Kidney stones: pathophysiology and medical management

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The formation of stones in the urinary tract stems from a wide range of underlying disorders. That clinicians look for the underlying causes for nephrolithiasis is imperative to direct management. There are many advances in genetics, pathophysiology, diagnostic imaging, medical treatment, medical prevention, and surgical intervention of nephrolithiasis. Here, I provide a brief general background and focus mainly on pathophysiology and medical treatment of kidney stones. Although important advances have been made in understanding nephrolithiasis from single gene defects, the understanding of polygenetic causes of kidney stones is still largely elusive. A substantial proportion of data that resulted in new methods of treatment and prevention, which can be empirical or definitive, has focused on urinary luminal chemical composition of the precipitating solutes. Manipulation of inhibitors and epithelial factors is important and needs further investigation. Advances in the management of nephrolithiasis depend on combined efforts of clinicians and scientists to understand the pathophysiology.

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Since the last review on this subject was published in *The Lancet* in 1998,[1] progress has been made in the field of kidney stones, including the understanding of pathophysiology and treatment. An exhaustive review of the interim published work would exceed the space and objective of this report. Instead, I provide and direct readers to the references, most of which are to reviews, for more information.[2]

Urinary tract stones (urolithiasis) can be traced to the earliest antiquity of human history,[3] although their pathogenesis has evolved to a different nature nowadays. Crystalline concretions have been identified in kidneys and equivalent excretory organs of vertebrates and lower invertebrates. The adoption of a calcium-based endoskeleton or exoskeleton obligates a finite amount of calcium turnover and excretion, but terrestrial subsistence mandates water conservation and a low urinary volume. Since the laws of physicochemistry cannot be readily altered by biological evolution, the above constraints place formidable challenges to keeping calcium salts and other solutes in solution in urine. Nephrolithiasis is not a true diagnosis because kidney stone formation can suggest a broad list of underlying diseases. Therefore, nephrolithiasis per se is not much more of a diagnosis than for example, arthritis, oedema, ascites, or fever. Efforts have been and should continue to be directed to unveiling the underlying pathophysiology of kidney stone formation.

Epidemiology

Urolithiasis is a worldwide problem, sparing no geographical, cultural, or racial groups. Occurrence of primary bladder stones (cystolithiasis) has substantially reduced over the past two decades, but they are still reported in parts of the developing world predominantly in children and in patients with neurogenic bladders and benign prostatic hypertrophy.[4,5] In this Review, I focus on kidney stones (nephrolithiasis).

The yearly incidence of nephrolithiasis is estimated to be about 0·5% in North America and Europe.[1] In the USA, the prevalence (frequency in population) has risen from 3·2% to 5·2% in just over two decades from the mid-1970s to the mid-1990s.[6] The lifetime risk is about 10–15% in the developed world, but can be as high as 20–25% in the middle east.[1] Nephrolithiasis is largely a recurrent disease with a relapse rate of 50% in 5–10 years and 75% in 20 years.[7,8] Once recurrent, the subsequent relapse risk is raised and the interval between recurrences is shortened.[9] Features associated with recurrence include a young age of onset, positive family history, and infection stones and those secondary to underlying medical conditions—eg, hyperparathyroidism. The recurrent nature underscores the importance of prevention. Nephrolithiasis is more common in men than in women throughout most of adult life except in the sixth decade, where the incidence falls in men but rises in women, a trend towards sex equivalence.[10–13] Wide geographical variations exist in stone incidence and composition, and regional stone belts have been identified,[12] where raised incidence has been attributed to genetic and environmental factors, such as hot climate (fluid loss) and sun exposure (vitamin D). Despite varying prevalence, no discernible differences in underlying risk factors in different regions of the USA were reported.[14]

Kidney stones are composed of inorganic and organic crystals amalgamated with proteins. Crystallisation and subsequent lithogenesis can happen with many solutes in the urine. Calcareous stones are still by far the most common nephroliths,[15–19] accounting for more than 80% of stones. Uric acid stones represent about 5–10%, trailed by cystine, struvite, and ammonium acid urate stones. Miscellaneous types of highly uncommon stones that will not be discussed are associated with xanthine, 2, 8-dihydroxyadenine, protein matrix, and drugs—eg, indinavir and triamterene. Stone composition on the basis of stone analysis is summarised in table 1. Stones of mixed composition are not uncommonly

Search strategy and selection criteria

For this Seminar I searched work published in English between 1995 and 2005 with the search terms "kidney stone" and "nephrolithiasis".

	Percentage of stones	Characteristics
Crystal		
Calcium oxalate-monohydrate	40–60%	Radio-opaque Well circumscribed
Calcium oxalate-dehydrate	40–60%	
Calcium phosphate (apatite; $Ca_{10}[PO_4]_6[OH]_2$)	20–60%	
Calcium phosphate (brushite; $CaHPO_4{\cdot}2H_2O$)	2–4%	
Uric acid	5–10%	Radiolucent Rarely staghorn
Struvite (magnesium ammonium phosphate)	5–15%	Can be staghorn
Cystine	1·0–2·5%	Mildly opaque Can be staghorn
Ammonium urate	0·5–1·0%	
Mixed stones		
Mixed calcium oxalate-phosphate	35–40%	
Mixed uric acid-calcium oxalate	5%	

Table 1: **Composition of kidney stones**[15,17–19]

encountered. A pure uric acid versus a uric acid-containing calcium oxalate stone might show quite different underlying pathophysiology, such as the presence of hypercalciuria.

Clinical manifestations

Nephrolithiasis per se should not be regarded as a diagnosis, particularly when dealing with calcareous stones. For some non-calcareous stones, stone composition strongly infers singular pathophysiology—eg, struvite stones and cystine stones. Thus, establishing the presence of a kidney stone should not herald an endpoint for any diagnostic and therapeutic efforts. Clinicians should understand that nephrolithiasis can be a mere sentinel of an underlying disorder and they should exercise vigilance to unveil that disease. For organisational reasons, clinical manifestations associated with kidney stones can be broadly partitioned into: (i) features of the underlying disorder that predisposes to nephrolithiasis; (ii) symptoms that stem from the stone itself; and (iii) manifestations of complications from the kidney stones. The clinical features for the first category can be extremely diverse, evidenced from perusing the vast causes underlying kidney stones listed in table 2. The features to be uncovered include not only signs and symptoms of the underlying diseases, but also dietary and lifestyle habits that predispose to kidney stone disease. Often, nephrolithiasis can be the sole manifestation of the underlying abnormality that can sometimes evade our diagnostic capabilities.

Whether a non-obstructing stone can cause symptoms is a matter of debate. There is no published work to provide proof, but anecdotes from expert clinicians suggest that a stone in the renal pelvis might cause mild lumbar discomfort. Full-blown renal colic, occurring during stone passage, seldom poses a diagnostic dilemma, because it is highly characteristic in its onset, locale, and the anatomical progression of a stone from the renal pelvis down the ureter. However, for less classic symptoms, the clinician will have to rely on imaging procedures.[20] A stone can also cause dysuria once it has reached the lower urinary tract. Some episodes of renal colic are accompanied by at least microscopic haematuria. With the widespread use of diagnostic imaging, another presentation of nephrolithiasis is an incidental finding on a radiograph, sonogram, or CT scan. Nephrolithiasis can also present as a secondary complication, such as an obstruction or a urinary tract infection. Acute renal failure can be precipitated in obstruction of a solitary functional kidney. Bilateral obstruction by calculi is uncommon unless in instances of acute massive crystallisation from tumour lysis or drug precipitation. Nephrolithiasis is probably not an important cause of renal failure with the exception of bilateral staghorn calculi associated with recurrent urinary tract infection, nephrocalcinosis, or ureteral stricture.[21] In the absence of the above, there are epidemiological data to suggest that the general stone-forming population does have a mild degree of compromised renal function.[22] The reason for the chronic kidney disease is unknown.

Unenhanced CT scan is becoming the diagnostic procedure of choice.[20] Under ideal conditions, spiral CT is much better than the sonogram, contrast urography, or even conventional CT, but the higher dose of radiation delivered and the expense should be considered.[23] CT has the added advantage of the ability of the Hounsfield unit to predict the fragility of the stone.[24] In children, sonography is still preferred because of radiation issues.[25] In addition to locating the stone by imaging, a more important component of the diagnostic effort is to discern why the patient formed the stone, so recurrences can be prevented and appropriate attention can be devoted to any underlying conditions.

Pathophysiology

Data on the pathophysiology of kidney stone formation have been acquired via population-based epidemiology, human metabolic studies, and basic science experiments. Lessons learnt from population databases are important. The major limitation to such data is its correlative nature and unsuitability for precise hypothesis testing. The power, however, lies in the fact that these are data obtained from the field and the numbers are frequently large enough for patterns to emerge from noise. Single centre-based studies in people in clinical research units are much more restricted in number, but the investigative power is more definitive. Finally, the importance of complementary basic science translational studies cannot be overemphasised. Table 2 summarises some of the diverse causes and pathogenetic mechanisms that can result in nephrolithiasis. Note that this list is not exhaustive, but highlights the most commonly encountered conditions.

Urinary volume

The physicochemistry of supersaturation is of great importance in the understanding of kidney stones,[26,27] but will not be discussed here. Since the concentration rather than the amount of the crystallising solutes is what ultimately establishes stone formation, reduced urinary volume will amplify the saturation of all solutes and raise the risk of all stone formation. Additionally, oliguria promotes urinary stasis. Low urine volume can result from inadequate intake or excessive loss of liquid through the intestinal tract or sweating. Theoretically, inducement of an undersaturated state that is incompatible to crystallisation of any crystals can be achieved simply by polydipsia and polyuria, although this approach obligates considerable social inconvenience.

Calcium nephrolithiasis

Calcium oxalate stones are much more frequent than calcium phosphate stones. Nearly seven decades ago, Randall[28] described plaque-like lesions in the renal papillae, which were invariably present in patients with calcium oxalate stones, although sometimes also present in individuals who did not form stones. Now called Randall's plaques, these lesions were believed to be the nidus upon which calcium oxalate stones arose and grew. The work by Evan and co-workers[29] on individual stone formers has shed new insights into the importance of this old observation. Microscopically, these plaques seem to arise from the basement membrane of the thin limbs of the loops of Henle, expand through the interstitium sometimes encasing the renal tubules and vas recta, and eventually protrude into the uroepithelium

	Cause	Pathophysiology	Stone composition	Clinical clues
All stones				
Low urine volume (raises production of solutes)	Reduced intake or increased loss of water	Renal water conservation	All stones	Urine volume <1 L per day Osmolarity >600 mOsm/kg
Calcium stones				
Hypercalciuria (raises saturation of calcium salts)	Absorptive hypercalciuria	Increased absorption in gut	Calcium oxalate or phosphate	Urine calcium concentrations >6 mmol/L (240 mg) per day
	Hyperparathyroidism	Increased absorption in gut and bone release		High concentrations of parathyroid hormone High concentrations of vitamin D
	Immobilisation	Bone resorption		
	Excess of sodium in diet	Sodium-induced physiological renal calcium leak. Possible component of gut hyperabsorption		Urine sodium concentrations >200 mmol/L per day
	Excess of protein or acid in diet	Protein-induced bone loss and renal leak.		Urine ammonium iron concentrations high Urine sulphate concentrations high Urine pH low Urine citrate concentrations <1·7 mmol/L per day
	Range of monogenic disorders	Bone loss, gut hyperabsorption, and renal leak in various combinations		
Hypocitraturia (raises levels of ionised calcium and reduces inhibitor activity against calcium salts)	Renal tubular acidosis (distal type)	Renal defence of acid–base balance	Calcium phosphate	Urine citrate concentrations <1·7 mmol/L per day Urine pH high
	High acid load (absence of detectable acidemia)	Physiological hypocitraturia	Calcium oxalate or phosphate	Urine citrate concentrations <1·7 mmol/L per day Urine pH low
Hyperoxaluria (raises saturation of calcium oxalate)	Excess of oxalate in diet	Increased delivery of luminal oxalate	Calcium oxalate	Urine oxalate concentrations >70·7 mmol/L per day
	Bowel pathology	Reduced formation of luminal calcium and calcium-oxalate complex		
	Increased production of endogenous oxalate	Primary hyperoxaluria (type 1 and type 2)		
Hyperuricosuria (sodium urate precipitation causes crystallisation of calcium salts)	High purine intake	Raised production and urinary excretion of sodium and urate	Calcium oxalate	Urine uric acid concentrations >600 mg per day Hyperuricaemia
	Myeloproliferative diseases			
	Enzymatic defects			Urine uric acid concentrations >600 mg per day Hypouricaemia
	Uricosuric drugs			
	Genetic primary renal leak	Increased excretion of uric acid		
Uric acid stones				
Low urine pH or hyperuricosuria	High acid load Metabolic syndrome	Titrates urate to poorly soluble uric acid	Uric acid	Urine pH <5·5
Cystine stones				
Cystinuria	Congenital mutations of dibasic aminoacid transporter subunits rBAT and b0+AT	Renal leak of basic aminoacids	Cystine	Urine concentrations of cystine high (>150 µmol/mmol creatinine)
Infection stones				
Urinary tract infection	Urea-splitting organisms	Production of ammonium and bicarbonate from urea	Magnesium ammonium phosphate Carbonate apatite	Urine pH high Pyuria Positive culture for urease and organism

Table 2: **Pathophysiology of nephrolithiasis by primary abnormality**

in the renal papillae.[29] However, in patients with enteric hyperoxaluria, the lesions originate from the tubular lumen in the collecting duct. Composed of calcium phosphate, Randall's plaques seem to provide the platform for calcium oxalate crystal to form through heterogeneous nucleation and grow to a nephrolith. The area covered by the plaques correlates negatively with urinary volume and positively with hypercalciuria and the number of stones formed.[30,31] Calcification of the basement membrane and interstitium are probably early events, but the relation between the urinary chemistry, the segmental functional abnormalities that generate the hypercalciuria, and the anatomical finding of calcium phosphate deposition around the loop of Henle is not clear. Stoller and co-workers[32] presented an alternative view of Randall's plaques as results of atherosclerosis, vascular injury, and calcification of the vasa recta.

The most important pathophysiological factor for calcium nephrolithiasis is hypercalciuria. Calcium increases the ionic activity and saturation of crystallising calcium salts (oxalate and phosphate) and binds stone inhibitors, such as citrate and glycosaminoglycans. There is no unifying nomenclature at present to classify hypercalciuria. The term idiopathic hypercalciuria has been generally applied to a heterogeneous group of disorders mainly by default. A more pathophysiology-oriented classification partitions hypercalciuria by defects in one or a combination of three organs—kidney (renal leak), bone (resorptive), and gut (absorptive).[33] These three categories can co-exist as a primary disorder and can simultaneously affect more than one organ. Furthermore, a primary defect in one organ can lead to secondary changes in others—eg, renal leak can lead to increased gut absorption and bone resorption. The syndrome is probably a range of combined gut and bone lesions with the most common identifiable abnormality being intestinal hyperabsorption overlapping with low bone density and reduced bone formation.[34–36] This notion is supported by the finding that a substantial proportion of individuals with idiopathic osteoporosis also has intestinal calcium hyperabsorption.[37] That individuals who do not get kidney stones will eventually come to medical attention with idiopathic osteoporosis is plausible. The underlying molecular defect is unknown at present.

Less common than primary gut hyperabsorption are primary resorptive and renal hypercalciuria. An example of a primary resorptive defect is primary hyperparathyroidism, although the secondary enhancement of calcitriol synthesis leads to amplified intestinal absorption, contributing to the hypercalciuria.[38] Other resorptive defects include immobilisation[39] and metastatic tumours, which seldom pose a diagnostic problem. Increased resorption from acid load will be discussed. Primary renal leak has been described,[40] but is unusual and the pathogenesis is unclear.

High dietary salt is associated with a high rate of nephrolithiasis and salt restriction diminishes the risk of kidney stones.[41,42] Although high sodium intake can promote crystallisation of calcium salts by reducing concentrations of citrate, excessive sodium ingestion confers stone risk principally via hypercalciuria.[41] There is a linear positive correlation between urinary sodium and calcium excretion.[41,43] The linear relation between urinary sodium and calcium is maintained, even in disease states of hypercalciuria where the concentration of urinary calcium exceeds that expected for the effect of high sodium alone.[44,45] The renal mechanism of salt-induced hypercalciuria is discussed in more detail elsewhere.[46]

Two very important causes of hypercalciuria are systemic acidosis and protein load with some overlapping pathogenetic mechanisms. Chronic metabolic acidosis causes hypercalciuria and hypocitraturia that can lead to calcium nephrolithiasis. In chronic acidosis of renal origin, such as distal renal tubular acidosis, the high urinary pH predisposes to the formation of calcium phosphate stones.[19] Acidosis produces renal calcium leak and bone calcium release.[47,48] Correction of acidosis leads to the improvement of hypercalciuria, hypocitraturia, and stone risk.[49] Increased acid load per se without clinically discernible decrements in serum bicarbonate concentration can cause identical changes in urinary chemistry to metabolic acidosis.[50] Excess dietary protein represents one such example. The role of dietary protein is more complicated than pure metabolic acidosis. The association of high protein intake with propensity to stone formation is well established from epidemiological and metabolic studies, and work in animals.[51–54] The following issues remain undetermined and are topics of ongoing research: (i) what components in protein other than acid are causing the hypercalciuria?; and (ii) is there a primary effect on intestinal absorption in addition to the effect on bone and kidney?

The consideration of hypercalciuria is inseparable from hypocitraturia. Citrate is the most abundant organic anion in human urine and has dual roles. Urinary citrate permits base excretion without raising urine pH, which permits defence against alkali loads without precipitating calcium phosphate. Furthermore, citrate complexes calcium in a soluble form and prevents crystal growth of calcium phosphate and calcium oxalate in urine.[55] In the face of obligatory low urine volumes typical of terrestrial mammals, citrate provides the safety net for mammals to accommodate a finite calcium turnover and urinary calcium excretion. Hypocitraturia in stone formers has been well known for decades,[56] and is estimated to be present in 20–60% of calcium stone formers.[55] The variation is mainly a result of a non-uniform definition of hypocitraturia. Although cut-off points are provided for convenience, in reality, there is no real absolute typical range of citrate excretion because judgment of whether urinary citrate excretion is appropriate relies on knowledge of the acid-base status of the organism. 24-h urine concentrations are much more meaningful with a

controlled diet, although such assessment is difficult with outpatient collections. In clinical practice, hypocitraturia assumes a central role because of its high rate and easily available therapeutic correction. The best known regulator of urinary citrate excretion is the pH of proximal tubule cells.[57] This intracellular acidification can be associated with conditions in which extracellular pH is low (metabolic acidosis, carbonic anhydrase inhibitors), normal (high protein intake), or high (potassium deficiency). Proximal tubule cellular acidosis amplifies citrate transport and metabolism in this nephron segment, leading to hypocitraturia.

Although less common than hypercalciuria,[57,58] hyperoxaluria might cause calcium oxalate stones by raising urinary saturation of calcium oxalate. This effect of oxalate is dependent on the so-called calcium-oxalate interaction,[55] whereby oxalate absorption from the bowel is affected by formation of poorly absorbed calcium oxalate, and the amount of free oxalate in urine is affected by formation of a soluble complex of calcium and oxalate. Findings of one study[58] suggest that oxalate is at least of equal importance to calcium in raising the level of saturation of calcium oxalate in the urine. Hyperoxaluria can result from ingestion of oxalate-rich foods, such as rhubarb, spinach, beetroot, almond (considered a nut), chocolate, and nuts. As a result of diminished binding of oxalate by calcium, increased absorption and urinary excretion of oxalate also result from any conditions that reduce intestinal luminal calcium, such as bowel inflammation or resection, leading to fat-induced precipitation of calcium, severe dietary calcium restriction, or hyperabsorption of calcium.[59]

Although urate is more soluble than uric acid in urine, it is not infinitely soluble. With high urine pH and sodium, sodium urate can be created in a colloidal or solid form, which then initiates calcium-oxalate crystallisation in the background of tenuous calcium-oxalate supersaturation.[60–62] Although not as efficient as sodium urate, uric acid itself (low urine pH) can also cause heterogeneous nucleation of calcium oxalate. This mechanism forms the basis for hyperuricosuric calcium urolithiasis. Hyperuricosuria results from hyperproduction states, such as myeloproliferative disorders, excessive purine ingestion, uncommon monogenic disorders of purine metabolism, or renal leak—eg, renal transport defects.[63,64] Some patients continue to have hyperuricosuria despite severe purine restriction indicative of overproduction.[61,62]

Uric acid nephrolithiasis

Second only to calcareous stones in prevalence, is uric acid calculi. Uric acid exists in equilibrium with urate at a pK of 5·5. As pH falls below 5·5, the concentration of undissociated uric acid greatly exceeds that of urate. Uric acid stones can result from either hyperuricosuria, acidic urine pH, or both. Although the end result is uric acid precipitation, the causes are quite diverse. Idiopathic gout, characterised by hyperuricaemia, recurrent monoarthritis, and hyperuricosuria, represents overlapping and varying contributions from both hyperuricosuria and unduly acidic urinary pH.[65] In the absence of hyperuricosuria, low urinary pH alone can convert urinary urate into the sparingly soluble uric acid.[66] Excessively low urine pH is much more common than hyperuricosuria as a cause of uric acid stones. Secondary causes of low pH can result from excessive acid load or alkali loss, such as arises with chronic diarrhoea.

The finding of hyperuricaemia without gouty arthritis in patients with uric acid nephrolithiasis, and hypertriglyceridaemia and obesity in most of the patients, led to the term gouty diathesis.[66] In the original description of gout, patients were obese with high triglyceride, but not all had hyperuricosuria. Those patients with arthritis had hyperuricaemia and most had low fractional excretion of urate. Patients with idiopathic uric acid stones have low fractional excretion of urate. Studies have emphasised the increasing importance of insulin resistance in the pathogenesis of uric acid stones. High body-mass index, glucose intolerance, and overt type 2 diabetes are common in uric acid stone formers.[67–69] Conversely, diabetic stone formers have a 30–40% rate of uric acid stones compared with the 5–8% rate of uric acid nephrolithiasis in the general stone-forming population.[70–73] The results of a retrospective analysis[74] of more than 4000 patients show that individuals with a high body-mass index tend to have low urinary pH. These findings link uric acid stones and excessively acidic urine to obesity and type 2 diabetes.

Metabolic studies in people indicate that uric acid stone formers maintain acid-base balance, but tend to have higher acid production of a non-dietary origin and use titratable acid rather than ammonium to excrete their acid.[69] Peripheral insulin resistance (impaired glucose disposal rate) is strongly correlated with low urine pH[75] and uric acid stone formers have impaired renal ammonium excretion in response to insulin and to acid challenge.[69,75] There are probably still many unrecognised renal manifestations of the metabolic syndrome. Uric acid nephrolithiasis secondary to low urine pH might only be the tip of the iceberg.

Infection stones

Infection stones are not associated with metabolic abnormalities intrinsic to the patient, but are a consequence of mostly luminal events during which microbial proliferation substantially alters urinary chemistry. Infection stones are largely composed of magnesium ammonium phosphate ($MgNH_4PO_4 \cdot 6H_2O$); also known as struvite with the classic coffin lid semblance. The primary disturbance here is chronic recurrent urinary infection frequently, but not invariably, associated with underlying anatomic predispositions. Urease-positive microorganisms (some *Proteus* sp, some

Klebsiella sp, some *Pseudomonas* sp, *Staphylococcus saprophyticus, Ureaplasma urealyticum*) produce two ammonium and one bicarbonate for each urea, thereby converting urinary divalent phosphate to the trivalent form, and providing ample ammonium for crystallisation of struvite. The high concentrations of urinary bicarbonate also increase carbonate, leading to the formation of carbonate apatite stones. The rate of growth of struvite can be rapid and extensive, and staghorn formation is literally a calcareous cast of the collecting system, a common feature with this stone type.

Cystine nephrolithiasis

Cystine stones are caused by inherited defects of renal transport[76] not, as suggested by the father of genetic disease, Sir Achibald Garrod, by a defect in metabolic enzymes.[77] Incidence and prevalence rates vary greatly dependent on geographic area and method of screening, so the actual allelic frequency is difficult to estimate. However, an incidence of one per 20 000 is often quoted.[78] Inactivating mutations in one of the two possible subunits (rBAT or b^0+AT1) of the multisubstrate basic aminoacid transporter in the kidney leads to urinary wasting of a host of aminoacids, such as cystine, arginine, lysine, and ornithine.[79] The phenotype is cystine stones because only cystine is soluble in urine. The solubility of cystine is improved with alkaline pH and homodimerisation of cystine to cysteine. The old clinical classification is now correlated with a molecular classification: in type I cystinuria (rBAT mutations), heterozygotic carriers have concentrations of urinary cystine within the normal range; in non-type I (ie, type II and III; b^{0+}AT mutations) intermediate aminoaciduria is seen in heterozygotes.

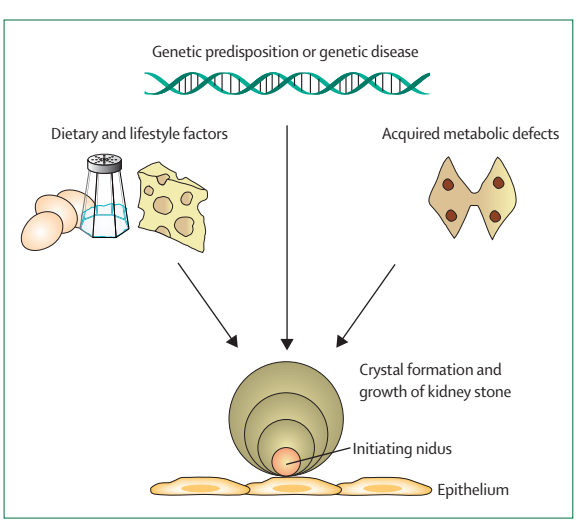

Figure: **Pathogenesis of kidney stones**
Using calcium oxalate stones as a model, three categories of factors (genetic, metabolic, and dietary) act in conjunction or in isolation to lead to kidney stone formation. The process probably needs an initiating nidus on the epithelium, which provides the platform for crystallisation and growth. The defect probably includes lesions in the cells and luminal factors.

The diagnosis of cystine stones relies on a high index of suspicion, since urinary cystine is not routinely measured. Factors that should raise suspicion are young age of presentation, mildly radio-opaque stones, family history, and characteristic hexagonal cystine crystals. It is noteworthy that absence of cystine crystals does not confer assurance of absence of cystinuria, particularly when urine alkalises by sitting in room temperature. A 24-h urine test is necessary to make the diagnosis.

Inhibitors of stone formation

The notion of metastable supersaturation refers to the fact that the activity products of solutes, such as calcium oxalate, calcium phosphate, sodium urate, or uric acid can greatly exceed their solubility in urine. The maintenance of supersaturation in non-stone formers[80] without precipitation of incriminating salts is believed to be a result of inhibitors of crystallisation. Urinary inhibitors can be categorised into multivalent metallic cations (eg, magnesium), small organic (eg, citrate) or inorganic (eg, pyrophosphate) anions, or macromolecules ranging in size from 10 kd to 100 kd (eg, Tamm-Horsfall protein). Tamm-Horsfall protein can be a promoter if aggregated. Inhibitors exert their effects in multiple ways, including inhibition of primary and secondary nucleation and crystal growth and aggregation. Urinary stone inhibitors are of immense importance in understanding stone formation and will be of clinical relevance.[80,81] To date, the measurement and manipulation of stone inhibitors has been part of clinical practice with the exception of citrate and magnesium, although the role of magnesium is still controversial. Citrate is the singular most important stone inhibitor in clinical practice.[55] The pathogenesis of kidney stones with calcium oxalate stones are presented in the figure.

Genetics

Hypercalciuria

The genetics of hypercalciuria have been reviewed in some detail.[82,83] About half of patients with idiopathic hypercalciuria have a family history of kidney stones.[84,85] Familial idiopathic hypercalciuria was labelled as autosomal dominant in earlier published works because it did not conform with a recessive or sex-linked transmission.[86,87] This finding is an oversimplification of the genetics of familial hypercalciuria. Although there are a multitude of monogenic diseases that can clearly cause hypercalciuria in both people and animals,[83] the most frequently encountered clinical hypercalciuria is a complex trait with environmental and polygenic determinants.[82,83] This places hypercalciuria in the same realm as hypertension, obesity, and diabetes, in which genetic dissection is extremely challenging. Several attempts have been made in sibling pairs to test candidate genes, but there is as yet no conclusive evidence to implicate any specific genes in polygenic hypercalciuria.[88–93] A whole genome search was done in

three pedigrees, which identified a locus and a possible candidate as the soluble form of adenylyl cyclase.[94,95] The biological importance of this finding is elusive at present.

Hyperoxaluria

Although less prevalent than dietary or enteric hyperoxaluria, genetic (or primary) hyperoxaluria can result in devastating consequences of not only stones but renal failure. Our understanding of the genetics of primary hyperoxaluria has advanced greatly in the past few years. Type I primary hyperoxaluria is caused by base changes in the gene that codes for the peroxisomal enzyme alanine-glyoxylate aminotransferase.[96] Mutations of alanine-glyoxylate aminotransferase can inactivate the enzyme by accelerated degradation, aggregation in the peroxizome, or mistargeting of a perfectly normal enzyme to the mitochondria where it is segregated from its substrate glyoxylate. In addition to mutations, there are polymorphisms of alanine-glyoxylate aminotransferase in the general population. One major allele (proline-11-leucine) has lower intrinsic catalytic activity, mistargets a small portion of alanine-glyoxylate aminotransferase to the mitochondria, and, when present in combination with true mutations, greatly amplifies the targeting defect. Type II primary hyperoxaluria is less common, milder in its clinical course, and is caused by inactivating mutations in the genes that code for glyoxylate reductase and hydroxypyruvate reductase.[97]

Hyperuricosuria

A major milestone in uric acid research was established when Enomoto and co-workers[64] identified the anion exchanger URAT1 as a urate transporter in the renal proximal tubule and showed that inactivating mutations in the gene coding for URAT1, *SLC22A12*, cause idiopathic hyperuricosuric hypouricaemia, or renal uric acid leak.[98] The relation of this transporter to the common idiopathic uric acid stone former who tends to have low fractional excretion of uric acid (renal uric acid retention)[69] is unclear. A locus and subsequently a putative gene were identified in a Sardinian kindred with familial uric acid stones,[99,100] but the function of this gene product is unknown.

Cystine

Advances in the genetics of cystinuria have been discussed in part. Multiple inactivating mutations have been described in the gene *SLC3A1* (encoding the protein rBAT; type 1 completely recessive cystinuria) and in the gene *SLC7A9* (encoding the protein b^{0+}AT, non-type 1 incompletely recessive).[79,101] Although these represent significant advances, there are still various unresolved issues. Are rBAT and b^{0+}AT truly subunits or are there other partners? What is the basis for the incomplete recessive phenotype in b^{0+}AT mutations? In 10–20% of patients with non-type 1 cystinuria without rBAT or b^{0+}AT mutations,[102] is there a third locus?

***Panel:* Recent advances in surgical management of kidney stones**

Miniaturisation of flexible ureteroscopes

- Improved ability to access all locations, including the lower pole of the kidney, the historic stumbling block for ureteroscopic approaches

Holmium:YAG (yttrium-aluminum-garnet) laser

- Any stone, irrespective of composition, can be fragmented
- Can be introduced through the smallest calibre endoscopes

Improved ureteral access sheaths

- Allow multiple entries and exits without causing repeated trauma to the ureter

Newly designed baskets

- Allow stones to be displaced from the difficult-to-access lower pole calyx to a more accessible upper pole calyx, where they can be fragmented ureteroscopically
- Provide an efficient means to retrieve stones remote from the nephrostomy tract with a flexible endoscope, precluding the need for additional percutaneous punctures

Treatment and prevention

Although I will focus on medical treatment, there have been advances in surgical management of nephrolithiasis over the past decade. Endoscopic technology and techniques have developed (panel).[103–106] Thus, although shock-wave lithotripsy remains the only non-invasive treatment method for stones, endoscopic management, both ureteroscopic and percutaneous, provides an efficient and efficacious way to treat stones irrespective of composition, anatomy, or burden.

The severe nature of renal colic has promoted a lower threshold at which narcotic analgesics can be prescribed, which has led to an increase in the number of time wasters who try to fabricate the classic renal colic history with little or no physical signs to get these drugs. Experienced malingerers have learnt that very minor self-induced urethral trauma before their visit to the emergency room can lead to a positive haematuria test by conventional dipsticks. Salient features that distinguish the malingerer are the 90% incidence of self-reported severe allergy to radiocontrast, universal refusal of invasive procedures, and a high incidence of self-discharge against medical advice.[107] For true renal colic, there are also alternatives to narcotics.[108] Here, I will focus more, however, on the long-term medical management of kidney stones (table 3).

Dietary modification

Since a substantial proportion of the risk factors for nephrolithiasis either stems from or can be modified by environmental changes, dietary modification assumes a pivotal and first-line role in treatment. The efficacy of

	Lifestyle or dietary modification	Pharmacological treatment
Low urine volume	Increase fluid intake: at least >2 L per day	
Hypercalciuria	Sodium moderation <200 mmol/L per day Protein moderation	Hydrochlorthiazide or indapamide+potassium alkali
Hypocitraturia	Protein moderation	Potassium citrate
Hyperoxaluria	Oxalate restriction Avoidance of calcium restriction	Pyridoxine for primary hyperoxaluria
Hyperuricosuria	Purine restriction	Allopurinol
Low urinary pH	Protein restriction	Potassium citrate
Cystinuria	High fluid intake >3 L per day	Potassium citrate D-penicillamine β-mercaptoproprionyl-glycine
Urinary tract infection		Antibiotics

Table 3: **Medical treatment of nephrolithiasis dependent on pathophysiological factor**

dietary regimens has been confirmed by examining the endpoints of urinary chemistry, stone recurrence, or both. Even in instances where there are no prospective trials, some of the physiological data are so overwhelmingly strong that they justify therapeutic recommendations. The dietary components that can be manipulated include intake of fluid, sodium, animal protein, fruits, calcium, and oxalate. The decision to initiate dietary modification is guided mainly by urinary chemistry.

The positive effect of fluid intake has been proven in epidemiological and prospective intervention studies.[109,110] The type of drink seems to matter, since orange juice, coffee, and alcohol are especially beneficial, but the most important component is probably water. The major effect of sodium restriction is to reduce urinary calcium, although it has additional effects, such as raising urinary citrate and reducing sodium urate saturation, all of which can reduce calcium oxalate precipitation. When instituted in conjunction with protein restriction, supplementation with dietary sodium is very effective in reducing stone recurrence.[42] The beneficial effects of long-term dietary sodium restriction might extend beyond reduction of risk for kidney stones to risk for osteoporosis.[111] Protein confers acid and other possible lithogenic factors.[112] The effect is more pronounced for animal versus plant proteins as a result in part to the higher acid content per gram of animal protein.[113] Protein restriction reduces hypercalciuria via effects on multiple organs and raises urinary citrate by acting on the renal proximal tubule. The rise in urinary pH and reduction in uric acid production from reduced intake of animal protein will also benefit uric acid stone formers. The efficacy in reducing stone risk is documented in population-based observations[114,115] and intervention studies.[42] Concomitant with animal protein reduction, the patient can increase their intake of fruits and vegetables.[116] Fruits with high potassium content are the best, since they provide organic anions that will be metabolised to alkali. The alkali in fruits effectively neutralises the acid load delivered by animal protein.

The above factors manipulate mainly modifiers of stone formation. Patients can also directly alter the amounts of calcium and oxalate in their diets. The recommendation for the optimum dietary calcium intake has changed from the traditional wisdom of calcium restriction to high dietary calcium being protective, to a position in between, although some clarification is needed. The continuing theory is that because calcium binds oxalate in the bowel, any gain from reduction of urinary calcium from dietary calcium restriction might be negated by a rise in urinary oxalate. Metabolic studies show that when daily dietary calcium intake is reduced from high (45 mmol/L per day; 1800 mg) to intermediate (30 mmol/L per day; 1200 mg) levels in healthy people, there is a small increase of oxalate absorption, but stringent reduction (5 mol/L per day; 200 mg) greatly raises the oxalate absorption.[117–120] Prospective population analysis in healthy individuals showed a modest rise in stone risk from 25 mmol/L per day (1000 mg) to 15 mmol/L per day (600 mg), but a pronounced rise in risk with a further fall in calcium intake.[52] However, the effect of dietary calcium on urinary oxalate and on stone formation depends on the degree of oxalate restriction, the state of intestinal calcium absorption, and whether other dietary factors are altered. Restricting intake of oxalate can avert secondary hyperoxaluria from calcium restriction. Caution is indicated when one generalises from studies done in healthy volunteers[117] and the general population[52] to stone formers. In patients with absorptive hypercalciuria with enhanced intestinal calcium absorption, the rise in urinary calcium from high calcium intake is so large as to overwhelm any reduction in urinary oxalate.[121] Conversely, dietary calcium restriction might produce a substantial reduction in urinary calcium in hypercalciuric patients, but a negligible change in normocalciuric patients. A diet high in calcium is sometimes rich in potentially protective factors, such as potassium, magnesium, and fluids. Thus, in stone formers with normocalciuria, a severe dietary restriction is not indicated because of the exaggeration of secondary hyperoxaluria and potential risk for bone loss. In those patients with hypercalciuria, calcium intake might be restricted especially when it is applied with a hypocalciuric agent. In both groups, dietary oxalate intake should be restricted.

Dietary oxalate restriction is more difficult and needs good counselling because oxalate-rich foods are more variable and more ubiquitous than calcium-rich food. Relative contribution of dietary intake of oxalate to endogenous generation has been controversial, but increase in dietary oxalate can substantially alter excreted oxalate in the urine.[118,120] Dietary excess usually causes mild-to-moderate degrees of hyperoxaluria, although bowel disease and congenital defects can yield more severe hyperoxaluria. In cases of severe hyperoxaluria, dietary restriction will produce modest results. With oxalate restriction, prescription of calcium restriction in absorptive hypercalciuria controls hypercalciuria successfully without inducing hyperoxaluria.[121] Excessive

intake of vitamin C and vitamin D can cause hyperoxaluria and hypercalciuria, respectively. Since these are over-the-counter supplements, they can be considered as dietary modification.

Thiazide diuretics

When dietary modification is ineffective, pharmacological treatment should be contemplated. The most effective and best tested hypocalciuric agents are thiazide diuretics.[122–124] Reduction of calciuria has been attributed to enhanced reabsorption of calcium in the distal convoluted tubule and sodium depletion; the latter effect can be nullified by excessive sodium consumption. One complication is thiazide-induced potassium depletion, which causes intracellular acidosis and can counter the hypocalciuric benefit by producing hypocitraturia. For treating nephrolithiasis, thiazides should always be prescribed with a potassium supplement, either dietary or pharmacological. Potassium citrate is the preferred choice,[125] because it provides both potassium and citrate. The theoretical concern of metabolic alkalosis with thiazide-potassium citrate combination has not been shown to arise in clinical trials.[126] Indapamide is as effective as hydrochlorthiazide with potentially fewer side-effects.[127,128]

Potassium citrate

Potassium alkali treatment is effective for calcareous stones. It reduces hypercalciuria, raising the soluble fraction of urinary calcium by chelation, and inhibits crystal growth. Potassium citrate reduces stone recurrence.[129] The combination of thiazide, potassium citrate, modification of dietary calcium, and oxalate restriction lowers urinary saturation of calcium oxalate, prevents stone recurrence, and improves bone mineral density.[121] Furthermore, countering calcium stones and bone loss, potassium alkali is an effective agent against uric acid stones,[130] which are caused by unduly acidic urine pH. Other forms of alkali, such as sodium citrate or sodium bicarbonate, are less ideal because the sodium load worsens hypercalciuria and raises sodium urate saturation. Potassium-magnesium citrate also confers an alkali load, raises urinary citrate, and diminishes stone recurrence.[131]

Other therapeutic agents

In hyperuricosuric uric acid stones and moderate-to-severe hyperuricosuria with calcium oxalate stones, allopurinol might be helpful in restoring normal urinary uric acid.[132,133] In hyperuricosuric calcium oxalate urolithiasis, potassium citrate treatment might retard urate-induced crystallisation of calcium oxalate by raising urinary citrate, but will not correct hyperuricosuria or hyperuricaemia. The use of recombinant uricase is currently limited to acute situations, such as tumour lysis syndrome,[134] and plays no part in the chronic management of uric acid hyperproduction. The primary aim in managing infection struvite stones is targeting eradication of the infection.[135] Manipulation of urinary chemistry is only modestly successful. Hyperoxaluria that is refractory to dietary manipulation is difficult to treat. The use of probiotic (colonisation with the oxalate consuming bacteria *Oxalobacter formigenes*) has not been overwhelmingly successful. The fact that it reduces oxaluria in patients with primary hyperoxaluria suggests that it might promote intestinal oxalate secretion.[136] The only available medical treatment for primary hyperoxaluria is pyridoxine, which promotes conversion of glyoxylate to glycine.[137] Pharmacological treatment of cystinuria depends on its severity. For moderate cystinuria (<500 mg per day), raising urine pH (>6·5) with potassium citrate or sodium bicarbonate, and fluid intake (>4 L per day) can suffice. In more severe cystinuria, chelating agents should be added (alpha-mercaptopropionylglycine or tiopronin, angiotensin converting enzyme inhibitors, and d-penicillamine) to promote formation of mixed disulfide-linked compounds with cystine.[138,139]

Future

Despite advances, there are still vast areas in nephrolithiasis that are poorly understood or even unexplored. To further the progression of research and clinical management of kidney stones, multilevel translational approaches are needed. Improved laboratory studies and animal and cell-culture models are needed, and a greater effort needs to be made to identify candidate loci and genes. Tackling complex traits, such as hypercalciuria, will be extremely challenging. At the clinical level, practitioners must subscribe to the concept that urolithiasis is merely a manifestation of an underlying defect rather than a diagnosis per se. The clinical assessment of the kidney should be pathophysiology-oriented in an attempt to unveil features more proximal to the underlying cause. Not only is this type of clinical data important for guidance of treatment, but it is essential in the bidirectional flow of information between patient and laboratory research.

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