT) of the kidneys, ureters, and bladder was the most frequently used imaging modality (12/14 studies) [6, 7, 8•, 9••, 10••, 11•, 12, 13, 14•, 15–17]. This was followed by ultrasound (US) of the kidneys, ureters, and bladder (7/14 studies) and x-ray (XR) of the kidneys, ureters, and bladder (4/14 studies). Intravenous urogram (IVU) was used in 3 studies [3, 12, 16]. Retrograde pyelogram (RP) and MAG3 renogram were each used in one study [9••, 12]. The mean stone diameter was recorded in 11 studies, with a cumulative mean of 16.5 mm (range: 9–30.9 mm) [6, 7, 8•, 9••, 10••, 11•, 13, 14•, 15, 17, 18]. Out of 12 studies utilising CT imaging, 6 measured HU, giving a mean of 417 HU [6, 7, 9••, 10••, 11•, 15]. Inconsistent reporting of stone position was observed between the studies. However, of those described, 522 stones were in the kidney, 205 in the ureter, and 6 in the kidney and the ureter. One hundred sixty were solitary stones, and 46 were multiple/bilateral stones (Table 2).

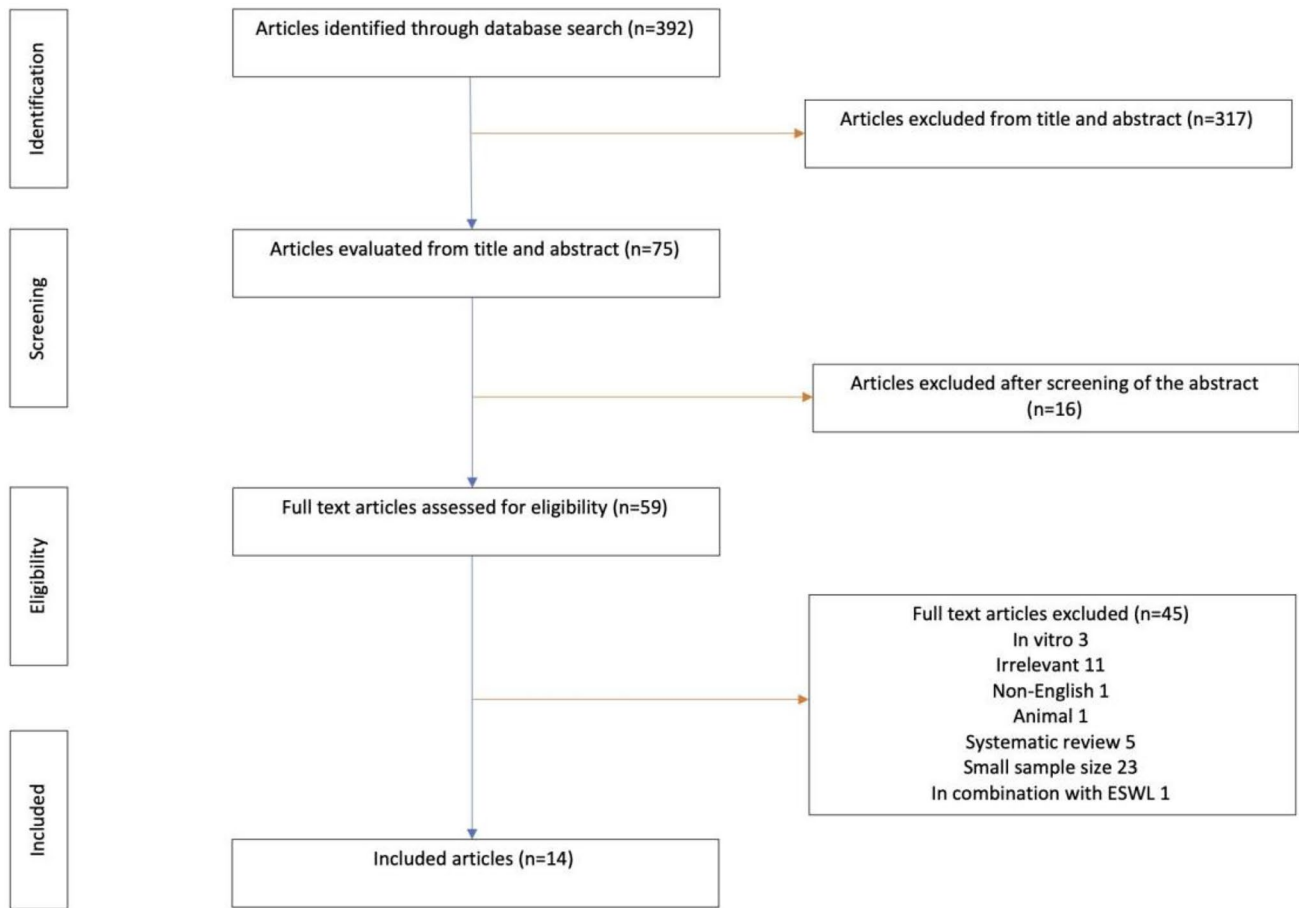


Fig. 1 A PRISMA flow chart of articles searched, analysed, and included in the systematic review

Table 1 The characteristics of the included studies

| Paper | Author | Publication | Type of study | Number of patients | Mean age | Male:female |
|-------|----------------------|-------------|-----------------------------|--------------------|----------|-------------|
| 1 | Elbaset et al. | 2019 | Randomised controlled trial | 50 | 47 | 24:26 |
| 2 | Kursh and Resnick | 1984 | Prospective | 14 | 44 | 13:1 |
| 3 | Moran et al. | 2002 | Prospective | 11 | 50 | 8:3 |
| 4 | Elderwy et al. | 2014 | Prospective | 48 | 3 | 33:15 |
| 5 | Elsawy et al. | 2019 | Prospective | 212 | 51 | 65:117 |
| 6 | Salem et al. | 2019 | Prospective | 139 | 45 | 74:65 |
| 7 | Petritsch | 1977 | Retrospective | 140 | ND | ND |
| 8 | Sharma and Indudhara | 1992 | Retrospective | 23 | ND | ND |
| 9 | Sinha et al. | 2013 | Retrospective | 48 | ND | ND |
| 10 | Alsinnawi et al. | 2016 | Retrospective | 27 | 59 | 18:9 |
| 11 | Gridley et al. | 2019 | Retrospective | 24 | 56 | 14:10 |
| 12 | Tsaturyan et al. | 2020 | Retrospective | 216 | 63 | 162:54 |
| 13 | Yunhua et al. | 2020 | Retrospective | 96 | 46 | 49:47 |
| 14 | Moore et al. | 2021 | Retrospective | 27 | 65 | 23:4 |

ND non-disclosed

Table 2 The diagnostic characteristics of the stones investigated in the included studies

| Paper | Author | Mean serum UA level (mg/dL) | Initial urinary pH | Initial imaging | Mean stone diameter (mm) | Hounsfield unit | Position of stone |
|-------|----------------------|-----------------------------|--------------------|-----------------------|--------------------------|-----------------|--|
| 1 | Elbaset et al. | 6.1 | 5.5 | CT | 16 | 415 | 47 solitary, 3 multiple |
| 2 | Kursh and Resnick | ND | 5.5–6 | US/CT/IVU/RP | ND | ND | 10 renal, 4 ureter |
| 3 | Moran et al. | ND | ND | CT | 26.3 | ND | Renal or proximal ureter |
| 4 | Elderwy et al. | ND | ≤5.5 | US/CT | 12 | ND | 23 renal pelvis, 27 solitary |
| 5 | Elsawy et al. | 5.2 | 6.4 | US/CT/MAG3 renography | 13 | 453.5 | 58 solitary calyceal, 23 multiple calyceal, 35 renal pelvis, 65 renal pelvis, and calyx staghorn |
| 6 | Salem et al. | ND | 5.17 | CT | 18.1 | 388.1 | 54 renal pelvis, 85 calyceal |
| 7 | Petrtsch | >6 | ND | IVU | ND | ND | 25 renal pelvis, 58 ureter, 4 bilateral |
| 8 | Sharma and Indudhara | ND | ND | US/CT/XR/IVU | ND | ND | Bilateral/unilateral/kidney/ureter (stone specific details ND) |
| 9 | Sinha et al. | 4.9 | 5.7 | US/XR | 17.45 | ND | ND |
| 10 | Alsinnawi et al. | ND | ND | US/CT | 9.8 | ND | 14 solitary, 9 bilateral |
| 11 | Gridley et al. | 7.6 | 5.4 | CT/XR | 30.9 | 403.9 | 13 renal, 2 ureter, 6 kidney and ureter |
| 12 | Tsaturyan et al. | ND | 5.2 | CT/XR | 9 | 430 | 131 renal, 141 ureter |
| 13 | Yunhua et al. | 9.87 | 5.85 | US/CT | 13 | ND | ND |
| 14 | Moore et al. | ND | 5.3 | CT | 16 | 416.5 | 14 solitary, 3 multiple unilateral, 4 bilateral |

Treatment Regimes

A wide variety of dissolution therapies were assessed; 6 studies used potassium citrate, 4 studies used sodium bicarbonate, 1 study used sodium potassium citrate, 1 study used intravenous (IV) molar lactate in combination with oral sodium bicarbonate or sodium potassium citrate, 1 study used magnesium bicarbonate, 1 study used potassium magnesium citrate, and potassium sodium hydrogen citrate was used in 3 studies. An oral route of administration was used in all the studies apart from one which administered intravenous molar lactate solution for 1 week prior to commencing oral dissolution therapy (ODT) [12]. The dosage of dissolution therapy varied between studies. Most of the regimes required patients to take multiple doses throughout the day [6, 7, 9••, 10••, 15, 17]. Additionally, 4 studies required patients to monitor their urinary pH levels and titrate the dosage of frequency to maintain a target urinary pH [7, 13, 16, 17]. The mean treatment duration was 178 days, ranging between 1 week and 4 years. Six out of fourteen studies reported the use of allopurinol as a complementary therapeutic agent [3, 7, 8•, 9••, 10••, 16]. However, Yunhua et al. identified a 48.4% reduction in stones using febuxostat

80 mg/d in combination with dissolution therapy, compared to a 26.2% reduction from allopurinol 300 mg/d [8•]. CT was the most frequently used modality for follow-up imaging (10/14 studies). The remaining studies used ultrasound apart from Petrtsch who used IVU for initial and follow-up imaging [3]. The follow-up period ranged from 1 week to 5 years (Table 3).

Clinical Efficacy of Dissolution Therapy

Complete or partial dissolution of UA urolithiasis was observed in 80.5% of patients (865/1075 patients). Moore et al. reported that 41% patients achieved complete or partial dissolution, measured as one outcome [11•]. Therefore, these patients could not be included in the separate analysis. Upon review of the remaining 13 studies, 61.7% (647/1048 patients) achieved complete dissolution, and 19.8% (207/1048 patients) achieved partial dissolution of UA urolithiasis. Twelve studies reported on the number of patients requiring further surgical intervention [3, 6, 7, 8•, 9••, 10••, 11•, 12, 13, 14•, 16, 17]. This identified a cumulative failure rate of 15.7% (169/1075 patients). Two of the

Table 3 The follow-up and treatment regime of dissolution therapy used in the included studies

| Paper | Author | Route of administration | Dissolution drug | Dosage | Target pH | Treatment duration | Allopurinol | End imaging | Follow-up |
|-------|----------------------|-------------------------|--|---|-----------|---------------------------------|------------------|-------------|---------------------|
| 1 | Elbaset et al. | Oral | Potassium sodium hydrogen citrate | 20 mEq 3 times a day | 6.9 | 3 months | No | CT | 3 months |
| 2 | Kursh and Resnick | IV/oral | Molar lactate +/- sodium bicarbonate or sodium potassium citrate | 0.16 M molar lactate in 500 ml infusion rate 40–50 ml/h | 7–7.5 | 1 week IV then oral as required | No | CT | 1 week, undisclosed |
| 3 | Moran et al. | Oral | Potassium citrate | 1 mEq/kg once a day and increased to maintain target pH | ND | 6 weeks | No | US/CT | 6 months |
| 4 | Elderwy et al. | Oral | Potassium sodium hydrogen citrate | 1 mEq/kg/day | 6.2–6.8 | 1–3 months | No | US | 3 months |
| 5 | Elsawy et al. | Oral | Potassium citrate | 20 mEq 3 times a day | 6.2–6.8 | 3–6 months | Yes | CT | 6 months |
| 6 | Salem et al. | Oral | Potassium sodium hydrogen citrate | 3 times a day | 6.2–6.8 | 3 months | No | CT | 3 months |
| 7 | Petrtsch | Oral | Sodium potassium citrate | ND | 6.2–7 | 6–8 weeks | Yes | IVU | 5 years |
| 8 | Sharma and Indudhara | Oral | Sodium bicarbonate | 5–15 g/day | 6.5–7 | 6 months to 4 years | Yes | US | 4 years |
| 9 | Sinha et al. | Oral | Potassium magnesium citrate | 7 mEq K/3.5 mEq Mg /10.5 mEq citrate | 6–7 | 1–6 months | No | US | 1–6 months |
| 10 | Alsinnawi et al. | Oral | Sodium bicarbonate | 2 g 3–5 times/day | 7 | 9 weeks | No | US/CT | ND |
| 11 | Gridley et al. | Oral | Potassium citrate | 20–30 mEq 3 times a day | 6.3 | 20 months | Yes | CT | 1–3 months |
| 12 | Tsaturyan et al. | Oral | Potassium citrate/sodium bicarbonate/magnesium bicarbonate | 20 mEq 3 times a day | 6.5–7.2 | 3 months | Yes | CT | 6–12 weeks |
| 13 | Yunhua et al. | Oral | Potassium citrate | ND | 6.92 | 6 months | Yes ^a | US/CT | 6 months |
| 14 | Moore et al. | Oral | Potassium citrate +/- sodium bicarbonate | ND | 6.8 | 154 days | No | CT | 180 days |

^a31 patients had ODT in combination with allopurinol and 59 patients with febuxostat (Yunhua et al. [8•])

14 studies reported the recurrence of UA calculi, showing a stone recurrence rate of 0.7% (7/1075 patients) [7, 13].

Patient Compliance

21.4% (3/14 studies) required patients to measure urinary pH levels and titrate the treatment regime accordingly. Fifty per cent (7/14 studies) advised patients to take more than one dosage of dissolution therapy per day. A discontinuation rate of 10.2% (110/1075 patients) was noted. This was attributed to patients lost to follow-up, congestive heart failure (CHF), non-compliance, intolerance of taste, gastrointestinal disturbance, hypertension, hyperkalaemia, failure to respond, unrelated psychiatric condition, unrelated death,

patient discretion/intolerance, urinary tract infection (UTI), prohibitive cost, and raised serum creatinine (Table 4).

Patient Safety

The most reported side effect was gastrointestinal disturbance, which was noted in 50% (7/14) of the studies [3, 6, 7, 8•, 9••, 13, 15]. Deranged blood tests were observed in two of the studies. Salem et al. identified hyperkalaemia, whilst Yunhua et al. reported hyperlipidaemia, an abnormal blood count, and deranged liver and kidney function [8•, 15]. Other documented side effects included CHF, hypertension, pyelonephritis, dizziness, renal injury requiring haemodialysis, UTI, and throat irritation (Table 4).

Table 4 The measured outcomes of the included studies

| Paper | Author | Main findings | Side effects/complications | Discontinuation | Reasons for discontinuation | Surgical intervention | Stone recurrence |
|-------|----------------------|---|---|-----------------|--|-----------------------|------------------|
| 1 | Elbaset et al. | 50% complete dissolution 42% partial dissolution | Gastrointestinal disturbance | 5 | Lost to follow-up | 23 | ND |
| 2 | Kursh and Resnick | 85.7% complete dissolution | Congestive heart failure | 1 | Congestive heart failure | 2 | ND |
| 3 | Moran et al. | 73% complete dissolution 36% partial dissolution | Gastrointestinal disturbance | ND | ND | 3 | 3 |
| 4 | Elderwy et al. | 72.9% complete dissolution | Pyelonephritis | 18 | Non-compliance, taste | 13 | ND |
| 5 | Elsawy et al. | 83% complete dissolution | Gastrointestinal disturbance, dizziness | 30 | Non-compliance | 31 | ND |
| 6 | Salem et al. | 64.8% complete dissolution | Gastrointestinal disturbance, hyperkalaemia, hypertension | 18 | Taste, gastrointestinal disturbance, hypertension, hyperkalaemia | ND | ND |
| 7 | Petritsch | 80% complete dissolution | Gastrointestinal disturbance, renal injury requiring haemodialysis | 13 | Failure to dissolve the stone ^a , gastrointestinal disturbance, lost to follow-up | 15 | ND |
| 8 | Sharma and Indudhara | 78% complete dissolution | None | 0 | NA | 3 | ND |
| 9 | Sinha et al. | 15% complete dissolution 19% partial dissolution | ND | 19 | Non-compliance | ND | ND |
| 10 | Alsinnawi et al. | 39% complete dissolution 15% partial dissolution | ND | 4 | Non-compliance, unrelated psychiatric condition, unrelated death | 0 | ND |
| 11 | Gridley et al. | 58% complete dissolution 29% partial dissolution | Gastrointestinal disturbance, UTI, throat irritation | 3 | Patient discretion, opted for ureteroscopy, UTI, prohibitive cost, gastrointestinal disturbance, and raised creatinine | 3 | 4 |
| 12 | Tsaturyan et al. | 61% complete resolution 14% partial resolution | ND | 11 | ND | 60 | ND |
| 13 | Yunhua et al. | 50% partial dissolution | Gastrointestinal disturbance, liver dysfunction, renal dysfunction, abnormal blood count, hyperlipidaemia, hypersensitivity | 6 | Deranged blood tests, gastrointestinal disturbance | 0 | ND |
| 14 | Moore et al. | 41% complete or partial dissolution | ND | ND | Non-compliance, intolerance | 16 | ND |

^athe authors attributed failed dissolution to phosphate deposition from over alkalinisation of urine (Petritsch [3])

Discussion

The role of medical dissolution therapy is to conservatively treat UA urolithiasis. This aims to reduce the need for surgical intervention, offering a valuable treatment option for high-risk patients and a solution to stone recurrence [19]. This summary of the existing literature suggests that medical dissolution therapy is a successful therapeutic option for the management of UA calculi. Using a consistent definition of complete and partial dissolution, we were able to compare findings from studies using different methodologies to show that dissolution therapy successfully reduced the burden of UA urolithiasis. Furthermore, the complete dissolution of UA calculi was achieved in a large proportion of the patients reviewed (61.7% of patients), eliminating the need for supportive surgery.

The methods used to diagnose the presence of UA calculi varied greatly between studies. However, most of the studies used urinary pH levels and CT imaging to facilitate diagnosis and treatment. This aligned with the European Association of Urology (EAU) guidelines that recommend the analysis of urinary pH and urinary UA levels in combination with non-contrast CT imaging [5]. Existing evidence suggests that attenuation coefficient measurements, as measured in HU, could facilitate the radiological differentiation of stone composites. Spettel et al. identified a positive predictive value of 90% in the diagnosis of uric acid stones > 4 mm, with ≤ 500 Hounsfield units, and a urinary pH ≤ 5.5 [20]. Whilst it was only included in 50% of the included studies, HU could be a valuable tool in the accurate radiological diagnosis of UA calculi. Greater standardisation of diagnostic investigations could improve the accuracy of measured outcomes, thus increasing the reliability of future research.

Current guidelines recommend the use of oral chemolysis for uric acid stones greater than 5 mm, through the alkalisation of urine to a target pH of 7.0–7.2. Patients are advised to titrate their treatment regime accordingly [5]. This review identified a lower treatment urinary pH ranging from 6.0 to 7.5. Tsaturyan et al. supported the EAU recommendation of a maximum pH of 7.2 but advised a wider pH range of 6.5–7.2 [10••]. In contrast, 10 of the studies titrated dissolution therapy to achieve a urinary pH less than the EAU recommendation [3, 6, 7, 8•, 9••, 11•, 14•, 15, 16, 18]. Two studies stated that the lower target urinary pH was selected to prevent the accumulation of calcium and phosphate deposits [3, 7]. Limited information about stone composites reduced the reliability of the diagnosis of UA calculi in the patient sample. Additionally, no randomised controlled trial evaluating the optimum treatment pH range was found in the literature search. Due to limited evidence, this review is unable to recommend a target urinary pH range for the dissolution of UA urolithiasis and suggests reliance upon serial imaging for treatment follow-up.

The choice of dissolution drug, dosage, and duration of administration varied greatly between studies. Therefore, no significant correlation could be drawn between treatment regime and the efficacy of urolithiasis dissolution. Several papers proposed a treatment regime requiring a high degree of patient compliance. This involved multiple doses throughout the day and continuous testing of urinary pH level. Patients could be trained to self-monitor urinary pH to titrate medication dosage. Nevertheless, the discontinuation rate of 10.2% suggested that dissolution therapy was well-tolerated by most patients. The primary reason for discontinuation was gastrointestinal disturbance. However, other noted side effects such as congestive heart failure, hypertension, and chronic kidney disease were observed and should be considered in the evaluation of patient eligibility for treatment.

The studies recommended a low purine diet alongside a daily oral fluid intake of 2 to 3 l. It was not possible to elicit the impact of this upon outcomes based on the information provided. EAU guidelines recommend the prescription of allopurinol to hyperuricosuric stone formers [5]. However, febuxostat has been recognised as an alternative for patients unable to tolerate allopurinol [1]. Yunhua et al. found that febuxostat was more effective than allopurinol at achieving the dissolution of UA calculi when used alongside ODT [8•]. The role of febuxostat as a potentially efficacious alternative to allopurinol in the pharmacological prevention of stone recurrence could be explored in future research.

Elbaset et al. achieved 72% complete dissolution of UA calculi by combining ODT (potassium sodium hydrogen citrate) with ESWL. They identified a higher rate of stone clearance with combined treatment than ESWL or ODT alone [6]. This supports the research by Mokhless et al. who showed 100% complete dissolution of UA calculi in 24 paediatric patients with combined ODT and ESWL [21]. ESWL aims to fragment UA calculi, thereby increasing the surface area exposed to ODT [6]. ODT in combination with ESWL could be an effective minimally invasive treatment for UA calculi, but the current evidence is insufficient to support this.

Limitations

The retrospective design of most of the included studies (8/14 studies) is vulnerable to observer bias and prevents the development of generalisable recommendations. The lack of stone composite analysis and inconsistent diagnostic imaging negatively impacts the reliability of diagnosis of pure UA calculi within the studies. This limits the conclusions which can be drawn regarding the effect of ODT on pure UA calculi due to potential misdiagnosis. This review is further limited by the high degree of variability in study design found in the included articles. The methodologies differed in investigation modalities, eligibility criteria, stone composite

analysis, dissolution therapy, and follow-up. Comparison between studies was hindered by inconsistent measurement of outcomes, with some reporting dissolution per patient and others per stone. Moreover, reliability is limited by interventions dependent upon patient adherence to self-testing and autonomous administration of treatment. Future studies should also look at the definition of stone-free rate and quality of life of these patients [22, 23].

Conclusion

Dissolution therapy is an effective alternative to surgery and a safe method of conservatively managing uric acid stones in the short term. Despite requiring high levels of patient compliance, it is well-tolerated with a limited side effect profile. It is not possible to derive meaningful recommendations from the existing body of research due to diversity in the methodologies. Literature supports the use of urinary pH levels in combination with Hounsfield unit measurement on CT imaging, for the accurate diagnosis of UA urolithiasis. Future research with robust methodologies and standardised approaches to the diagnosis and management should be undertaken. This will facilitate the development of guidelines to optimise the efficacious dissolution of UA urolithiasis.

Author Contribution AO and GB: data collection and writing. TT, ZH, and JP: editing. BKS: conceptualisation and editing.

Compliance with Ethical Standards

Conflict of Interest The authors wish to highlight that Professor Bhaskar Somani is an endourology section editor for *Current Urology Reports*. All other authors declare no competing interests. All authors have reviewed and approved the submitted manuscript. We confirm that this work has not been published or submitted for publication elsewhere. All reported studies/experiments with human or animal subjects performed by the authors have been previously published and complied with all applicable ethical standards (including the Helsinki declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines). All tables and figures are original.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:

- Of importance
- Of major importance

1. Manish K, Stephen LW. Uric acid nephrolithiasis [Internet]. StatPearls - NCBI Bookshelf. 2022 [cited 2022 Dec 21]. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK560726/>.
2. Mandel NS, Mandel GS. Urinary tract stone disease in the United States veteran population. II. Geographical analysis of variations in composition. *J Urol* [Internet]. 1989 [cited 2022 Dec 21];142(6):1516–21. Available from: <https://pubmed.ncbi.nlm.nih.gov/2585627/>.
3. Petritsch PH. Uric acid calculi. Results of conservative treatment. *Urology*. 1977;10(6):536–8.
4. Gonzalez RD, Whiting BM, Canales BK. The history of kidney stone dissolution therapy: 50 years of optimism and frustration with Renacidin. *J Endourol*. 2012;26(2):110–18.
5. European Association of Urology. Urolithiasis - metabolic evaluation and recurrence prevention - Uroweb [Internet]. 2022 [cited 2022 Dec 10]. Available from: <https://uroweb.org/guidelines/urolithiasis/chapter/metabolic-evaluation-and-recurrence-prevention>.
6. Elbaset MA, Hashem A, Eraky A, Badawy MA, El-Assmy A, Sheir KZ, et al. Optimal non-invasive treatment of 1–2.5 cm radiolucent renal stones: oral dissolution therapy, shock wave lithotripsy or combined treatment—a randomized controlled trial. *World J Urol* [Internet]. 2020;38(1):207–12. Available from: <https://doi.org/10.1007/s00345-019-02746-2>.
7. Gridley CM, Sourial MW, Lehman A, Knudsen BE. Medical dissolution therapy for the treatment of uric acid nephrolithiasis. *World J Urol* [Internet]. 2019 Nov 1 [cited 2022 Nov 13];37(11):2509–15. Available from: <https://pubmed.ncbi.nlm.nih.gov/30810833/>.
- 8.● Yunhua M, Hao Z, Ke L, Wentao H, Xiaokang L, Jie S. Febuxostat promoted dissolution of radiolucent nephrolithiasis in patients with hyperuricemia. *Urol J*. 2021;18(1):34–9. **This paper reviewed the role of febuxostat as an alternative to allopurinol as an adjunct therapy for the prevention of uric acid urolithiasis.**
- 9.●● Elsayy AA, Elshal AM, El-Nahas AR, Elbaset MA, Farag H, Shokeir AA. Re: Can we predict the outcome of oral dissolution therapy for radiolucent renal calculi? A prospective study. *J Urol*. 2019;202(4):825–6. **Identified that oral dissolution therapy achieved 83% complete clearance of uric acid urolithiasis, with a low discontinuation rate.**
- 10.●● Tsaturyan A, Bokova E, Bosshard P, Bonny O, Fuster DG, Roth B. Oral chemolysis is an effective, non-invasive therapy for urinary stones suspected of uric acid content. *Urolithiasis* [Internet]. 2020 Dec 1 [cited 2022 Nov 16];48(6):501–7. Available from: <https://pubmed.ncbi.nlm.nih.gov/32770255/>. **Identified 61% complete dissolution of uric acid urolithiasis with oral dissolution therapy and a low discontinuation rate.**
- 11.● Moore J, Nevo A, Salih S, Abdul-Muhsin H, Keddiss M, Stern K, et al. Outcomes and rates of dissolution therapy for uric acid stones. *J Nephrol* [Internet]. 2022;35(2):665–9. Available from: <https://doi.org/10.1007/s40620-021-01094-y>. **Reported that 41% patients achieved complete or partial dissolution.**
12. Kursh ED, Resnick MI. Dissolution of uric acid calculi with systemic alkalization. *J Urol* [Internet]. 1984 [cited 2022 Nov 15];132(2):286–7. Available from: <https://pubmed.ncbi.nlm.nih.gov/6330382/>.
13. Moran ME, Abrahams HM, Burday DE, Greene TD. Utility of oral dissolution therapy in the management of referred patients with secondarily treated uric acid stones. *Urology*. 2002;59(2):206–10.
- 14.● Elderwy AA, Kurkar A, Hussein A, Abozeid H, Hammooda HM, Ibraheim AF. Dissolution therapy versus shock wave lithotripsy for radiolucent renal stones in children: a prospective study. *J Urol* [Internet]. 2014 [cited 2022 Nov 15];191(5 Suppl):1491–5. Available from: <https://pubmed.ncbi.nlm.nih.gov/24679880/>. **Reported a 72.9% rate of complete dissolution of urolithiasis with oral dissolution therapy in a paediatric population.**
15. Salem S, Sultan M, Badawy A. Oral dissolution therapy for renal radiolucent stones, outcome, and factors affecting response: a

- prospective study. *Urol Ann* [Internet]. 2019 Oct 1 [cited 2022 Nov 15];11(4):369–73. Available from: <https://pubmed.ncbi.nlm.nih.gov/31649455/>.
16. Sharma SK, Indudhara R. Chemodissolution of urinary uric acid stones by alkali therapy. *Urol Int* [Internet]. 1992 [cited 2022 Nov 16];48(1):81–6. Available from: <https://www.karger.com/Article/FullText/282302>.
 17. Alsinnawi M, Maan Z, Rix GH. Oral dissolution therapy for radiolucent kidney stones. An old treatment revisited. *J Clin Urol*. 2016;9(4):268–73.
 18. Sinha M, Prabhu K, Venkatesh P, Krishnamoorthy V. Results of urinary dissolution therapy for radiolucent calculi. *Int Braz J Urol* [Internet]. 2013 Jan [cited 2022 Nov 16];39(1):103–7. Available from: <https://pubmed.ncbi.nlm.nih.gov/23489502/>.
 19. Tzelvels L, Mourmouris P, Skolarikos A. Outcomes of dissolution therapy and monitoring for stone disease: should we do better? *Curr Opin Urol* [Internet]. 2021 Mar 1 [cited 2022 Dec 10];31(2):102–8. Available from: <https://pubmed.ncbi.nlm.nih.gov/33332876/>.
 20. Spettel S, Shah P, Sekhar K, Herr A, White MD. Using Hounsfield unit measurement and urine parameters to predict uric acid stones. *Urology*. 2013;82(1):22–6.
 21. Mokhless IA, Sakr MA, Abdeldaeim HM, Hashad MM. Radiolucent renal stones in children: combined use of shock wave lithotripsy and dissolution therapy. *Urology* [Internet]. 2009 Apr 1 [cited 2022 Nov 13];73(4):772–5. Available from: <http://www.goldjournal.net/article/S0090429508019353/fulltext>.
 22. Somani BK, Desai M, Traxer O, et al. Stone-free rate (SFR): a new proposal for defining levels of SFR. *Urolithiasis*. 2014;42(2):95.
 23. New F, Somani BK. A complete world literature review of quality of life in patients with kidney stone disease (KSD). *Curr Urol Rep*. 2016;17(12):1–6.

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