nature reviews nephrology

https://doi.org/10.1038/s41581-025-00990-x

Review article

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Kidney stone disease: risk factors, pathophysiology and management

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Abstract

Nephrolithiasis is the most common health condition affecting the kidney and urinary tract and constitutes a major global health-care problem. The prevalence of nephrolithiasis has increased substantially over the past five decades, irrespective of age, sex or ethnicity. Kidney stones cause substantial morbidity, reduced quality of life and enormous health-care expenditure, largely due to their frequent recurrence. Furthermore, nephrolithiasis is now recognized as a systemic condition associated with increased risks of chronic kidney disease, cardiovascular disease, metabolic syndrome and low bone mass. Nephrolithiasis exhibits marked pathophysiological heterogeneity. Dietary and environmental exposures interact with genetic predisposition to shape individual disease risk. Calcium oxalate stones are most prevalent, commonly driven by hypercalciuria, hyperoxaluria, hypocitraturia and low urine volume, whereas the formation of uric acid and calcium phosphate stones is commonly linked to urinary pH. A comprehensive clinical evaluation can uncover underlying metabolic abnormalities, distinguish idiopathic, secondary and Mendelian forms of nephrolithiasis, identify systemic disease associations and guide therapy. Recurrence prevention requires individualized strategies that combine dietary and pharmacological interventions. For established stones, surgical management is effective, with ureteroscopy and percutaneous nephrolithotomy achieving high stone-free rates. Despite its considerable clinical and societal burden, nephrolithiasis remains under-recognized, underserved and under-researched. Greater awareness and investments in research, innovation and education are urgently needed.

Sections

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Key points

- Adults and children with recurrent kidney stone disease (KSD) can benefit from a metabolic evaluation, which can be used to identify metabolic abnormalities, exclude secondary and monogenic KSD, and recognize systemic disease manifestations.
- Dietary interventions and pharmacotherapy for prevention of kidney stone recurrence should be tailored to the underlying pathophysiology, disease activity, comorbidities and specific needs of the patient.
- Disease activity should be monitored regularly and treatment adjusted accordingly. Careful patient education and follow-up are key to long-term treatment success.
- Patients must be empowered and supported to understand their disease, implement self-selected lifestyle changes and make informed choices on pharmaceutical and surgical interventions.
- Crucial KSD knowledge gaps persist and require further investigation. Future research priorities include the development of novel treatment options and the generation of randomized clinical trial evidence that can inform the management of KSD.

Introduction

Nephrolithiasis (also known as kidney stone disease (KSD)) is the most common condition to affect the kidney and urinary tract. The prevalence of kidney stones in the USA was reported at 11%, with a 12-month incidence of 2.1%[1]. Similarly, a large Chinese cross-sectional study[2] involving nearly 100,000 individuals reported an overall prevalence of 11.4%. KSD remains more prevalent in men than in women; however, a notable rise in incidence among women has led to a narrowing sex gap[3]. In women, the risk increases steadily with age, whereas in men, it peaks in mid-life and subsequently declines[2]. White men are disproportionately affected, whereas the prevalence is lowest among Asian women, reflecting significant variations across gender and ethnicity[4,5]. Extraordinarily high prevalence rates have been reported in uranium workers in eastern Tennessee (18.5%) and adults in northeast Thailand (16.9%), indicating that a substantial portion of the population can form kidney stones if exposed to high-risk conditions[4]. Paediatric nephrolithiasis exhibits a distinct sex-related pattern, with a higher incidence of kidney stones observed in adolescent girls than in boys. However, in prepubertal children, no significant sex-based differences in incidence have been reported[6].

The prevalence of KSD has risen worldwide in recent decades, regardless of age, sex or ethnicity[4,7]. A notable increase has been reported among populations traditionally deemed at lower risk, such as children, women and Black individuals[8]. Possible contributing factors include the increasing prevalence of obesity and diabetes, changes in dietary habits and employment conditions, global warming and urbanization, as well as variable health-care accessibility[8,9].

Not only is KSD associated with substantial morbidity and decline in overall quality of life[10]; it also has enormous economic and societal consequences. Substantial direct and indirect costs include those associated with medical treatment, disability, pain management and lost productivity (particularly among individuals of working age)[11–13].

KSD should also be regarded as a systemic condition rather than an isolated disorder. It is increasingly recognized for its associations with cardiovascular disease, hypertension, obesity, metabolic syndrome, chronic kidney disease (CKD) and low bone mineral density (BMD) with increased fracture risk[14–18].

In this Review, we describe the epidemiology and pathogenesis of the most common stone types, provide an update on the genetics of nephrolithiasis and discuss the evaluation as well as the medical and surgical treatment of individuals with kidney stones.

Pathophysiology of stone formation

Physicochemistry of stone formation and supersaturation

Stone formation is a complex process that starts when molecules in solution reduce their energy interactions with water molecules to the extent that they exit the solution as so-called solid-phase nuclei[19]. This process, known as nucleation, occurs when the concentration of a solute exceeds its solubility. An aqueous solution containing dissolved calcium oxalate (CaOx) and CaOx crystals, or additional lithogenic salts, is in equilibrium when crystals neither expand nor diminish in size. In this context, the product of the free ionized calcium and oxalate concentrations in solution (that is, the activity product (AP)) is equal to the equilibrium solubility product (SP). The AP divided by the corresponding SP yields the activity product ratio (APR). An APR of >1 indicates urinary supersaturation, whereas an APR of <1 indicates urinary undersaturation (Fig. 1). Spontaneous nucleation without a pre-existing solid phase occurs only if the AP exceeds the formation product (FP), which is an empirical limit also known as the upper limit of metastability. Therefore, urine can be undersaturated, metastable or unstable with respect to lithogenic salts (Fig. 1).

Although AP, FP and APR can be determined empirically, the methods are delicate and labour intensive and mainly used in research. In clinical routine, APs are typically estimated based on standard 24 h urine collection measurements. EQUIL2 is a software frequently used for these estimations and it calculates the relative supersaturation ratio (RSR), an equivalent to the empirically determined APR[20]. RSRs calculated from routine 24 h urine collections are robust measurements of long-term crystallization forces and correlate well with main stone components[21]. Furthermore, the risk of stone formation correlated closely with calculated RSR in randomized controlled trials (RCTs) and prospective studies[22–26].

Concentrations of AP components are key determinants of urinary saturation. Thus, absolute excretion rates measured in 24 h urine samples must always be considered in the context of 24 h urinary volume. Additional factors such as complex formation and urine pH substantially influence the free ionic concentrations of AP components. For example, citrate forms soluble complexes with calcium, thereby reducing ionized calcium levels[27]; a similar relationship exists for magnesium and oxalate[28]. As for urinary pH, it determines the monovalent-to-divalent phosphate and urate-to-uric acid ratios, and therefore affects the formation of calcium phosphate (CaP) and uric acid stones. Assessment of the risk of kidney stone formation based solely on the concentration of individual chemicals can therefore be challenging, but software-based supersaturation estimations help to integrate the complex physicochemical interactions of urinary solutes.

In metastable supersaturated urines (that is, when AP < FP), heterogeneous nucleation — initiated on a pre-existing substrate — is common (Fig. 1). Specifically, crystals already present in urine provide a substrate for the formation of new crystal nuclei at a lower APR than that required for homogeneous nucleation, which occurs only in unstable supersaturated urines (that is, AP > FP). Monosodium urate and uric acid provide an excellent substrate for heterogeneous

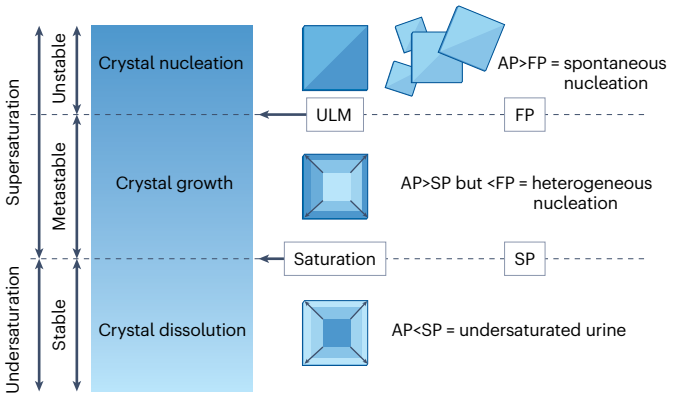

Fig. 1 | Physicochemistry of kidney stone formation. The figure illustrates the three states of urine saturation and crystal development. Kidney stone formation begins when dissolved minerals such as calcium oxalate form solid crystals through nucleation. This process occurs when the mineral concentration in urine (that is, the activity product (AP)) exceeds its equilibrium solubility (that is, the solubility product (SP)). The AP ratio (APR), calculated as AP/SP, reflects urinary saturation. Specifically, if the APR is <1, urine is undersaturated and crystals dissolve. When the APR is >1 but the AP is lower than the formation product (FP), which is an empirical limit also known as the upper limit of metastability (ULM), urine is metastable and crystals form only if existing crystals or nuclei are present (that is, heterogeneous nucleation). However, when AP > FP urine is unstable and spontaneous (that is, homogeneous) nucleation occurs even in the absence of pre-existing crystals.

CaOx nucleation; such heterogeneous nucleation might explain the link between hyperuricosuria and the formation of CaOx stones[29–33]. Brushite (a form of CaP) formidably nucleates CaOx[34], which is probably how subepithelial Randall plaque (rich in CaP) acts as an initiator of CaOx stone formation in the kidney papilla. The underlying mechanism is not yet completely understood but the proteinaceous coating of the mineral phase seems to have an active modulatory role[35–37]. Ultrastructural and in vitro studies highlight that this mineral–organic interface is complex, with nucleation events observed on both mineral and organic surfaces. Moreover, localized dissolution of CaP might elevate supersaturation in situ, further enhancing CaOx crystallization[38,39].

Importantly, nucleation alone will not cause disease. Crystals need to grow and aggregate to become large enough to be pathogenic. The growth rate parallels the degree of supersaturation and is most rapid in urine samples with the highest APR[40].

Histopathology of stone formation

Supersaturation is the essential condition for the formation of all kidney stones, but the pathogenetic events that lead to stone formation vary considerably between stone types. Three distinct pathways of stone formation have been proposed that can be categorized as 'fixed' or 'free' particle theories[41,42] (Fig. 2). Of note, retention of crystals within the kidney is required for stone formation, regardless of whether nucleation occurs freely in tubular fluid or in association with cellular injury. In the 'free' particle formation pathway, crystals form by homogeneous nucleation in the lumen of the nephron or in the renal collection system at the level of the minor calyx. As crystals grow, they eventually lodge in the lumen of distal nephron segments and cause obstruction. Free particle formation has been proposed to contribute to stone formation in medullary sponge kidney, cystinuria and enteric hyperoxaluria.

Two principal pathways have been proposed within the fixed-particle hypothesis: the 'plug' and 'plaque' pathways, both of which were first described by Alexander Randall in the 1930s[43]. The plug pathway requires crystal nuclei to form in the nephron lumen at sites of cell injury (Fig. 2). Growth of stones eventually leads to plugs that obstruct and massively dilate inner medullary collecting ducts (IMCDs) and ducts of Bellini and project into the kidney collection system. Stone formation on tubular plugs has been observed in all types of stone except in idiopathic CaOx stones[44]. Plugging seems to be the predominant mechanism of stone formation in individuals with CaP stones (brushite, carbonate apatite), cystinuria, primary hyperparathyroidism or CaOx stones due to obesity bypass procedures. Plugging is also associated with destruction of lining cells and focal sites of interstitial fibrosis[45–49]. Papillae affected by plugging appear distorted, scarred and flattened. Elevation of urinary pH seems to promote the formation of both plugs and stones[19]. A rise in pH increases CaP supersaturation and thereby promotes the formation of CaP (brushite and apatite) crystals. Given that IMCDs are not only affected by plugging but are also an important site of urinary acidification, a vicious cycle might ensue, whereby impaired urinary acidification follows IMCD injury, which raises CaP supersaturation and further promotes CaP stone formation. In individuals with recurrent kidney stones, CaP content in kidney stones has been rising in recent decades[50]. Tubular injury from extracorporeal shock wave lithotripsy (ESWL) and an increase in urine pH owing to widespread use of potassium citrate for stone prevention have been postulated as possible mechanisms[50–52].

In the plaque pathway, stones grow attached to interstitial apatite depots, termed Randall plaques (Fig. 2). Plaque formation starts in the basement membrane of thin loops of Henle and eventually extends into the adjacent interstitial space beneath the urothelium, ultimately disrupting the integrity of the urothelium[47,53]. After breaching the urothelium, urinary protein, for example, uromodulin (also known as Tamm–Horsfall protein) and osteopontin, and amorphous apatite overlay the plaque. As plaque overgrowth increases, conversion of apatite into CaOx occurs, ultimately leading to a cauliflower-like outgrowth of CaOx that is macroscopically visible as a kidney stone. This sequence of events seems to be the primary mechanism of kidney stone formation in individuals with idiopathic CaOx KSD, but similar lesions are observed in individuals with primary hyperparathyroidism, ileostomy and small bowel resection. The amount of papillary surface covered by plaque correlated strongly with clinical stone activity[54].

A renal microcirculatory hypothesis, known as the 'vas washdown' theory, has been proposed to explain the formation of Randall plaque. In idiopathic hypercalciuric stone formers, increased calcium delivery from the proximal tubule enhances its re-absorption in the thick ascending limb of the loop of Henle. The re-absorbed calcium enters the descending vasa recta and is transported into the deep inner medulla, potentially raising local CaP supersaturation. This environment favours apatite crystallization in the basement membranes of the thin limbs of Henle. A key prediction of the vas washdown model is that plaque should form preferentially on ascending thin limbs, which are water impermeable, in contrast to descending limbs, which allow water flux and therefore reduce local supersaturation. Recent ultrastructural studies confirm this prediction, showing that Randall plaque forms predominantly along ascending thin limbs. These findings suggest that interventions that enhance proximal calcium re-absorption, such as a

low sodium diet or the use of thiazide diuretics, might reduce plaque formation and subsequent stone risk[55].

Stone types and urinary risk factors

In both children and adults, most kidney stones contain calcium[56] (Table 1). Among these, 70–80% are CaOx stones, whereas CaP stones account for ~15%. Uric acid stones constitute 5–10% of kidney stones, and their prevalence increases with age. Overall, struvite stones account for 7–8% of cases. Cystine stones are rare in adults (1–2%) but are substantially more common in children (6–8%)[57,58]. CaOx and uric acid stones are more common in men, whereas CaP and struvite stones are more common in women[56].

Calcium stones

CaOx and CaP stones share several common risk factors, including hypercalciuria, hypocitraturia and low urine volume. A key differentiating factor is urinary pH, as CaP stones preferentially form in alkaline urine (pH >6.5). By contrast, CaOx stone formation is not pH dependent. Hypercalciuria is the primary risk factor for the formation of calcium kidney stones and is present in ~60% of adults and ~45% of children with calcium nephrolithiasis[59]. Historically, hypercalciuria has been classified into three primary subtypes: absorptive, renal leak and resorptive hypercalciuria. However, this classification is now considered outdated and is seldom used in clinical practice, as these traits often coexist[59] (Fig. 3). Absorptive hypercalciuria is caused by increased intestinal calcium absorption, which can be either $1,25(OH)_2$ vitamin D dependent or independent. In the $1,25(OH)_2$ vitamin D-dependent form, elevated levels of $1,25(OH)_2$ vitamin D result from both increased production and reduced clearance. Potential contributors include renal phosphate wasting owing to pathogenic variants of *SLC34A3* (encodes sodium-dependent phosphate transport protein 2C (NPT2C); see below) or inactivating variants of *CYP24A1* (encodes the enzyme responsible for vitamin D inactivation). Both types of variant result in elevated circulating $1,25(OH)_2$ vitamin D levels[60,61]. The pathway responsible for reduced renal tubular calcium re-absorption (renal leak hypercalciuria) remains incompletely understood but might involve activating polymorphisms in the calcium-sensing receptor (CaSR)[62]. The resulting hypercalciuria leads to secondary increases in parathyroid hormone (PTH) and $1,25(OH)_2$ vitamin D, which may further enhance intestinal calcium absorption. Resorptive hypercalciuria is caused by augmented calcium mobilization from the bone, which can be either PTH dependent or PTH independent, with the former being primarily associated with primary hyperparathyroidism[59]. Interestingly, data suggest that reduced calcium re-absorption in the kidney is often not accompanied by elevated PTH levels[63].

Urinary citrate serves as a key protective factor against kidney stone formation through two primary mechanisms. First, it binds to calcium, forming soluble complexes that reduce the availability of free calcium for crystal formation. Second, it directly inhibits crystallization and aggregation of CaOx and CaP. Hypocitraturia can occur in the setting of systemic metabolic acidosis (for example, in distal renal tubular acidosis or chronic diarrhoea) but is also observed in normobicarbonataemic conditions, for example, in the context of a high-protein diet or a diet deficient in fruits and vegetables, or in thiazide-induced hypokalaemia[64,65].

Hyperoxaluria is present in 8–50% of individuals with calcium kidney stones[66,67]. In CaOx stone formers, urine oxalate and urine calcium are equally effective in increasing CaOx supersaturation, although the activity of calcium is one order of magnitude higher than that of oxalate[68]. CaOx monohydrate stones form predominantly in urine with a high oxalate-to-calcium ratio, whereas CaOx dihydrate stones form in urine with high calcium-to-oxalate ratio[69].

Hyperoxaluria can be caused by several mechanisms. Increased dietary intake occurs through the consumption of oxalate-rich foods such as leafy vegetables, nuts and seeds, dark chocolate and beverages such as black tea[70]. Oxalate bioavailability has a key role in determining its intestinal absorption. Foods high in soluble oxalate, such as raw spinach, have greater bioavailability, whereas those containing predominantly insoluble oxalate, such as black beans, are absorbed to a lesser extent[71,72]. Additionally, low dietary calcium intake can substantially increase intestinal oxalate absorption. Notably, vitamin C is metabolized to oxalate in the liver, contributing to elevated urinary oxalate levels[73]. Enteric hyperoxaluria is observed, for example, in people with conditions that lead to steatorrhoea such as inflammatory bowel disease, patients who have

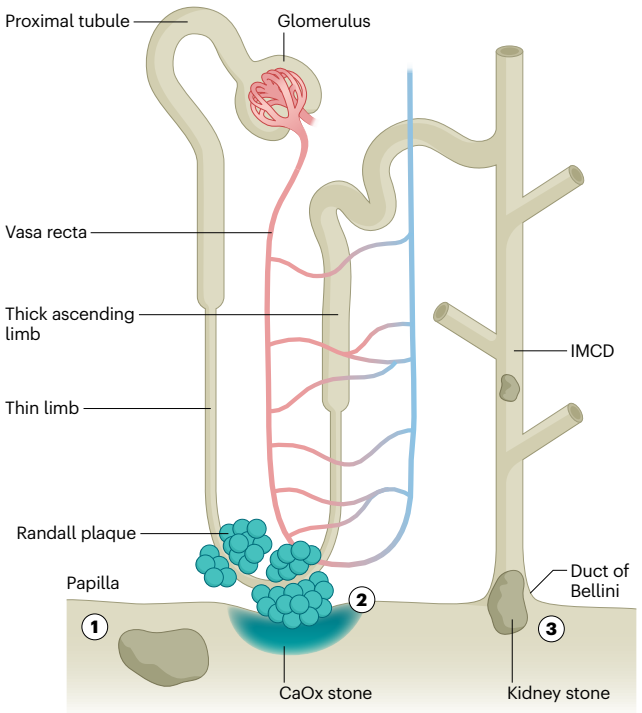

Fig. 2 | Histopathology and pathogenesis of kidney stone formation. Kidney stone formation and growth occur via three major pathways. (1) The free particle formation pathway involves direct crystallization in free urine, driven by urinary supersaturation, and can occur either in the collection system of the kidney or along the nephron. This process begins with nucleation, whereby free particles form and can aggregate into larger stones that become retained in the kidney tubules or urinary tract to form clinically significant stones. The two fixed-particle formation pathways are shown in (2) and (3). (2) Randall plaque formation starts as apatite depots in the basement membrane of thin loops of Henle that subsequently extend into the interstitial space beneath the urothelium and ultimately disrupt the integrity of this epithelium, which facilitates the appositional growth of calcium oxalate (CaOx) stones. (3) Crystal retention can also occur through interactions between crystals and kidney epithelial cells, leading to crystal attachment and plug formation in inner medullary collecting ducts (IMCDs) and Bellini ducts. Additionally, crystals can aggregate and form larger particles that block the tubules, especially at sites where the luminal diameter changes, such as the ducts of Bellini. Adapted from ref. 199, Springer Nature Limited.

undergone malabsorptive bariatric surgery (such as Roux-en-Y gastric bypass), chronic pancreatitis or coeliac disease. In these individuals, intestinal malabsorption leads to the presence of unabsorbed fatty acids, which bind to calcium, preventing it from complexing with oxalate in the gut. As a result, free oxalate remains available for enhanced intestinal absorption. Additionally, unconjugated bile acids and long-chain fatty acids are hypothesized to contribute to increased intestinal permeability, further exacerbating oxalate absorption[74,75]. Massive hyperoxaluria >1,000 µmol in 24 h (>90 mg in 24 h) is typically observed in individuals with primary hyperoxaluria (PH), a group of rare autosomal-recessive disorders that lead to hepatic oxalate overproduction[76].

Some people with CaOx stones also have concomitant hyperuricosuria but do not have the low urine pH typically observed in people with uric acid stones[77]. This condition is referred to as hyperuricosuric calcium urolithiasis (HUCU). Three different but not mutually exclusive mechanisms have been proposed for the pathogenesis of HUCU. Uric acid crystals act as nidus for CaOx crystallization (heterogeneous nucleation), uric acid crystals bind to and neutralize inhibitors of CaOx stone formation and, lastly, uric acid leads to a competitive reduction of CaOx solubility (salting out)[77].

Uric acid stones

The primary risk factors for uric acid stone formation are low urine volume, hyperuricosuria and low urine pH (<5.5), with pH having a predominant role. Uric acid nephrolithiasis is common in people with metabolic syndrome[78]. Low urine pH in these individuals is caused by increased dietary acid load, augmented endogenous acid production as well as impaired ammonium excretion in the kidney[79]. Another group of people who form uric acid stones owing to low urine pH are those with chronic diarrhoea. Hyperuricosuria can result from genetic, metabolic or dietary factors, such as a diet rich in purines and animal protein[79]. Genetic causes include enzyme disorders of purine metabolism and pathogenic variants in uric acid transporter genes (see Genetics section). Additionally, conditions characterized by high cell turnover, such as myeloproliferative disorders, or catabolic states, can lead to excessive uric acid production and, consequently, hyperuricosuria[80].

Struvite stones

Struvite ($MgNH_4PO_4 \cdot 6H_2O$) stones are found in people with urinary tract infections and often also contain carbonate apatite ($Ca_{10}(PO_4)_6 \cdot CO_3$)[81]. These stones can grow rapidly and fill the entire renal collecting system

Table 1 | Major kidney stone types

Stone type	Chemical composition and crystal morphology	Frequency (%)	Risk factors	Secondary or non-idiopathic causes
Calcium oxalate	CaOx monohydrate (also known as whewellite; $CaC_2O_4 \cdot H_2O$); dumbbell-shaped urinary crystals CaOx dihydrate (also known as weddellite; $CaC_2O_4 \cdot 2H_2O$); envelope-shaped urinary crystals	70–80	Low urine volume Hypercalciuria (dihydrate stones) Hypocitraturia Hyperoxaluria (monohydrate stones) Hyperuricosuria (HUCU) High sodium intake	Associated with hyperoxaluria: diet (high oxalate consumption), enteric hyperoxaluria (caused, for example, by IBD or bariatric surgery); excessive vitamin C intake; genetic variants of primary hyperoxaluria Associated with hypercalciuria: idiopathic hypercalciuria; excessive calcium and vitamin D supplementation; genetic variants (for example, pathogenic *CYP24A1* or *SLC34A3* variants)
Calcium phosphate	Hydroxyapatite ($Ca_5(PO_4)_3OH$) Brushite ($CaHPO_4 \cdot 2H_2O$) Prism-shaped urinary crystals	15	Low urine volume Hypercalciuria Hypocitraturia High sodium intake High urinary pH (>6.5)	Distal renal tubular acidosis Hyperparathyroidism Drugs (carbonic anhydrase inhibitors) Conditions causing hypercalciuria (see CaOx stones above)
Uric acid	$C_5H_4N_4O_3$ Polymorphic, rhomboid-shaped urinary crystals	5–10	Low urine volume Hyperuricosuria Low urinary pH (<5.5) Strong association with metabolic syndrome	High cell turnover (cancer, chemotherapy, TLS) Uricosuric drugs (for example, probenecid) Chronic diarrhoea Genetic: HGPRT deficiency, pathogenic *SLC2A9* or *SLC22A12* variants
Struvite	Magnesium ammonium phosphate (also known as struvite; $MgNH_4PO_4 \cdot 6H_2O$) Carbonate apatite ($Ca_{10}(PO_4)_6 \cdot CO_3$) Coffin-lid-shaped urinary crystals	7–8	Prerequisite: infection with urease-producing bacteria, leading to very high urine pH (>7.5) Low urine volume Urinary stasis	NA
Cystine	$(SCH_2CHNH_2COOH)_2$ Hexagon-shaped urinary crystals	1–2 (6–8 in the paediatric population)	Prerequisite: high urinary cystine (>250 mg/l or 1,000 µmol/l) Low urine volume Low urinary pH High sodium intake Excessive consumption of animal protein	NA

CaOx, calcium oxalate; HGPRT, hypoxanthine–guanine phosphoribosyltransferase; HUCU, hyperuricosuric calcium urolithiasis; IBD, inflammatory bowel disease; NA, not available; TLS, tumour lysis syndrome.

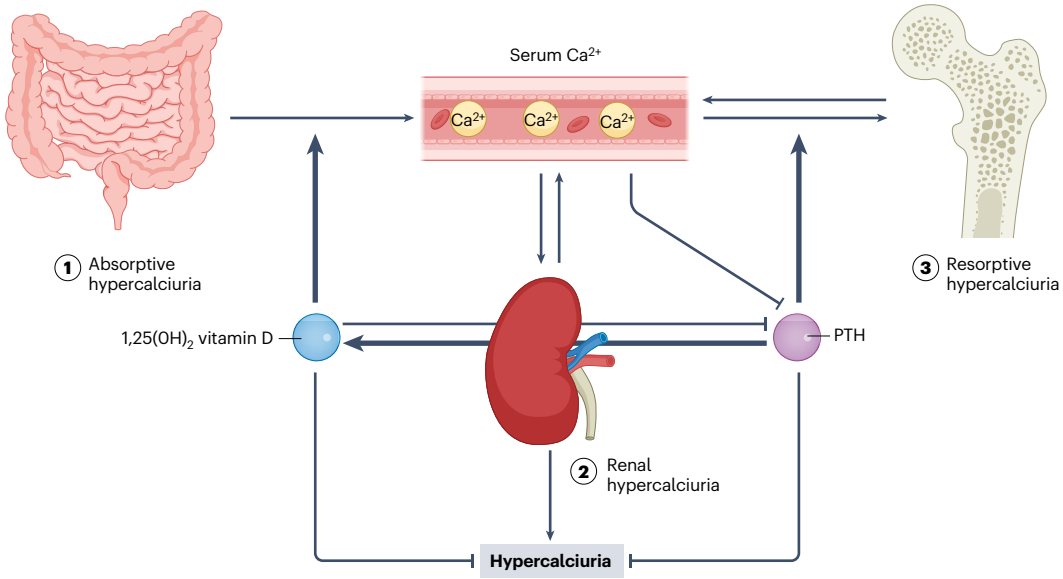

Fig. 3 | Pathophysiology of hypercalciuria. Three primary pathways can lead to excessive urinary calcium excretion. (1) Absorptive hypercalciuria (that is, increased intestinal calcium absorption) can be either $1,25(OH)_2$ vitamin D dependent or independent. Potential contributors include renal phosphate wasting that results in a decline in circulating fibroblast growth factor 23 (FGF23), which increases $1,25(OH)_2$ vitamin D through activation of 25-hydroxyvitamin D 1α-hydroxylase and inhibition of 1,25-dihydroxyvitamin D_3 24-hydroxylase, or inactivating variants in *CYP24A1* (encodes 1,25-dihydroxyvitamin D_3 24-hydroxylase, the enzyme responsible for vitamin D inactivation) that result in increased $1,25(OH)_2$ vitamin D. (2) Renal hypercalciuria (that is, impaired renal calcium re-absorption) remains incompletely understood but might involve activating polymorphisms in the gene that encodes the calcium-sensing receptor (*CaSR*). (3) Resorptive hypercalciuria (that is, enhanced bone resorption) is thought to be caused by increased calcium mobilization from the bone, which can be either parathyroid hormone (PTH) dependent (primary hyperparathyroidism) or PTH independent (elevated $1,25(OH)_2$ vitamin D or amplified sensitivity to $1,25(OH)_2$ vitamin D).

(staghorn stones). Struvite stones form exclusively in the presence of a urinary tract infection caused by a urease-splitting bacterium, especially *Proteus* species[82]. The conversion of urea into ammonia and bicarbonate creates a highly alkaline urinary environment that promotes supersaturation and precipitation of struvite and carbonate apatite[82]. The presence of large kidney stones in a patient with alkaline urine and predisposing risk factors — such as female sex, older age, indwelling urinary catheter or urinary tract abnormalities — should alert clinicians to this serious condition that might require urgent intervention[82].

Uncommon acquired kidney stones

Ammonium urate stones are rare acquired stones found in people with chronic intestinal fluid and alkali losses, low urine sodium and high urine ammonium, such as those with a history of laxative misuse[83]. The risk is further amplified in individuals with hyperuricosuria, particularly those with eating disorders experiencing catabolic states[83].

Various drugs can induce nephrolithiasis through diverse mechanisms. Certain medications have intrinsic poor solubility and, when administered in high doses, can precipitate in urine and crystallize, resulting in stone formation. Notable examples include protease inhibitors (indinavir, atazanavir), antibiotics (sulfonamides, amoxicillin, ciprofloxacin) and other compounds such as methotrexate, guaifenesin and ephedrine[84]. Additionally, some drugs have direct metabolic effects that can promote stone formation. Carbonic anhydrase inhibitors such as acetazolamide or topiramate frequently induce at least mild metabolic acidosis with hypocitraturia, hypercalciuria and alkaline urine pH, which facilitates the formation of CaP stones[85]. High-dose vitamin C supplementation can also cause massive hyperoxaluria resulting in CaOx nephrolithiasis and even oxalate nephropathy[86].

Genetics

More than 35 genes have been associated with monogenic forms of KSD[87] (Supplementary Table 1). These disorders are identified in ~3% of adults but are present in up to 30% of individuals under the age of 25 years with kidney stones[57,88]. In this section, we highlight the most common monogenic forms of KSD.

Cystinuria

In both children and adults, cystinuria is the most common Mendelian diagnosis in individuals with KSD[57]. Cystinuria is caused by loss-of-function mutations in *SLC3A1* (cystinuria type A) or *SLC7A9* (cystinuria type B), which encode the neutral and basic amino acid transport protein rBAT and $b^{0,+}$-type amino acid transporter 1 ($b^{0,+}$AT), respectively. rBAT and $b^{0,+}$AT comprise the $b^{0,+}$ amino acid transport system as a heterodimer[89]. When $b^{0,+}$ amino acid transport is impaired, tubular dibasic amino acid re-absorption is reduced, leading to increased tubular concentrations of cysteine, ornithine, lysine and arginine[89,90]. Ornithine, lysine and arginine are soluble; however, cysteine forms a dimer — cystine — that is relatively insoluble, leading to cystine stone formation. Historically, cystinuria has been classified as type A when inherited in an autosomal-recessive manner, whereas type B has an autosomal-dominant inheritance pattern with incomplete penetrance and variable expressivity. However, the latest population genetic

analyses have highlighted that the clinical prevalence of cystinuria significantly exceeds the predicted genetic prevalence based on known pathogenic *SLC3A1* or *SLC7A9* variants, suggesting that additional genetic, regulatory or environmental factors probably contribute to disease development[91].

The mainstay of treatment of patients with cystinuria is aggressive urinary dilution, urinary alkalinization (pH >7.5) to increase cystine solubility and a reduction in dietary methionine, which is the precursor of cysteine[90]. Thiol derivatives are indicated in severe cases of cystinuria when urinary alkalinization and dietary measures are ineffective. These derivatives act as chelating agents by reducing cystine into more soluble cysteine–drug complexes[92]. Some evidence suggests that thiol derivatives are more effective than hydration and alkalinization alone in reducing stone recurrence[93,94]. Tiopronin (α-mercaptopropionylglycine) is preferred over D-penicillamine owing to fewer side effects (gastrointestinal symptoms, liver enzyme elevation, pancytopenia, allergy and proteinuria)[95].

Hypercalcaemia and hypercalciuria

Disease-causing biallelic loss-of-function mutations in *CYP24A1* are found in ~0.5% of adults with KSD[57] (Supplementary Table 1). *CYP24A1* encodes 24-hydroxylase, an enzyme that inactivates 25(OH) and $1,25(OH)_2$ vitamin D via 24-hydroxylation. Impaired 24-hydroxylase function causes hypercalcaemia, hypercalciuria and vitamin D sensitivity[96]. Phenotypes linked to *CYP24A1* variants vary considerably. Some biallelic *CYP24A1* mutations manifest in childhood with hypercalcaemia, nephrocalcinosis, weight loss, failure to thrive, dehydration, polyuria and lethargy, a condition known as infantile hypercalcaemia type 1, whereas others present in adulthood with kidney stones[96,97]. Furthermore, heterozygous *CYP24A1* loss-of-function variants probably have some physiological effect as monoallelic *CYP24A1* variants are enriched in individuals with kidney stones, and altered vitamin D metabolism associated with kidney stones or nephrocalcinosis has been reported in individuals carrying variants in the *CYP24A1* 3′-untranslated region[57,98]. Effective therapeutic strategies for patients with these conditions are currently lacking. Although not studied prospectively, a diet low in calcium and vitamin D might offer some benefit. Inhibitors of vitamin D synthesis, such as fluconazole or ketoconazole, reduce hypercalcaemia and nephrolithiasis associated with *CYP24A1* variants[99,100]. However, these drugs can cause long-term side effects and interact with other medications owing to the inhibition of CYP3A4. A similar phenotype — infantile hypercalcaemia type 2 — is caused by biallelic mutations in *SLC34A1* (ref. 101). *SLC34A1* encodes sodium-dependent phosphate transport protein 2A (NPT2A) expressed in the kidney and, when its function is impaired, increased renal phosphate excretion causes elevated $1,25(OH)_2$ vitamin D_3 concentrations by suppressing fibroblast growth factor 23 (FGF23), activating 25-hydroxyvitamin D 1α-hydroxylase and inhibiting $1,25(OH)_2$ vitamin D_3 24-hydroxylase[101]. *SLC34A1* variants can also cause a digenic form of hereditary hypophosphataemic rickets with hypercalciuria (HHRH), in combination with *SLC34A3* variants[102]. HHRH is a normocalcaemic autosomal-recessive disorder characterized by increased renal phosphate clearance, hypercalciuria, rickets, short stature, elevated $1,25(OH)_2$ vitamin D concentrations and suppressed PTH secretion[103]; HHRH typically arises owing to biallelic *SLC34A3* mutations[104]. People with renal phosphate wasting caused by *SLC34A1* or *SLC34A3* mutations should avoid vitamin D supplementation and might benefit from phosphate supplementation to normalize serum phosphate concentrations[101,105]. Population-based studies indicate that heterozygous predicted loss-of-function variants in *SLC34A1* and *SLC34A3* are more common in individuals with kidney stones, increase the risk of renal calcification and might alter urinary calcium excretion and BMD[57,60,96].

Distal renal tubular acidosis

Distal renal tubular acidosis arises owing to heterozygous mutations in *SLC4A1* or biallelic mutations in *ATP6V1B1*, *ATP6V0A4*, *CA-II*, *FOXI1* or *WDR72* (Supplementary Table 1). Such loss-of-function mutations cause impaired hydrogen ion secretion by α-intercalated cells with metabolic acidosis, hypercalciuria, hypocitraturia and unduly alkaline urine, which increases the likelihood of CaP stone formation[64,106,107]. Correction of any metabolic acidosis using alkali supplementation reduces urinary calcium excretion and increases urinary citrate excretion, thereby reducing kidney stone risk and protecting bone health[64].

Hyperoxaluria

PH is a rare autosomal-recessive disorder that is present in fewer than 0.5% of adults with kidney stones caused by excess oxalate production owing to mutations in *AGXT* (PH type 1 (PH1)), *GRHPR* (PH2), *HOGA1* (PH3) or *SLC26A1* (refs. 57,108) (Supplementary Table 1). Increased urinary oxalate excretion commonly leads to nephrocalcinosis and kidney failure, inadequate oxalate excretion and systemic oxalate deposition[108]. Nephrocalcinosis and kidney failure occur frequently in people with PH1. Traditionally, the treatment of PH was supportive, focusing on hydration and citrate supplementation; the use of pyridoxine was also beneficial in PH1 caused by the most common *AGXT* mutation (p.Gly170Arg)[76]. Historically, combined liver–kidney transplantation was the definitive treatment for PH1 and, rarely, for PH2. However, two RNA interference therapies, lumasiran and nedosiran, have now become available for people with PH1, offering a considerably less complex, albeit very costly, therapeutic option. Lumasiran silences the gene that encodes glycolate oxidase, which promotes the conversion of glycolate into glyoxylate, whereas nedosiran attenuates conversion of glyoxylate into oxalate by silencing the gene that encodes lactate dehydrogenase[109,110].

Polygenic risk factors for kidney stone disease

For many years, the heritable polygenic component of common idiopathic forms of KSD has been supported by the importance of family history in kidney stone risk and twin studies demonstrating that the heritability of KSD and urinary calcium excretion is >45%[111,112]. Over the past 15 years, genome-wide association studies (GWAS) in KSD have rapidly expanded our understanding of this polygenic inheritance and more than 45 kidney stone-associated genetic loci reportedly account for ~20% of kidney stone heritability[113,114] (Supplementary Table 2).

The first two kidney stone-associated loci to be reported are in proximity to *ALPL* and *CLDN14*, and these findings have been replicated consistently[96,113–116]. *ALPL* encodes tissue non-specific alkaline phosphatase (ALP), which is expressed in the proximal tubule and hydrolyses pyrophosphate to free phosphate. Kidney stone *ALPL* risk alleles are associated with reduced levels of ALP, and loss-of-function mutations in *ALPL* cause hereditary hypophosphatasia, which results in hypomineralization, reduced BMD and dental abnormalities, occasionally in association with hypercalcaemia and/or hypercalciuria[116]. Reduced ALP levels are thought to increase kidney stone risk through altered pyrophosphate hydrolysis[116]. *CLDN14* encodes claudin 14, which is expressed in the thick ascending limb of the loop of Henle, along with claudins 16 and 19 (ref. 116) (Supplementary Table 2). A 2023 GWAS identified associations in proximity to *CLDN10*, which encodes claudin 10

(ref. 114); deletion of *Cldn10* in a murine model results in low urine magnesium, hypermagnesaemia and nephrocalcinosis[117]. Claudins are components of transmembrane tight junctions that modulate paracellular sodium, calcium and magnesium re-absorption, and alterations in urinary calcium excretion owing to changes in claudin expression probably underlie these observations.

Several kidney stone-associated loci are in proximity to genes that cause monogenic forms of KSD, including *CASR*, *SLC34A1*, *WDR72* and *CYP24A1*, suggesting that attenuated biological perturbations associated with these monogenic disorders contribute to the pathogenesis of common forms of nephrolithiasis[113,114] (Tables 2 and 3). Other associated loci indicate the importance of altered CaP homeostasis (*EPB41L2*, *DGKD*, *TRPV5*, *DGKH*), inhibition of urinary crystallization (*UMOD*, *KCNK5*, *TRPM6*) and adiposity (*GCKR*, *FTO*, *TFAP2B*) in the pathogenesis of KSD[113,114]; Mendelian randomization analyses have provided evidence that some of these pathways have a causal role in KSD[114]. Furthermore, kidney stone GWAS data have been leveraged to generate polygenic risk scores, although the clinical utility of these scores has not yet been demonstrated[118,119]. In summary, genetic panel testing is recommended for people with kidney stones who present with early-onset, recurrent or bilateral stones, nephrocalcinosis, a positive family history, consanguinity or unexplained stone formation despite standard evaluation, in line with current guidelines from the American Urological Association[120].

Metabolic evaluation

The objective of a metabolic evaluation is to identify primary prolithogenic factors, exclude secondary and Mendelian forms of KSD, identify systemic disease manifestations and initiate personalized treatments. Guidelines recommend a metabolic evaluation in all people with recurrent kidney stones and in those with a first stone episode and additional risk factors (including age <25 years, a family history of KSD, medications or comorbidities associated with an increased risk of KSD, bilateral or multiple stones, solitary kidney or kidney transplant and the presence of CKD or nephrocalcinosis)[120–123]. In people with a single stone event and no additional risk factors, general dietary advice might suffice, and further investigations can be avoided[120–123]. A metabolic evaluation consists of a comprehensive dietary and clinical assessment, review of stone composition results, as well as blood and 24 h urine analyses. Although high-quality evidence is lacking, a small study suggested that this evaluation should be done at least 3 months after a symptomatic stone event in people who have resumed their usual diet and activity[124]. Given that results from different 24 h urine samples can vary considerably, at least two 24 h urine collections on a free-choice outpatient diet are recommended[120–123]. A 24 h urine analysis should include measurements of the following: volume, pH, sodium, potassium, calcium, phosphate, magnesium, chloride, urea, creatinine, uric acid, citrate and oxalate. If available, urine sulfate and ammonium should also be quantified. Given that creatinine excretion can be approximated from body weight, its determination in 24 h urine can be used to establish urine collection adequacy[125]. Traditionally, absolute urinary excretion rates are considered for result interpretation (Table 2). These values are intended to indicate clearly abnormal solute excretion ranges but should be interpreted as graded risk factors rather than strict cut-offs, with the ultimate therapeutic goal being reduction in urinary supersaturation. Indeed, relying solely on this approach can be misleading, and software-based supersaturation estimation can help to capture the complex physicochemical interactions in the urine.

Stone composition analysis has a crucial role in defining the underlying pathology and serves as a valuable complement to metabolic evaluation[126]. Determination of stone phenotype is particularly useful for detection of rare stone types (for example, cystine, 2,8-hydroxyadenine or medication-induced stones)[127]. Although laboratory methods for stone analysis are not yet standardized, consensus guidelines advocate replacement of traditional semi-quantitative chemical analysis with more precise techniques, such as Fourier-transform infrared spectroscopy and X-ray diffraction[123].

Table 2 | Reference values for single 24 h urine abnormalities

Urinary solutes	mmol/24 h	mg/24 h
Calcium	>7.5 (men) >6.2 (women)	>300 (men) >250 (women)
Phosphate	>39	>1,200
Magnesium	<3.0	<80
Uric acid	>4.8 (men) >4.5 (women)	>800 (men) >750 (women)
Oxalate	>0.5	>45
Citrate	<1.7	<320
Cystine	>0.13 (for individuals with cystinuria homozygous mutations often >1.7)	>30 (for individuals with cystinuria homozygous mutations often >400)
Creatinine	0.11–0.26 mmol/kg (men) 0.08–0.22 mmol/kg (women)	13–29 mg/kg (men) 9–26 mg/kg (women)

These values are intended to indicate clearly abnormal solute excretion ranges but should be interpreted as graded risk factors rather than strict cut-offs.

Prevention of kidney stone recurrence

Dietary interventions

Treatment options for the prevention of kidney stone recurrence can be broadly divided into dietary interventions and pharmaceutical therapies. Although RCT evidence for the efficacy of dietary interventions is limited, many observational studies have highlighted a strong cause–effect association[128]. Current guidelines endorse dietary interventions as the basis for recurrence prevention in all people with KSD[120–123] (Table 3). Dietary interventions are unique in that they empower people to make self-selected dietary changes for stone prevention and thereby take direct responsibility for their health. Comprehensive patient education is key to long-term treatment success.

Fluid intake. Urine volume is the most important determinant of urinary supersaturation. Multiple observational cohorts, case–control studies and single-centre reports suggest that increased fluid intake is associated with reduced recurrence[129–132]. Yet, only one RCT has evaluated the effect of increased fluid intake for the prevention of kidney stone recurrence[24]. In this trial, which involved 199 individuals with idiopathic calcium stones, the recurrence rate in the group with high fluid intake was 12% compared with 27% in the group with usual fluid intake at 5 years of follow-up. The median 24 h urine volumes were 2.6 l and 1.1 l, respectively. This trial forms the basis for the current guideline recommendation to increase fluid intake to achieve a daily urine volume of at least 2.5 l (refs. 120,121). The type of beverage consumed also seems to have a role. In large cohort studies, sugar-sweetened sodas and punch were associated with a higher risk of stone formation, whereas coffee, tea, wine, beer and orange juice were associated with a lower risk[133].

Sodium intake. Urinary sodium, which reflects sodium intake, positively and strongly correlates with urinary calcium excretion, and this association is more pronounced in individuals with idiopathic hypercalciuria[134–136]. In a RCT involving individuals with calcium KSD and idiopathic hypercalciuria, sodium restriction substantially reduced urinary calcium excretion at 3 months[137]. Based on these pathophysiological considerations and its potential cardiovascular benefits, current guidelines recommend a low sodium intake (<2.3 g/day or 100 mmol/day) in all people with kidney stones[120,121].

Calcium and oxalate intake. Insufficient calcium intake is associated with increased risk of kidney stones in the general population[129]. A 5-year RCT in men with recurrent CaOx stones and hypercalciuria demonstrated a 50% higher risk of stone recurrence in participants randomly assigned to the group with a low calcium diet (0.4 g/day), compared with those randomly assigned to a diet with a normal calcium content (1.2 g/day) and low in sodium (50 mmol/day) and animal protein (50–60 g/day)[23]. The relationship between dietary calcium intake and urinary oxalate excretion is well known: calcium acts as a chelator for oxalate in the gut, consequently reducing intestinal oxalate absorption and urinary excretion[138]. By contrast, the effectiveness of dietary oxalate restriction seems weaker. Although high urinary oxalate is associated with increased risk of kidney stone formation, the amount excreted seems to be primarily influenced by calcium intake rather than by dietary oxalate consumption[139]. Another reason to avoid a low-calcium diet in people with kidney stones is the high prevalence of osteopenia and osteoporosis and elevated fracture risk in this population[17,140]. Current guidelines recommend a balanced calcium intake of 1–1.2 g per day, timed with meals, and avoidance of excessive intake of food with very high oxalate content[120–122]. In people with enteric hyperoxaluria, calcium supplements at mealtimes might be required to lower urinary oxalate[141,142].

Animal protein, fruits and vegetables. Owing to its high content of sulfuric amino acids, animal protein represents an acid load that causes a decrease in urine citrate, as well as an increase in net acid excretion and urinary calcium, thereby increasing the risk of stone formation. Total protein intake of animal and plant origin can be estimated by 24 h urea excretion, whereas 24 h sulfate excretion reflects animal protein intake. By contrast, fruits and vegetables serve as the primary source of dietary alkali, and 24 h urinary potassium excretion can be used as a marker of daily fruit and vegetable intake. A diet rich in fruits and vegetables combined with a low animal protein intake has been reported to significantly decrease the risk of kidney stone recurrence in men with calcium KSD[23]. Similarly, large observational cohort studies indicate that diets such as the Mediterranean diet, which is high in fruits and vegetables, with moderate consumption of animal protein, are associated with a decreased risk of incident stone events[143,144]. Furthermore, the type of animal protein consumed might have an important role: dairy-derived animal protein has been linked to a lower risk of kidney stones, whereas non-dairy animal protein is associated with an increased risk[145]. Current guidelines recommend a diet rich in vegetables, fruits and fibre, with balanced protein (0.8–1 g/kg/day) intake emphasizing plant-based over animal protein sources in people with KSD[120–122].

Table 3 | Dietary interventions for the prevention of kidney stone recurrence

Dietary factor	Indication	Rationale
Fluid intake	>2.5 l/day, circadian drinking, avoidance of soft drinks	Reduced urine saturation
Sodium	<2.3 g/day	Decreased urinary calcium
Calcium	1–1.2 g/day during mealtimes	Decreased urinary oxalate
Animal protein	0.8–1 g/kg/day	Higher urine pH, decreased urinary calcium, increased urinary citrate
Fruits and vegetables	3–5 portions/day	Higher urine pH, increased urinary citrate
Oxalate	Avoidance of foods high in oxalate (for example, spinach, rhubarb, beets, black tea, chocolate, peanuts, almonds, soybeans and wheat bran)	Reduced urinary oxalate

Social and environmental factors. Social and environmental factors also contribute to recurrence risk. Insufficient physical activity, a Western diet and the associated obesity can lead to stone formation[15,114]. Global warming also contributes to dehydration, leading to increased urine concentration and acidification[146]. Additionally, excessive heat can encourage higher consumption of sugar-sweetened beverages, further exacerbating KSD risk[147]. These issues are particularly relevant in high-risk geographical areas, such as urban heat islands and the stone belts in Asia and the USA, and disproportionately affect certain occupational groups, including factory workers, taxi drivers and health-care professionals[146,148,149]. Effective patient education strategies are essential to increase awareness and encourage preventive behaviour. Implementing targeted interventions and ensuring equitable health-care access also have a crucial role in reducing stone recurrence.

Pharmacological interventions

In people with idiopathic calcium KSD, pharmacological prevention of recurrence is usually commenced when dietary interventions fail to correct identified metabolic abnormalities or if patients continue to experience stone recurrence. In people with very active KSD or non-calcium-containing stones (for example, uric acid stones and cystinuria), medical treatment might be initiated earlier (Table 4).

Calcium stones

Society guidelines and expert panels recommend potassium citrate for the prevention of calcium kidney stone recurrence[120–122]. Several RCTs have investigated the use of citrate salts in people with calcium kidney stones, and most trials reported a benefit for citrate compared with placebo or control (that is, no pharmacological intervention)[120,121,150–155]. However, a recent Cochrane Review concluded that the quality of the reported literature remains moderate to poor, and that high-quality RCT evidence is needed to answer relevant questions concerning the efficacy of citrate salts[153]. Gastrointestinal side effects are common with alkali therapy, leading to poor adherence and a high rate of treatment discontinuation; tolerability can be increased if potassium citrate is timed with meals. Although alkali administration increases urine citrate, it also raises urine pH and CaP supersaturation, which might trigger CaP stone formation[64,156]. Both urine pH and citrate must therefore be considered when using alkali treatment in patients with calcium

Table 4 | Pharmacological interventions for the prevention of kidney stone recurrence

Drug category	Medication	Indication	Frequently used dose
Calcium stones			
Thiazides	Hydrochlorothiazide	Hypercalciuria	25–50 mg/day
	Indapamide	Hypercalciuria	1.25–2.5 mg/day
	Chlorthalidone	Hypercalciuria	25 mg/day
Alkali treatment	Potassium citrate	Hypocitraturia Low urine pH	20–80 mEq/day
Xanthine oxidase inhibitors	Allopurinol	Hyperuricosuria	300 mg/day
	Febuxostat	Hyperuricosuria	40–80 mg/day
Calcium supplements	Calcium carbonate	Enteric hyperoxaluria	500–1,500 mg/day, mealtimes
Uric acid stones			
Alkali supplements	Potassium citrate	Target urine pH: 6.0–7.0	20–80 mEq/day
Xanthine oxidase inhibitors	Allopurinol	Hyperuricosuria, in adjunction to alkalinization	300 mg/day
	Febuxostat	Hyperuricosuria, in adjunction to alkalinization	40–80 mg/day
Cystine stones			
Alkali supplements	Potassium citrate	Target urine pH >7.5	40–80 mEq/day
Thiol derivates	Tiopronin	Urine cystine >1,000 mg/day	750–1,500 mg/day
Struvite stones			
Antibiotics	Nitrofurantoin or trimethoprim–sulfamethoxazole	Perioperative, reduced risk of urosepsis	Careful individual dose adjustment required
Urease inhibitors	Acetohydroxamic acid	Rarely used, mainly in patients with remaining stone fragments and no surgical options in adjunction with antibiotics	500 mg/day
Acidifying agents	L-Methionine	Very high urine pH (>8.0)	1,500–3,000 mg/day

stones. If the increase in urinary pH is not paralleled by a concomitant rise in urinary citrate, alkali therapy might be harmful[64].

Thiazides reduce urinary calcium and have been the mainstay of prevention of calcium stone recurrence. Hydrochlorothiazide (HCT), the most widely prescribed thiazide, reduced kidney stone events in past RCTs, but these trials all had major methodological limitations[157]. To address these problems, the NOSTONE trial, a double-blind, randomized, placebo-controlled study, evaluated various HCT doses (12.5, 25 and 50 mg) in people with recurrent calcium stones[158]. Over 3 years, recurrence rates did not differ between groups, and no dose–response effect was observed. A lower than expected reduction in urinary calcium excretion, elevated dietary salt intake despite repeated dietary counselling and a trend towards reduced urinary citrate excretion might explain the lack of benefit. Patients treated with HCT also had a higher incidence of adverse events compared with those taking placebo, including hypokalaemia, gout and new-onset diabetes[159].

Low bone mass and fractures are common among kidney stone formers, but whether thiazides can help to preserve bone mass in individuals with calcium kidney stones remains unclear. A post hoc analysis of the NOSTONE trial revealed no benefit of HCT up to 50 mg daily on BMD compared with placebo[160]. The increased risk of skin cancer associated with prolonged use of HCT is also a growing concern[161–163]. The thiazide-like diuretics indapamide and chlorthalidone are more potent than HCT and might therefore be more effective for the prevention of recurrence[164–166]. However, to date, no direct comparison between different thiazides has been conducted for either prevention of kidney stone recurrence or surrogate markers of recurrence risk, such as urine supersaturation. This important knowledge gap is being addressed by an ongoing randomized, double-blind, crossover trial (INDAPACHLOR; NCT06111885)[167]. Until the results of this trial are available, we propose that decisions related to the use of thiazides should be made on a case-by-case basis. In people who are intolerant or not responsive to citrate supplementation as monotherapy, and/or in people with high stone burden and elevated urinary calcium excretion despite repeated dietary counselling on dietary sodium and animal protein restriction, long-acting thiazides such as chlorthalidone or indapamide can be considered.

Clinical trials in people with HUCU treated with allopurinol revealed a pronounced decline in recurrent kidney stone events[168–170]. By contrast, a large population-based study did not show a relationship between urinary uric acid and CaOx stone formation[171]. Thus, although indicated in patients with HUCU, the role of xanthine oxidase inhibition for recurrence prevention in people with calcium stones without hyperuricosuria remains unclear.

Uric acid stones

No RCTs have been conducted in individuals with uric acid stones. Although mainly based on observational studies, it is well established that urine alkalinization to a pH range of 6–7 is highly effective in preventing recurrence of uric acid stones[172]. These stones can be dissolved

using urinary alkalinization (chemolysis) obviating the need for surgical intervention[173,174]. Xanthine oxidase inhibitors, such as allopurinol or febuxostat, have only a minor role in the treatment of uric acid stones and can be used in patients intolerant of alkali therapy, or in people with severe hyperuricosuria or concurrent gout.

Struvite stones

Surgery is the preferred approach to management of infection-associated stones. However, in people with substantial comorbidities who are not candidates for surgery, medical therapy can be considered. Despite the potential side effects and the lack of RCT evidence, options include antibiotics, dissolution therapy, urease inhibitors, urinary acidification and general supportive measures[175–179].

Management of symptomatic and asymptomatic kidney stones

Management of ureteric stones

The presence of a stone in the ureter typically causes severe colicky pain that radiates from loin to groin; however, ureteric stones can present without pain either incidentally, with kidney impairment or in the context of infection. Where a ureteric stone is suspected, a non-contrast enhanced CT scan can determine stone size, location and density with high sensitivity and specificity[180].

NSAIDs (nonsteroidal anti-inflammatory drugs) probably afford better pain relief than opioids in renal colic; however, care must be taken regarding potential side effects, including gastrointestinal bleeding, cardiovascular events and kidney impairment[181,182].

The likelihood of spontaneous ureteric stone passage is affected by stone size and location. Thus, stones smaller than 5 mm in the lower third of the ureter pass in 89% of cases, whereas only 14% of those greater than 7 mm and in the upper third pass spontaneously. The online tool MIMIC Calculator for predicting spontaneous stone passage, which is based on observational data, can help to estimate the likelihood of stone passage on an individualized basis.

α-Adrenoreceptor blockers (α-blockers) might have utility in promoting stone passage, particularly in the case of larger (>5 mm) distal stones, but the evidence that α-blockers improve stone passage rates for stones in other locations and sizes is conflicting[183–187]. Nonetheless, α-blockers probably have analgesic qualities in ureteric colic, suggesting that these drugs are a useful adjunct in ureteric colic, despite the lack of clear evidence of effects on stone passage. The use of α-blockers for pain relief in ureteric colic and as a medical expulsive therapy remains an off-label indication[188].

Where analgesia cannot be satisfactorily achieved, stone passage is unlikely or kidney function is impaired, primary stone removal, decompression with percutaneous nephrostomy or ureteric stenting should be considered. Evidence of urinary tract infection or anuria in the context of a ureteric stone is a urological emergency and should prompt urgent decompression and antimicrobial therapy, where appropriate.

Conservative management of kidney stones

The natural history of kidney stones is poorly understood and reported rates of symptoms, emergency admission and intervention are highly variable[189]. Thus, for stones or residual fragments smaller than 10 mm, rates of progression to symptoms varies from 0% to 59%, emergency admission from 14% to 19%, and intervention over a 2-year period from 12% to 35%[189]. A 2024 study demonstrated that asymptomatic spontaneous passage of kidney stones detected on CT is very common in people with recurrent calcium stones[190]. Management decisions related to kidney stones must be undertaken collaboratively with patients and consider symptomatology, stone volume, location, number, composition, renal anatomy, patient preference, age, lifestyle and comorbidities. Surveillance of asymptomatic kidney stones, or those causing minimal symptoms in people with comorbidities is often a reasonable choice and there is evidence to support annual observation of asymptomatic lower pole stones smaller than 10 mm[191]. Oral chemolysis with alkali should be considered for potential uric acid stones[174,192].

Surgical management of nephrolithiasis

Kidney and ureteric stones can be fragmented with ESWL or ureteroscopy, and percutaneous nephrolithotomy (PCNL) can be used to treat kidney stones.

Extracorporeal shock wave lithotripsy. ESWL is a non-invasive, day-case procedure that aims to induce stone fragmentation with shock waves that are targeted using fluoroscopic or ultrasound guidance. ESWL might be suitable for ureteric stones or kidney stones up to 20 mm in diameter. However, as stone volume increases the risk of 'steinstrasse' (that is, the formation of a column of stone fragments that block the ureter) and the formation of residual fragments rises[193]. In most cases, ESWL can be undertaken using simple analgesia, although general anaesthesia or sedation might be required in some cases, such as in paediatric practice. The success of ESWL is dependent on the passive wash-out of fragments and is therefore not appropriate if urinary flow is lacking or impaired. Furthermore, efficacy is influenced by stone factors, including size, location and hardness, patient factors including skin-to-stone distance, infundibulopelvic angle and calyceal anatomy, the efficacy of the lithotripter, as well as factors that affect treatment delivery such as careful acoustic coupling between lithotripter head and the skin of the patient. ESWL is contraindicated in pregnancy, untreated urinary tract infection, in people with bleeding disorders or those receiving anticoagulation treatment, with skeletal malformations or obesity that prevent targeting of the stone, or with arterial aneurysm in proximity to the stone. For ureteric calculi, stone-free rates (that is, the frequency of cases in which no further treatment is required) are comparable for ESWL and ureteroscopy. For kidney stones smaller than 10 mm, stone-free rates are higher after ureteroscopy compared with ESWL.

Ureteroscopy. Ureteroscopic stone extraction is typically performed under general anaesthetic via a retrograde approach. In some cases, spinal anaesthesia or, occasionally, sedation might be appropriate, and percutaneous antegrade approaches might be required where access is difficult or a large proximal and impacted ureteric calculus is present[194]. Rigid ureteroscopy allows access to the ureter, whereas flexible ureteroscopy is useful for access to the ureter and renal collecting system. Stones that cannot be extracted intact must be disintegrated, which can be achieved with laser lithotripsy[195]. Stone-free rates of >90% are reported using ureteroscopy for kidney stones larger than 2 cm; these rates are likely to increase further as new technologies develop[195]. Of note, a 2022 trial report[196] supports the removal of small, asymptomatic stones during ureteroscopy for symptomatic stones, as this approach can reduce future symptomatic episodes and the need for repeat interventions in stone formers, particularly when no increased perioperative risk is anticipated.

Percutaneous nephrolithotomy. PCNL enables direct access to the renal collecting system with a nephroscope to facilitate the

fragmentation of large kidney stones. PCNL is typically considered for stones larger than 2 cm where stone clearance will be challenging via a ureteroscopic approach and is undertaken under general anaesthetic in either a prone or supine position, depending on patient factors and surgeon preference. RCT evidence suggests that stone clearance rates and measures of health might be superior for PCNL compared with ureteroscopy for stones measuring 10–25 mm (ref. 197). However, PCNL can result in kidney haemorrhage requiring blood transfusion (7%), embolization (0.5%) or emergency nephrectomy (<0.1%)[198].

Conclusions

KSD is a major global health-care problem in both children and adults. Considering the dismal clinical and societal impact of the disease, prevention is of utmost importance. People with recurrent KSD should undergo a thorough metabolic evaluation, followed by individualized treatment tailored to the underlying pathophysiology. Dietary interventions form the basis of recurrence prevention and can be combined with pharmacological treatments in individuals with active, recurrent disease. Individuals with KSD should be regularly monitored for disease activity and preventive measures adapted accordingly. Careful patient education is key to long-term treatment success.

Although KSD is associated with a large burden of morbidity, reduced quality of life and enormous health-care expenditure, this disorder continues to be under-researched and crucial knowledge gaps that require further investigation persist. Novel treatment options and randomized evidence are needed to guide evaluation, treatment and follow-up of people with KSD. Future research must also address the concerning rise of KSD among women and adolescents, sex- and ethnicity-specific disparities, the socioeconomic impact of KSD on vulnerable populations, the influence of environmental and occupational changes and the landscape of KSD in low-income regions. Ultimately, current stakeholders must dedicate time and resources to recruit, train and mentor emerging health-care professionals to expand the global workforce for this prevalent condition.

Published online: 11 August 2025

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Acknowledgements
S.A.H. is a Wellcome Trust Clinical Career Development Fellow.

Author contributions
All authors researched data for the article, made substantial contributions to discussion of the content and wrote, reviewed or edited the manuscript before submission.

Competing interests
D.G.F. served as a consultant for Otsuka, Alnylam, Boehringer Ingelheim and Kyowa Kirin, and received unrestricted research grants from Otsuka, Boehringer Ingelheim and CSL Vifor. S.A.H. has received payment from CJ Medical and Boston Scientific for educational activities. The other authors declare no competing interests.

Additional information
Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41581-025-00990-x.

Peer review information *Nature Reviews Nephrology* thanks John Lieske, Kristina Penniston and the other, anonymous, reviewer(s) for their contribution to the peer review of this work.

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