Crystal nephropathies: mechanisms of crystal-induced kidney injury

Shrikant R. Mulay and Hans-Joachim Anders

Abstract | Crystals can trigger a wide range of kidney injuries that can lead to acute kidney injury, chronic kidney disease, renal colic or nephrocalcinosis, depending on the localization and dynamics of crystal deposition. Studies of the biology of crystal handling by the kidney have shown that the formation of different crystals and other microparticles and the associated mechanisms of renal damage share molecular mechanisms, such as stimulation of the NLRP3 inflammasome or direct cytotoxicity through activation of the necroptosis signalling pathway. By contrast, crystal granuloma formation is limited to chronic crystallopathies that lead to chronic kidney disease and renal fibrosis. Here, we discuss current understanding of the pathomechanisms underlying the different types of crystal-induced kidney injury and propose a classification of crystal nephropathies based on the localization of crystal deposits in the renal vasculature (type 1), the nephron (type 2), or the draining urinary tract (type 3). Further exploration of the molecular mechanisms of crystal-induced kidney injury and renal remodelling might aid the development of innovative cures for these diseases.

Crystallization
Periodic self-aggregation of atoms, ions or misfolded proteins into a highly ordered solid structure consisting atoms, molecules or ions.

Crystalluria
Presence of crystals in urine.

Medizinische Klinik und Poliklinik IV, Klinikum der Universität München, LMU Munich, Ziemssenstrasse 1, 80336 München, Germany.

Correspondence to H.-J.A.
hjanders@med.uni-muenchen.de

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The kidney is susceptible to crystal formation as mineral secretion and urine concentration favour supersaturation, which promotes crystallization and crystalluria and can lead to the development of several different crystal nephropathies and kidney stone diseases. The different types of crystal-induced renal diseases are not only determined by the physicochemical properties and urine concentration of the minerals involved; they also depend on other regulators of crystallization and on the signalling pathways triggered by crystals, leading to different types of kidney injury. For example, the formation of tubular crystal deposits is dependent on the presence or absence of crystallization inhibitors and on the presence of proteins that facilitate crystal adhesion to tubular cell membranes[1,2]. Research in the crystal nephropathy field was once largely driven by the procedural approach of kidney-stone removal or by the morphological and descriptive approach of disease histopathology. Moreover, experimental studies focused on 2D *in vitro* cultures and on rodent models of kidney injury associated with specific crystals. Despite these experimental efforts, the molecular mechanisms of crystal-induced kidney injury remained largely unknown.

A landmark study published a decade ago showed that phagocytosis of any type of crystal or particle activates a signalling pathway involving the NLRP3 inflammasome —a multiprotein oligomer formed by the three cytosolic proteins[3] NLRP3, ASC, and caspase-1 — which specifically triggers IL-1β-dependent inflammation[4]. This mechanism drives several forms of acute and chronic crystal deposit-induced kidney diseases[5–7]. Further studies revealed that crystal-associated diseases with apparently diverse clinical presentations share several molecular and cellular pathomechanisms, and might therefore be considered a unique disease entity referred to as the 'crystallopathies' (REF. 8,9).

In this Review, we apply this general concept to kidney diseases that involve crystal precipitates or deposits as the predominant causative element of kidney injury and dysfunction. We propose a classification of 'crystalline nephropathies' (TABLE 1) and discuss the current pathophysiological mechanisms underlying kidney injury, dysfunction and remodelling in these diseases. This conceptual approach will hopefully increase the understanding of disease pathogenesis by stimulating broader research activities, leading to the identification of molecular targets and the development of innovative cures for affected patients.

Renovascular crystallopathies (type 1)

Degenerative changes in the vascular wall can involve several types of crystals. For example, cholesterol crystals are present in atheromatous plaques and apatite crystals exist in vascular calcifications (TABLE 1).

Key points

- Crystals cause several types of kidney injury: renovascular damage (type 1), tubular damage (type 2), and urolithiasis (type 3)
- Renovascular damage (type 1) due to cholesterol crystals (from plaques in cholesterol embolism, for example) leads to ischaemic renal necrosis; stenotic atherosclerosis of renal arteries causes renal atrophy owing to chronic ischaemia
- Tubular crystallopathy type 2 involves crystals of endogenous metabolites, minerals or proteins or exogenous drugs and toxins and causes acute necroinflammation, tubule obstruction or crystal granuloma formation and chronic tissue remodelling
- In urolithiasis (type 3 crystallopathy), crystals form at the papilla or in the ducts of Bellini and grow to form calculi and stones, which cause colic, infections, and obstruction-related nephron loss
- The molecular mechanisms of crystal-induced tissue injury and remodeling have become an exciting area of basic and translational research

Crystal embolism

Clinical presentation. Cholesterol embolism (also called atheroembolic renal disease) is characterized by a sudden or subacute increase in serum creatinine levels and occurs predominately in male smokers with hypertension and systemic atherosclerosis, and often (but not always) in temporal association with cardiac or thoracic aorta surgery, cardiac catheterization, and coronary angioplasty[10]. Atheroembolic renal disease is different from contrast media-induced nephrotoxicity and from thromboembolic peripheral artery disease as diagnostic signs include maintained peripheral pulses and clinical signs of small vessel embolism of both lower limbs, such as *livedo reticularis* or blue toe syndrome[10–12]. In addition, kidney colour Doppler sonography shows regional hypoperfusion and an increase in vascular resistance in affected patients. In kidney biopsy samples, cholesterol crystals appear as empty clefts in the vascular lumen as the crystals are lost during tissue processing (FIG. 1). However, a kidney biopsy sample might not always be diagnostic owing to the patchy nature of cholesterol embolism. Of note, one study found that only three of 18 cases of histologically proven atheroembolic renal disease were diagnosed clinically before biopsy[13].

Pathophysiology. Large atheroma contain bulks of sharp-edged cholesterol crystals that can pierce the cap of the plaque[14]. Spontaneous, traumatic or procedure-induced rupture of plaques in the aorta can mobilize incident or repetitive showers of cholesterol crystals that obstruct small arteries (100–200 μm in diameter). In the lower limbs this obstruction does not affect peripheral pulse whereas thromboembolic peripheral artery disease, which affects larger vessels, causes pulseless acral ischaemia. In the kidney, emboli induced by cholesterol crystals obstruct arcuate and interlobar arteries causing cortical and medullary infarcts[15].

In vitro studies have shown that endothelial injury caused by cholesterol crystals involves complement activation[16] although hypocomplementemia occasionally occurs in patients with cholesterol embolism[17]. Whether cholesterol crystals induce endothelial cell necroptosis, as described for other crystals and cell types (discussed below) is unclear[9]. In atherosclerosis, macrophages ingest small cholesterol crystals that activate the NLRP3 inflammasome and induce IL-1β-dependent inflammation, a process that involves the complement system as well as C-type lectin receptors[18–20]. A contribution of complement, NLRP3 inflammasome or other innate immune receptors to atheroembolic renal disease is still speculative, mostly owing to the lack of a suitable animal model. Old descriptive studies in rabbits and rats injected with human atherosclerotic material or a suspension of cholesterol crystals showed that cholesterol crystals trigger neutrophil recruitment[21,22]. Subsequently, intravascular crystals induce a foreign-body reaction, which involves the recruitment of macrophages that form giant cell granulomas, luminal thrombosis and long-term obstruction with fibrotic narrowing of the vascular lumen[22,23]. The long-term prognosis of atheroembolic renal disease is therefore poor and largely determined by the numbers of irreversibly occluded arterioles[15,24,25] and that of lost nephrons[10].

Atherosclerosis and nephroangiosclerosis

Clinical presentation. Hypertension is the most common clinical sign of ischaemic kidney disease caused by renal stenotic arterial vessels. In patients with diabetes or in elderly patients with non-diabetic atherosclerotic renal artery stenosis, vascular obstruction caused by cholesterol and/or apatite calcium phosphate crystals of various sizes induces diffuse nephroangiosclerosis of intrarenal arterioles[11,26–28].

Pathomechanisms. The development of atherosclerosis involves cholesterol crystals, which cause lysosomal leakage in macrophages of the arterial wall[18]. This process activates the NLRP3 inflammasome, induces IL-1β-dependent inflammation and promotes the progression of atherosclerosis in mice[18,19]. Renal hypoperfusion induces persistent activation of the renin–angiotensin system and hypertension. Persistent renal ischaemia causes renal atrophy and chronic kidney disease (CKD), characterized by glomerulosclerosis, nephron loss, and interstitial fibrosis, in a process that results exclusively from narrowing of the vascular lumen owing to the deposition of crystals, or from intimal hyalinosis and media thickening[29]. Apatite deposits in the vascular wall are an occasional feature of nephroangiosclerosis and are therefore not discussed in detail here. The pathomechanisms of vascular calcification have been described elsewhere[30,31].

Therapeutic options

Currently, no specific therapies exist for atheroembolic renal disease and management is limited to supportive care of renal failure and secondary prevention of further embolization episodes. Surgical or catheter-based revascularization of atherosclerotic renal artery stenosis does not provide clear short-term or long-term benefits on renal outcomes and mortality[32]. Therefore, management of renal artery stenosis and nephroangiosclerosis requires rigorous control of systemic blood pressure and other modifiable cardiovascular risk factors such as hyperlipidaemia, hyperglycaemia, obesity, and hypertension[32].

Inflammasome
Multiprotein oligomer complex present in the cytosol that activates the inflammatory caspase 1 and sometimes caspase 5 (in mice caspase 11) to cleave pro-IL-1β and pro-IL-18 into respective mature forms and eventually induce pyroptosis, a form of regulated necrosis that mainly occurs upon recognition of bacterial endotoxin inside the cytoplasm of infected macrophages.

Crystallopathies
Diseases caused by crystals or crystal-like microparticles.

Cholesterol embolism
Obstruction of a blood vessel by cholesterol crystals that are released from an atherosclerotic plaque in veins.

Acral ischaemia
Ischaemia of the tips of the fingers or toes due to the obstruction of terminal arteries.

Necroptosis
Form of regulated necrosis that involves the RIPK3/MLKL pathway triggered by TNFR1, TLR4/TRIF, TLR3/TRIF, CD95 or IFNγ/STAT3 signalling pathways.

Table 1 | **Classification of crystal nephropathies**

Disease	Disease subtype	Crystal (source of the crystal-forming factor)	Renal damage	Treatment and management
Vascular crystallopathies (type 1)				
Cholesterol embolism	NA	Cholesterol	AKI	Control of cardiovascular risk factors, avoid catheter interventions and anticoagulants
Atherosclerotic renal artery stenosis	NA	Cholesterol, apatite, calcium–phosphate	CKD	Control of cardiovascular risk factors, especially hypertension
Tubular crystallopathies (type 2)				
Diet-induced crystal nephropathy	NA	Calcium oxalate monohydrate (whewellite), calcium oxalate dihydrate (weddelite), calcium–phosphate (oxalate and vitamin C-rich foods and drinks)	AKI	Stop exposure, increase fluid intake
Drug-induced crystal nephropathies	Tumour lysis syndrome	Uric acid	AKI	Rasburicase, increase fluid intake
	Drug-induced crystalluria	Drug crystals	AKI	Stop exposure, increase fluid intake
	Acute phosphate nephropathy	Calcium–phosphate		
Enteric crystal nephropathy	NA	Calcium oxalate monohydrate (whewellite) (bariatric surgery, IBD, coeliac disease)	AKI	Avoid dietary oxalate intake, increase fluid intake, treat enteric disease
Short bowel syndrome	NA	Calcium oxalate dihydrate (weddelite)		
Myogen crystal nephropathy	NA	Myoglobin (rhabdomyolysis)	AKI	Increase fluid intake
Cholemic crystal nephropathy (bile cast nephropathy)	NA	Bile pigment	AKI	Increase fluid intake, treat liver disorder or transplant
Paraprotein-induced crystal nephropathy (light chain cast nephropathy)	NA	Monoclonal light chains	AKI	Treat plasma cell dyscrasia, increase fluid intake
Genetic disorders	Genetic forms of RTA	Brushite, calcium carbonate, calcium oxalate, calcium–phosphate, hydroxapatite, struvite	CKD	Increase fluid intake, specific interventions to reduce mineral or metabolite excretion
	Genetic forms of hyperuricosuria	Uric acid		
	Primary hyperoxaluria	Calcium oxalate monohydrate (whewellite), calcium oxalate dihydrate (weddelite)		
	APRT deficiency	Adenine		
	Cystinosis	Cystine	CKD	Cysteamine
Genetic diseases that cause nephrocalcinosis	Dent disease, Lowe syndrome, idiopathic infantile hypercalcaemia and hypercalciuria	Calcium–phosphate, Calcium–pyrophosphate	CKD	Increase fluid intake, specific interventions to reduce mineral or metabolite excretion
Diet and drug-induced crystal nephropathy	NA	Uric acid (diets rich in sodium, fructose, sucrose)	CKD	Stop exposure, diet modifications, increase fluid intake, xanthine oxidase inhibition
Tophaceous gout	NA	Uric acid (diets low in potassium, calcium, phytate, fluid administration as part of Mesoamerican nephropathy treatment)	CKD	Xanthine oxidase inhibition, uricosuric drugs
Immunoglobulin-induced crystal nephropathies	Light chain cast nephropathy, proximal tubulopathy with or without Fanconi syndrome, crystalglobulinaemia, crystal-storing histiocytosis	Monoclonal light chains	CKD	Treat plasma cell dyscrasia, increase fluid intake
Chronic glomerular crystal nephropathies	Cryoglobulinaemia	Monoclonal and polyclonal IgG	CKD	Treat plasma cell dyscrasia, increase fluid intake
	Crystalglobulinaemia	Monoclonal light chains		
	Cystinosis	Cystine	CKD	Cysteamine

Table 1 (cont.) | **Classification of crystal nephropathies**

Disease	Disease subtype	Crystal (source of the crystal-forming factor)	Renal damage	Treatment and management
Urolithiasis (type 3)				
Genetic disorders	Genetic forms of RTA	Brushite, calcium carbonate, calcium oxalate, calcium–phosphate, Hydroxapatite, struvite	Colic	Increase fluid intake, specific interventions to reduce mineral or metabolite excretion
	Primary hyperoxaluria	Calcium oxalate monohydrate (whewellite), calcium oxalate dihydrate (weddelite)		
	Cystinosis	Cystine		
	APRT deficiency	Adenine		
	Genetic forms of hyperuricosuria and hypercalciuria (as listed above)	Uric acid, calcium oxalate, calcium–phosphate		
Diet or drug-induced crystal nephropathy	NA	Calcium oxalate, calcium–phosphate (diets rich in oxalate, sodium, fructose, vitamin C, sucrose, diets low in potassium, calcium, phytate)	Colic	Increase fluid intake, specific interventions to reduce mineral or metabolite excretion
Hyperuricosuric syndromes	NA	Uric acid	Colic	Increase fluid intake, specific interventions to reduce mineral or metabolite excretion
Drug crystalluria	NA	Drug crystals	Colic	Increase fluid intake, specific interventions to reduce mineral or metabolite excretion
Enteric oxalosis	NA	Calcium oxalate monohydrate (whewellite)	Colic	Avoid dietary oxalate intake
Short bowel syndrome	NA	Calcium oxalate dihydrate (weddelite) (bariatric surgery, IBD, coeliac disease)	Colic	Increase fluid intake, treat enteric disease

AKI, acute kidney injury; APRT, Adenine phosphoribosyl transferase; CKD, chronic kidney disease; IBD, inflammatory bowel disease; RTA, renal tubular acidosis.

A 2016 report described the ability of cyclic oligosaccharide 2-hydroxypropyl-β-cyclodextrin to induce regression of atherosclerotic plaque size *in vivo*[33] through the direct dissolution of intracellular and extracellular cholesterol crystals, followed by increased efflux of cholesterol from foam cells and urinary cholesterol excretion[33]. This compound can also increase the efflux of sphingomyelin from overloaded lysosomes and is currently under study for treatment of the neurological manifestations of Niemann–Pick disease[34]. One could speculate that this compound could induce regression of crystal nephropathies associated with atherosclerosis.

Tubular crystallopathies (type 2)

Clinical presentation

Tubular crystallopathies result from precipitates of minerals, proteins or drugs inside the tubular lumen[35]. The dynamics of crystal deposition determine whether a patient might present with acute kidney injury (AKI) or CKD. Dehydration and acute supersaturation promote a sudden onset of crystal formation that can lead to AKI, whereas persistent mild supersaturation rather fosters a chronic dynamic of crystal formation and hence, CKD. Rapid and diffuse crystallization causes considerable cell necrosis and inflammation leading to AKI, whereas subacute crystal plug formation in distal tubules or collecting ducts injures the kidney by persistent tubule obstruction, causing CKD.

Niemann–Pick disease
Inherited metabolic disorder caused by sphingomyelin accumulation in lysosomes.

Crystalglobulinaemia
Presence of cryoglobulin crystals in serum.

Crystal-storing histiocytosis
Presence of cryoglobulin crystals in histiocytes (tissue macrophages).

Clinical scenarios that foster crystalline AKI

In the following five clinical settings, tubular crystallopathy should be a considered differential diagnosis of kidney disease (TABLE 1).

First, patients with haematological disorders such as monoclonal gammopathy, who produce immunoglobulin light chains, or patients starting chemotherapy for leukaemia or lymphoma can develop a tubular crystallopathy[36]. Immunoglobulin light chains can precipitate in the kidney in diverse ways, depending on their specific physicochemical properties[37]. Some light chains precipitate as β-sheets forming extracellular amyloid fibril deposits that cause amyloid light-chain amyloidosis[38], which often leads to nephrotic syndrome. Immunoglobulin light chain crystals can damage the proximal or the distal tubule[36] (FIG. 2). Occasionally, light chain crystals also precipitate in podocytes (FIG. 2) or mononuclear phagocytes inside the kidney to cause crystalglobulinaemia or crystal-storing histiocytosis, respectively[39].

Patients who are receiving chemotherapy for leukaemia or severe lymphoma can develop tumour lysis syndrome. This condition is characterized by a marked release of uric acid from widespread cell necrosis, which promotes acute urate-crystal precipitation inside the nephrons[40]. These crystal precipitates are thought to induce renal failure primarily by obstructing distal tubules and collecting ducts, the latter representing the main drainage system of many nephrons. Whether direct crystal toxicity and tissue inflammation contribute to kidney injury in this setting is not yet known.

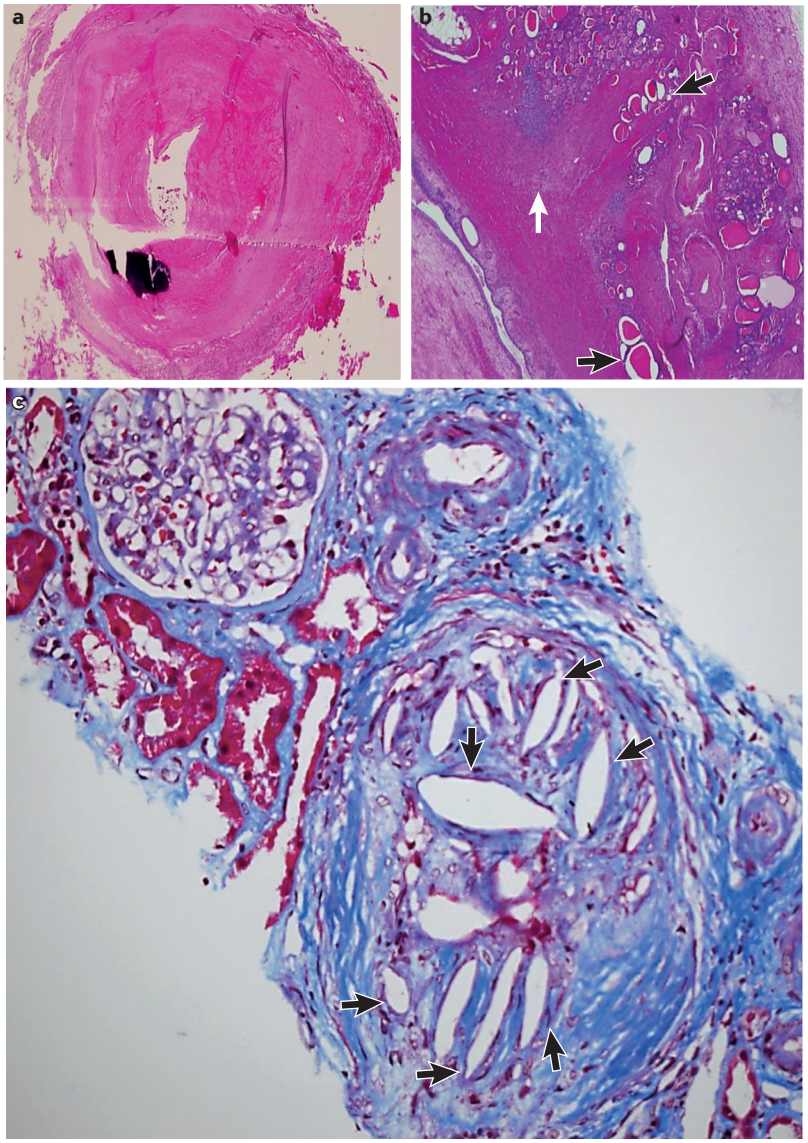


Figure 1 | **Histopathological changes in vascular crystal nephropathies (type 1).** **a** | Crystals induce the thickening of the renal artery through the proliferation of intimal and medial layer smooth muscle causing severe narrowing of the lumen (haematoxylin and eosin staining). **b** | The corresponding renal parenchyma shows diffuse cortical atrophy, marked arterial wall thickening, thyroidization-type tubular atrophy (black arrows), diffuse interstitial fibrosis and chronic inflammation (white arrow) (haematoxylin and eosin staining). **c** | Cholesterol atheroemboli fill in the lumen of this medium size artery stained with trichrome. Cholesterol crystals appear as spindle-shaped empty spaces (clefts, indicated by arrows) often engulfed by inflammatory cells (cholesterol crystals dissolve during formalin fixation). Images courtesy of Helen Liapis, Arkana Laboratories, USA.

Hepatorenal syndrome
Particular type of kidney failure that affects patients with hepatic dysfunction (cirrosis, fulminant liver failure or portal hypertension and ascites).

Rhabdomyolysis
Condition involving rapid break down of damaged skeletal muscles.

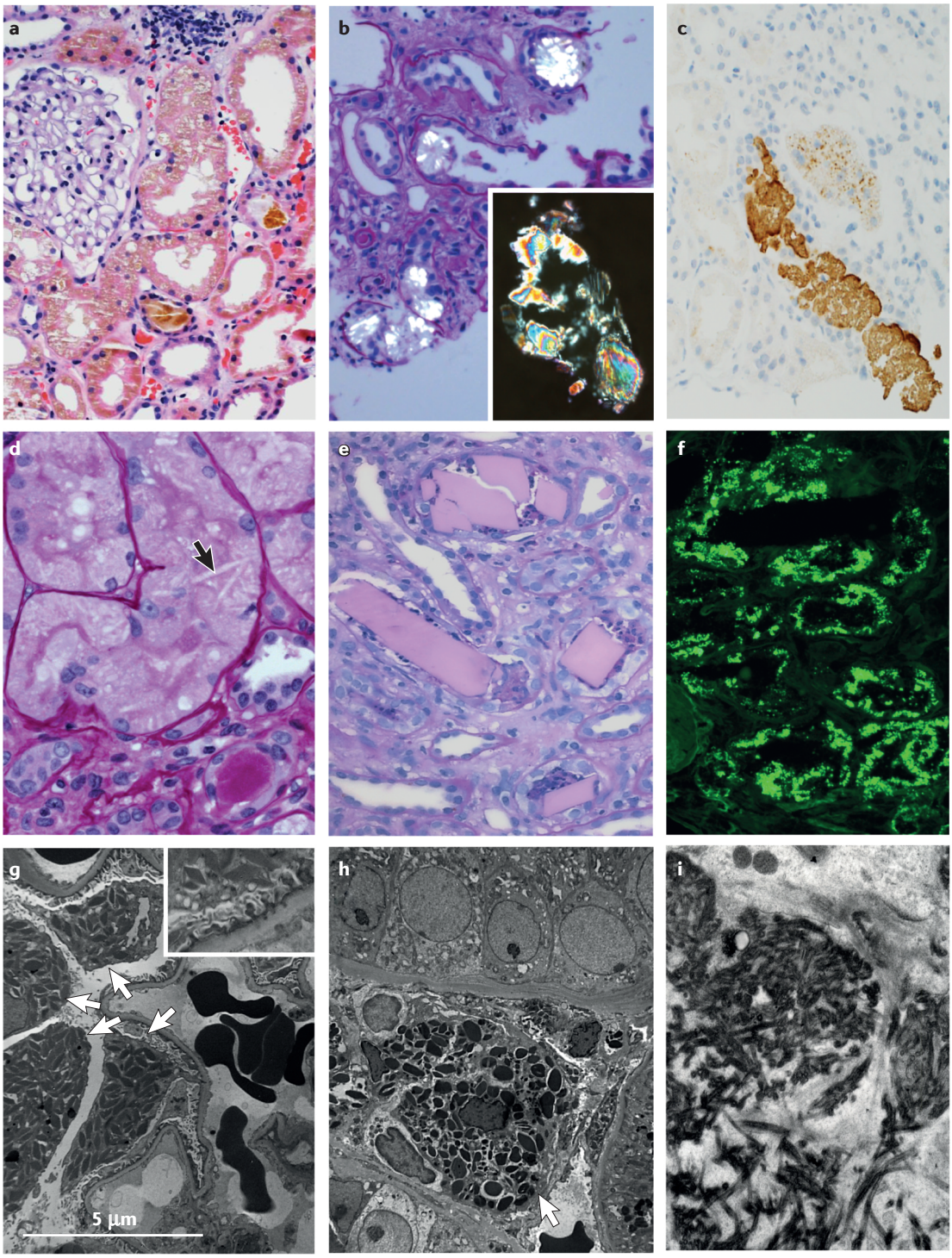
Second, patients with liver and gastrointestinal problems can also develop tubular crystallopathies. Advanced liver disease can cause the formation of bile salt precipitates, which form casts that obstruct the nephrons. The toxicity of bile salt and bilirubin might also directly contribute to tubular cell injury[41,42]. Bile cast nephropathy can occur in severely jaundiced patients with advanced liver failure and can contribute to the hepatorenal syndrome[43]. By contrast, inflammatory bowel disease, coeliac disease and a history of intestinal bypass surgery are associated with secondary oxalate nephropathy[44]. These conditions increase the uptake of oxalate from the ileum and the colon, which is then excreted via the nephrons where hyperoxaluria promotes calcium oxalate crystal formation and retention[45]. Hyperoxaluria can cause AKI either via diffuse intrarenal crystal precipitates or less frequently, via obstructive nephropathy.

The third setting that favours the development of tubular crystallopathies occurs in patients with acute or chronic exposure to drugs, toxins or dietary elements that tend to crystallize in the urine. For example, dietary sources of oxalate (such as nuts, spinach, rhubarb, black tea, and citrus fruits[46,47]) can commonly cause secondary hyperoxaluria and acute oxalate nephropathy[48], and can be associated with intestinal abnormalities that increase oxalate uptake. Oxalate can also accumulate after the ingestion of vitamin C supplements or following polyethylene glycol intoxication, which can occasionally trigger acute oxalate nephropathy[49,50]. Massive intake of oral sodium phosphate, a common form of oral bowel purgative, can also cause intratubular calcium phosphate precipitates, which can lead to acute phosphate nephropathy[51]. Crystalluria can also be induced by certain drugs such as indinavir (an antiretroviral agent), acyclovir (an anti-viral agent), sulfamethoxazole (an antibiotic), especially when used at high doses or with low fluid intake[52,53]. Moreover, exercise or heat stress-associated dehydration can induce hyperuricaemia and uricosuria, which have been suggested to cause Mesoamerican nephropathy[54]. However, the putative injurious role of crystal formation in this form of nephropathy and in rhabdomyolysis (detailed below) remains speculative[55].

Fourth, rhabdomyolysis-associated myoglobinuria induces the formation of intratubular crystals and crystal casts, especially in hypovolaemia, which can occur in earthquake or car-crash victims with severe muscle trauma[56]. Rhabdomyolysis can also be triggered by non-traumatic events, which include severe infections and ingestion of certain drugs such as cocaine, colchicine or statins[57]. Lastly, children or adolescents with CKD and genetic metabolic or renal disorders that promote nephrocalcinosis or other types of intrarenal crystal deposits (TABLE 1) can develop tubular crystallopathies[58,59].

Pathomechanisms of crystalline AKI

Supersaturation is an important mechanism in crystalline AKI that usually combines dehydration-induced urine concentration with sudden exposure to components that crystallize in concentrated urine such as dietary oxalate[60]. However, extensive exposure to substances with crystal-forming potential (such as light chain antibodies or polyethylene glycol) can alone be sufficient to cause AKI[61]. Once crystals have formed in the tubular lumen, they can contribute to kidney injury in several ways. In the following sections, we discuss the mechanisms of direct and indirect crystal cytotoxicity, crystal-induced inflammation, and inflammation-driven cell necrosis, an auto-amplifying loop termed necroinflammation[62].



Nephrocalcinosis
Deposition of calcium salts such as calcium phosphate and calcium oxalate in the parenchyma of the kidney.

Necroinflammation
Amplification loop between cell necrosis and inflammation.

Direct and indirect crystal cytotoxicity. Crystals can be directly cytotoxic but the underlying molecular mechanisms have remained largely unknown. Tubular cells can phagocytose crystals <10 µm into intracellular phagosomes that fuse with lysosomes in an attempt to digest the crystals with proteolytic enzymes[63] (FIG. 3). The lysosomal acidity drives calcium release from amorphous calcium phosphate into the cytosol, a process that triggers cell necrosis[64]. Indigestible lysosomal particles can destabilize lysosomal membranes and cause leakage of lysosomal enzymes into the cytosol, which leads to profound cell stress characterized by actin depolymerization, the production of reactive oxygen species (ROS) and enhanced autophagy[65]. For example, crystals of calcium oxalate, calcium pyrophosphate, cystine or monosodium urate (MSU) can trigger tubular epithelial cell necrosis by activating receptor-interacting protein (RIP) kinase-3-mediated phosphorylation of the pseudokinase MLKL[9], in a

Figure 2 | **Histopathological changes in nephron-associated crystal nephropathies (type 2). a** | In a patient with acute kidney injury (AKI) (serum creatinine levels of 4 mg/ml [353.6 µmol/l]) and increased serum bilirubin and liver function tests, tubular epithelial cells were swollen, stained yellow to brown (positive for bile with Faucet stain) and had focal tubular brown casts (haematoxylin and eosin staining). **b** | In a patient with metabolic acidosis, ethylene glycol intoxication, serum creatinine levels of 2.41 mg/ml (213.0 µmol/l), and an estimated glomerular filtration rate of 28 ml/min/1.73 m2, tubular cells stained with haematoxylin and eosin had numerous colourless fan-shaped calcium oxalate tubular crystals. The crystals polarize light and some of them are polychromatic (insert). **c** | Rhabdomyolysis-induced tubular casts (stained in brown with an anti-myoglobin antibody) in a young man with a history of strenuous exercise and severe AKI requiring dialysis. **d** | A 70-year-old man with chronic kidney disease and a history of monoclonal gammopathy of undetermined significance had needle-shaped paraprotein intracytoplasmic crystals (arrow) in the proximal tubules. **e** | Numerous pale rhomboid tubular crystals were present in a renal biopsy sample from a 60-year-old man with refractory multiple myeloma and κ light chain restrictions (haematoxylin and eosin staining). **f** | A 62-year-old woman with AKI and clinical suspicion of multiple myeloma had a proximal tubulopathy, as shown by an intense cytoplasmic κ light chain staining. **g,h** | In a 55-year-old man with long-standing hypertension, nephrotic range proteinuria, slowly progressive renal function impairment (serum creatinine levels of 2.4 mg/ml [212.2 µmol/l]), crystal podocytopathy and crystal cast nephropathy, podocytes (panel **g**) and tubules (panel **h**) are filled with rectangular or rhomboid crystals (arrows), as seen by transmission electron miscropscopy. The insert in **g** pictures the rhomboid crystals inside the podocyte at high magnification. **i** | A patient with immunotactoid glomerulopathy had thick tubular deposits in the glomeruli (electron-dense material seen by transmission electron miscropscopy), and expanded glomerular mesangium and thickened capillary loops (not shown here); congo red stain and immunofluorescent staining of immunoglobulins and complement were negative. Images courtesy of Helen Liapis, Arkana Laboratories, USA.

regulated form of necrosis referred to as necroptosis[66,67] (FIG. 3). Indeed, mice deficient in either *Ripk3* or *Mlkl* are protected from oxalate crystal-induced AKI[9]. The RIPK3–MLKL pathway also mediates haeme-associated cytotoxicity[68] (in rhabdomyolysis, for example) and necrosis of neutrophils induced by MSU crystals[69]. Whether necrosis of neutrophils contributes to crystal nephropathies has not yet been formally demonstrated. Ferroptosis also contributes to renal injury during oxalate crystal-induced AKI[70]; however, whether crystals directly induce ferroptosis in tubular cells remains unclear.

Crystals can also trigger cell necrosis through an auto-amplification loop involving the release of damage-associated molecular patterns (DAMPs), which include the nucleoprotein high mobility group protein B1 (HMGB1), histones, mitochondrial DNA, demethylated DNA and RNA, ATP, uric acid and double-stranded DNA[71]. Crystal-induced tubular cell necrosis releases large amounts of histones into the extracellular space[72] (FIG. 3). Extracellular histones are disconnected from the acidic DNA and their strong basic charge can potentially disrupt plasma membranes or neighbouring intact cells, a process that amplifies the numbers of dying tubular cells and thus aggravates kidney injury, which can eventually lead to crystal-induced AKI.

Crystal-induced renal inflammation. Crystal-induced cytotoxicity triggers inflammation indirectly via the release of alarmins, proteases, and DAMPs from necrotic cells. These molecules can activate Toll-like receptors and trigger the formation of inflammasomes in renal dendritic cells (FIG. 3). In addition, tubular cell necrosis induces the expression of cytokines, kinins and lipid mediators that further promote vasodilation, vascular permeability, leukocyte influx and complement activation, which enhances renal inflammation[19]. These processes contribute to the amplification of renal necroinflammation and AKI.

Of note, crystals can also trigger renal inflammation directly[73] by inducing the secretion of mature IL-1β by interstitial renal dendritic cells through the activation of NLRP3 (REF. 4). Crystals can trigger NLRP3 activation in different ways. Cholesterol crystals can bind to human macrophage-inducible C-type lectin (hMINCLE) on the surface of macrophages and dendritic cells in a mechanism that involves oligomerization of hMINCLE with the Fcγ receptor[20]. Silica and MSU crystals can attach directly to the plasma membrane and activate the NLRP3 inflammasome via potassium efflux from the cell[74]. Alternatively, MSU crystals taken up into acidic lysosomes by phagocytosis can release sodium ions into the cell, which causes water influx and dilutes the intracellular potassium concentration — a signal that activates the NLRP3 inflammasome[75]. Calcium released from amorphous calcium phosphate crystals in acidic phagolysosomes also activates NLRP3 and the calcium-dependent protease calpain[76], which processes pro-IL-1α into its mature form[73]. However, most crystals and microparticles probably activate NLRP3 by destabilizing lysosomal membranes and by leaking lytic proteases such as cathepsin B into the cytosol[77–79] (FIG. 3). NLRP3 integrates these intracellular danger signals (protease leakage from lysosomes, mitochondrial ROS or potassium efflux) and activates caspase-1, which cleaves pro-IL-1β into its active and secreted form[3]. As the IL-1 receptor (IL-1R) is ubiquitously expressed, IL-1β release spreads the inflammatory signal to surrounding parenchymal cells[80,81]. IL-1R activates the expression of NF-κB-dependent cytokines and chemokines[81]. In addition, crystals activate dendritic cells via direct membrane binding, in a receptor-independent manner that involves cell-surface lipid sorting and subsequent activation of the tyrosine-protein kinase SYK[82].

Crystal-induced release of IL-1β from renal dendritic cells and crystal-induced tubular cell necroptosis cause inflammation. In turn, inflammatory cytokines drive regulated cell death. For example, TNF activates TNF receptor 1, which can trigger necroptosis. This process drives the auto-amplifying loop of renal necroinflammation that promotes AKI[62]. In addition, tubular casts formed by crystals and/or necrotic cell debris can transiently obstruct the tubular lumen, which further contributes to the sudden decline in glomerular filtration rate (GFR) and urine volume (in rhabdomyolysis, cast nephropathy, or tumour lysis syndrome, for example)[83].

Pathomechanisms of crystalline CKD

CKD is a common consequence of genetic disorders that permanently increase the urine concentration of certain minerals or metabolites, such as oxalate in primary hyperoxaluria, uric acid in genetic forms of gout, cystine in cystinosis, and adenine in adenine phosphoribosyltransferase deficiency (TABLE 1). Crystal deposits can accumulate in a so-called stony kidney, which gives a white appearance on ultrasound examination[58] (FIG. 4). The presence of calcium phosphate and calcium oxalate

Ferroptosis
Iron-dependent form of regulated necrosis that involves impaired glutathione peroxidase 4 function and leads to lethal accumulation of lipid peroxides.

Damage-associated molecular pattern
(DAMP). Intracellular components that induce inflammation by activating receptors of the innate immune system on other cells when released into extracellular space after cell necrosis.

Cystinosis
Genetic metabolic disease involving accumulation of cystine in various organs.

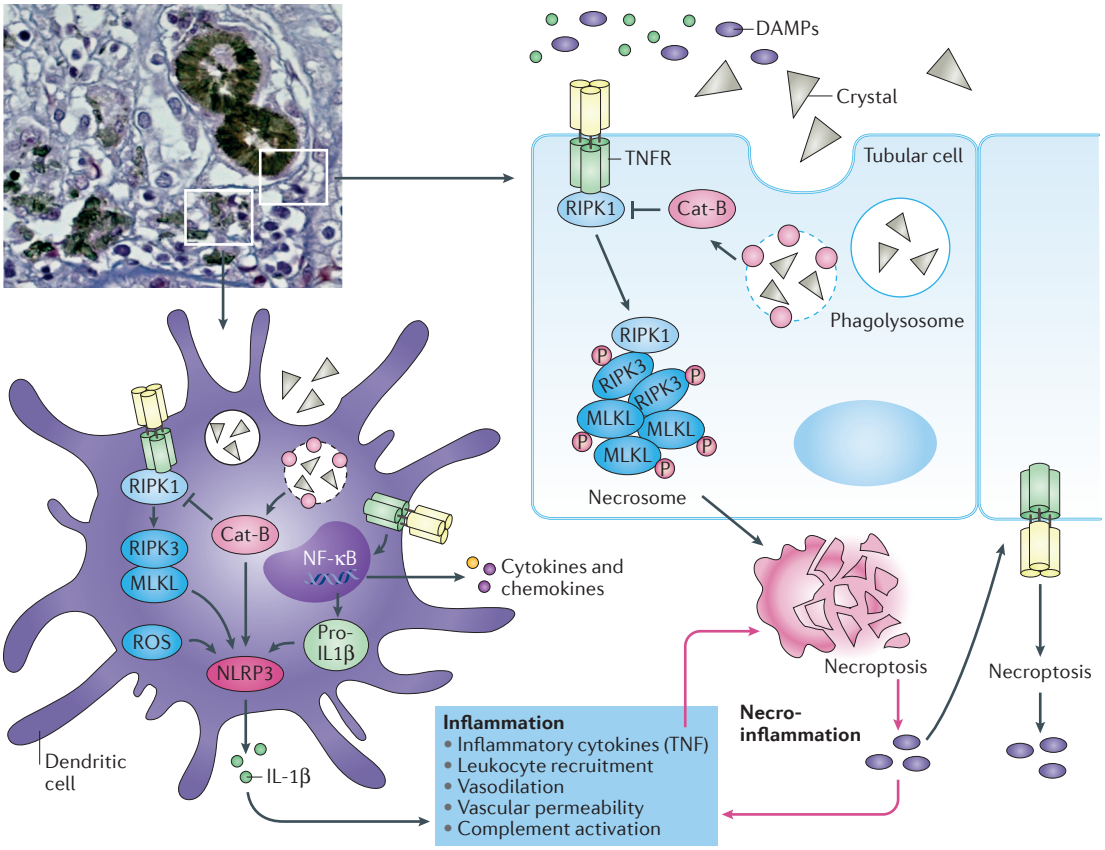


Figure 3 | **Molecular mechanisms of crystal-induced necroinflammation.** Supersaturation of solutes in the urine leads to deposition of crystals in the tubular lumen, which activate signalling pathways that lead to tubular cell death (through necroptosis). Phagocytosis of crystals causes lysosomal destabilization and release of cathepsin B (cat-B), which cleaves receptor-interacting serine/threonine-protein kinase (RIPK) 1, a negative regulator of necroptosis. In conditions where caspase-8 is inhibited, RIPK1 degradation triggers the formation of the RIPK3–MLKL necrosome complex, resulting in tubular cell necroptosis. Dying tubular cells release numerous damage-associated molecular patterns (DAMPs) and alarmins, which initiate inflammation. Dendritic cells and macrophages phagocytose crystals present in the interstitial compartment. Subsequent lysosomal destabilization releases cat-B and reactive oxygen species (ROS), which activate the NLRP3 inflammasome and induce secretion of mature IL-1β by dendritic cells, triggering IL-1 receptor (IL-1R)-dependent inflammation in the kidney. The TNF receptor (TNFR) pathway can activate NF-κB, which contributes to the activation of the inflammasome. RIPK3 and MLKL can also activate the NLRP3 inflammasome but whether this process is triggered by crystals is still unknown. Certain proinflammatory cytokines such as TNF can trigger regulated necrosis in renal cells through the TNFR, leading to further DAMP release. This process leads to an auto-amplification loop of crystal-induced necroinflammation. DAMPs such as histones act as a central mediator of the necroinflammation loop as they induce both Toll-like receptor-dependent inflammation and charge-dependent cell necrosis.

crystals deposits in the renal parenchyma is known as nephrocalcinosis; however, adenine or urate crystals can also form diffuse and prominent deposits without a calcium component.

Crystal precipitates that cause CKD are present in four different intrarenal compartments. First, the proximal tubule reabsorbs large parts of the glomerular filtrate in a process that can lead to the accumulation of small proteins such as immunoglobulin light chains, which can crystallize in the endosomal compartment of proximal tubular cells (FIG. 2). Depending on the dynamics (speed) of crystal accumulation, this process can lead to AKI or CKD. Fanconi syndrome-like dysfunction of the proximal tubule is a typical consequence of this type of tubular injury.

Second, the thick ascending limb of the loop of Henle secretes uromodulin, a sticky glycoprotein that forms waxy aggregates and casts in the distal tubules. Light chains, myoglobin or necrotic tubular cells debris enhance cast formation, which can compromise renal function by obstructing the distal tubules[84]. The distal tubule is also the site of urine acidification, which promotes the precipitation of certain lithogenic solutes such as uric acid. Moreover, the distal tubule also secretes calcium, which contributes to various forms of nephrocalcinosis[58]. Uric acid crystal formation has immunostimulatory and mechanical effects such as activation of the NLRP3 inflammasome and tubule obstruction by crystal plugs[6]. In addition, high concentrations of soluble uric acid can also activate

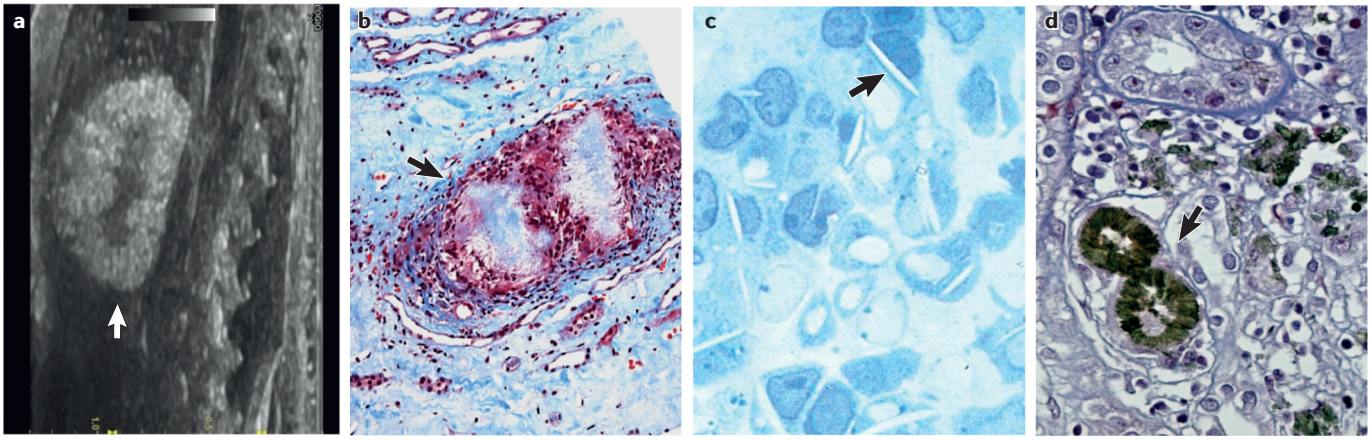


Figure 4 | **Tissular changes in crystalline CKD. a** | Calcium oxalate crystals (white arrow) deposited in murine kidneys visualized by ultrasonography as a 'stony kidney'. **b** | Uric acid tophus (black arrow) found in a renal biopsy sample (trichrome stain) of a 56-year-old patient with a history of hypertension and gout, proteinuria (2.8 g per day) and IgA nephropathy. Urate crystals are surrounded by inflammatory cells including giant cells (seen in haematoxylin and eosin-stained biopsy samples (not shown here)). Image courtesy of Helen Liapis, Arkana Laboratories, USA. **c** | Cystine needle-shaped crystals (black arrow) in interstitial macrophages from a patient with cystinosis. The crystals are water-soluble and appear colourless on formalin-fixed tissue stained with toluidine blue. Image courtesy of Helen Liapis, Arkana Laboratories, USA. **d** | 2,8-dihydroxyadeninuria (DHA) crystals (abundant brown tubular deposits, black arrow) in haematoxylin and eosin stained biopsy samples of a middle-aged adult with chronic kidney disease diagnosed with DHA disease on the basis of decreased adenine phosphoribosyltransferase (APRT) enzyme activity on blood spot. DHA disease due to APRT deficiency leads to conversion of adenine to DHA, which is insoluble and can lead to either nephrolithiasis or crystalline nephropathy. Image courtesy Stanley de Almeida Araujo, Bello Horizonte, Brazil.

innate immune receptors such as TLR4 and induce the expression of components of the inflammasome such as NLRP3 and ASC[85].

Third, with urine concentration, uric acid preferentially precipitates and forms casts in medullary collecting ducts[86]. Cast formation requires crystal adhesion to the luminal tubular cell membrane as an initiating event[87]. Crystal adhesion is mediated or enhanced by several surface molecules such as CD44, annexin II, osteopontin, phosphatidylserine, and hyaluronan[88–90].

Fourth, certain chronic renal crystallopathies are characterized by the presence of crystal granulomas in the interstitial compartment[91–94]. Deposits of intratubular crystals are translocated into the interstitial compartment through extratubulation[93,95,96]. During this process, newly generated tubular epithelial cells encapsulate the intraluminal crystal aggregates by forming new basement membranes at the luminal surface of the crystal plug (FIG. 5). Then, the cells in contact with the crystals undergo atrophy, the tubular basement membrane at this site dissolves and the crystal deposit reaches the interstitial compartment[93]. Through this process, the crystal aggregates are cleared from the tubular lumen and translocated to the interstitial compartment, where they are exposed to mononuclear phagocytes and fibroblasts[97,98]. Interstitial crystal masses are surrounded by macrophages that often have the phenotypic appearance of epithelioid cells or giant cells, hence the name 'crystal granuloma' (REFS 93,99) (FIG. 5). Macrophages contribute to the removal of crystals through phagocytosis and digestion[100–102]. In hyperoxaluric mice, induction of M2 macrophages with CSF-1 suppressed renal crystal formation[103]. Giant cells form in the interstitium by fusion of several macrophages, probably as the result of attempts to ingest large crystal aggregates[104] (FIG. 5).

Although the upregulation of macrophage inhibitory factor expression induced by uric acid crystals is associated with the formation of granulomatous lesions in urate nephropathy[99], the molecular mechanisms that trigger granuloma formation in crystalline CKD are still unknown. Failure to clear crystal masses maintains a local inflammatory response at the centre of the granuloma that is conceptually similar to that triggered by granulomas caused by infectious organisms[105]. The immune response at the periphery of the granuloma rather resembles a wound-healing response characterized by activation of mesenchymal cells that promote tissue fibrosis. This pattern is particularly obvious in gout tophi of the renal medulla (FIG. 5).

Mechanistically, crystal deposits in different regions of the kidney activate the NLRP3 inflammasome and contribute to renal dysfunction. Indeed, *Nlrp3*-deficiency led to reduced renal inflammation during progressive renal failure induced by an oxalate-rich diet in mice[6,7,106]. In addition, inflammasome-independent functions of NLRP3 promote TGF-β receptor signalling and thereby contribute to fibrosis[107–110]. This effect is independent of IL-1β and IL-18 secretion and rather, contributes directly to fibrogenesis. Consistent with these findings, administration of the NLRP3-specific inhibitor CP-456773 attenuated oxalate and adenine crystal-induced inflammation and kidney fibrosis in preclinical nephropathy models induced by oxalate or adenine-rich diets in mice, respectively[111]. Delayed treatment was, however, unable to reverse renal fibrosis once it was established.

Extratubulation
Process of translocation of crystal plugs from the tubular lumen to the interstitium.

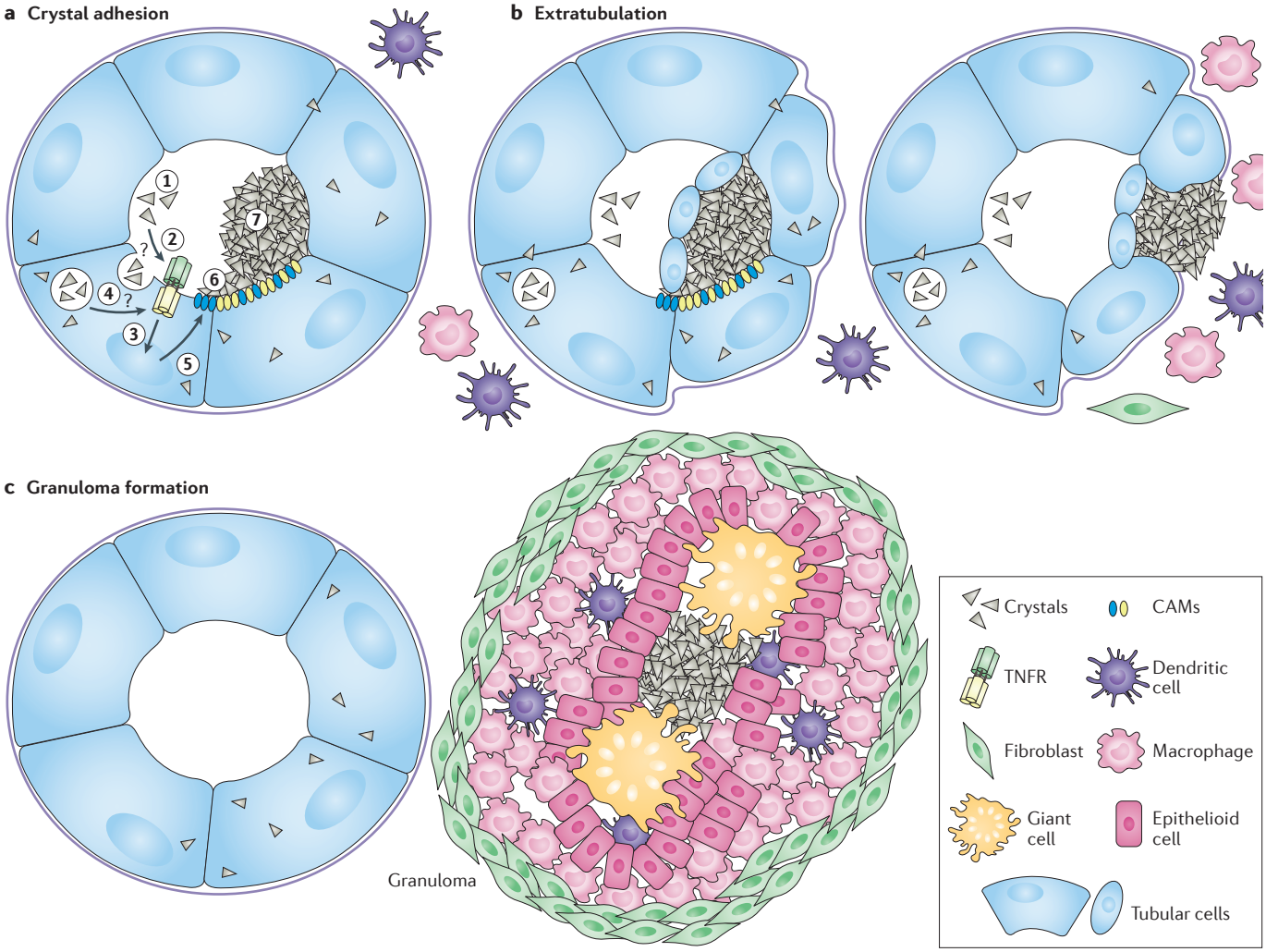


Figure 5 | **Mechanisms of crystal granuloma formation. a** | Supersaturation of calcium oxalate (CaOx) in the urine leads to the formation of CaOx crystal nuclei (1). CaOx crystals activate TNF receptors (TNFRs) 1 or 2 on the tubular cell surface (2), which leads to internalization of TNFRs and activation of the TNF signalling pathway (3). Crystal phagocytosis by tubular cells and lysosome formation could be involved in this process and contribute to activation of theTNFR pathway (4). Activation of the TNF pathway results in increased expression of crystal adhesion molecules (CAMs) such as CD44 and annexin II on the tubular cell surface (5). Crystal nuclei adhere to the CAMs (6) and create a nidus for crystal growth, which leads to crystal plug formation in the tubular lumen and obstruction of the tubule (7). **b** | Tubular cells dedifferentiate and grow on the hard surface of the crystal plug, eventually leading to translocation of the crystal plug into the interstitial compartment. **c** | In the interstitial compartment, frustrated phagocytosis of the large crystal plugs triggers the formation of giant cells (polyploid proinflammatory macrophages), subsequently leading to a granuloma, which isolates the crystal plug from the renal parenchyma.

Therapeutic options

The general approach to limit supersaturation is to increase of fluid intake, ideally with plain water, to reduce the concentration of lithogenic substrates in the glomerular filtrate and the urine. This approach consists of fluid therapy in trauma victims with a diffuse muscle injury, as seen in disaster or battle settings[60].

The central element to curing type 2 crystalline nephropathy is, however, elimination of the lithogenic substrate, which depends on the type of crystal. This strategy can be as simple as stopping the causative drug but it might require stronger courses of action such as chemotherapy to reduce the overproduction of crystal-forming immunoglobulin light chains in the case of multiple myeloma, Controlling inflammatory bowel disease might be needed to normalize oxalate reabsorption from the intestinal tract, or liver transplantation to correct the genetic abnormality that causes metabolism-mediated overproduction of oxalate in primary hyperoxaluria. A calcium-rich diet might help to prevent the intestinal uptake of dietary oxalate[44], or bicarbonate therapy, which can raise urinary pH, might prevent uric acid crystal formation and renal failure in tumour lysis syndrome[112].

In established crystal nephropathy, the aim is to dissolve crystal deposits. To date, only recombinant uricase can dissolve crystals in acute and chronic urate nephropathy[113]. However, currently available formulations of recombinant uricase induce marked

hypersensitivity reactions and lose their efficacy with repetitive use[114]. Experimental studies suggest that inhibitors of necroptosis, such as necrostatin-1, or of the NLRP3–IL-1 axis, such as anakinra (an IL-1 antagonist) or CP-456773, can limit crystal-induced tubular cell necrosis, intrarenal cytokine expression and leukocyte influx as well as renal dysfunction in mice[84,115–117]. An inhibitor of the TNF receptor (TNFR) signalling pathway markedly reduced renal failure in experimental hyperoxaluria-induced nephrocalcinosis[118]. However, the findings of these preclinical studies need to be confirmed.

Urinary tract crystallopathies (type 3)

Urolithiasis refers to the occurrence of stones anywhere in the urinary system (in the kidney (nephrolithiasis), ureter (ureterolithiasis) or bladder (cystolithiasis)). Stones are often present in the renal pelvis, a site that is not necessarily considered as forming part of the kidney; however, stones can cause kidney injury by obstructing urinary outflow, a process that can be associated with inflammation and fibrosis of the kidney. We therefore discuss urolithiasis as a form of crystal nephropathy.

Prevalence and risk factors

Urolithiasis affects 7–11% of the US population with the highest prevalence in white non-Hispanic males[119] and is recurrent in one-third of patients. The presence of kidney stones leads to nephropathy in only a small proportion of stone formers[44].

Minimization of fluid loss and maximization of solute excretion predisposes the urinary tract to stone formation by supersaturation. A large number of factors can contribute to urolithiasis. For example, genetic metabolic diseases that increase the endogenous production and, subsequently, the urinary secretion of oxalate, cystine or uric acid promote crystalluria and calcium oxalate, cystine or uric acid stones, respectively[59]. Another group of disorders induced by stones is associated with variants of genes encoding solute transporters in the nephron that induce abnormal mineral concentrations in the urine[120]. Oxalate-rich diets, fructose-rich drinks, low urine volume due to low fluid intake or excessive extrarenal fluid losses (through sweating or diarrhoea) can contribute to urate microcrystal and stone formation[44,54]. A combination of these factors was proposed to cause kidney injury and renal colic in patients with Mesoamerican nephropathy[54,121].

Clinical presentation

Acute renal colic. Renal colic presents as sudden-onset fluctuating pain in the flank or inguinal region. Unless both urinary tracts are simultaneously affected, oliguria is absent[122]. Pain subsides upon stone passage or removal. The factors leading to calculus mobilization from the calyces of the renal pelvis are still poorly understood. At sites of obstruction, the mechanical forces of ureteric peristalsis together with the rough surface of the calculus can cause mucosal injury, swelling, and bleeding[122]. Renal colic is usually associated with mild hydronephrosis, the degree of which depends on the diameter of the calculi[123]. Although renal colic presents as severe from a clinical perspective, it does not seem to be associated with long-term impairments in urinary tract function[124].

Chronic obstruction. Patients with chronic urolithiasis can present with flank pain, haematuria, dysuria, urinary tract infection or no symptoms. The complaints also vary with the age of the patient — for example, young patients (<60 years) have flank pain more often than older patients (≥60 years), who present more often with other symptoms[125].

Mechanisms of stone formation

Stones do not necessarily form in the bulk urine but their formation can initiate in a tissue-based nidus such as inRandall plaques in the renal pelvis. Randall plaques are interstitial apatite deposits that form along the basement membrane of the thin limb of the loop of Henle, creating apatite plaques at the surface of papillae in the renal pelvis[126,127] (FIG. 6,7). These plaques, which reach deep into the papilla and extend into the basement membrane of the vasa recta[128], are not always associated with stone formation as they are also present in non-stone formers but are the preferred formation sites of stones predominantly composed of calcium oxalate[124]. This association between plaques and stones is visible by endoscopic examination or from obvious plaque attachment sites or the presence of apatite at the former attachment site on free stones[124,129] (FIG. 6). The plaque–stone interface is a multilayer ribbon composed of an alternation of crystals and matrix molecules including urinary proteins such as Tamm–Horsfall urinary glycoprotein (also known as uromodulin)[130,131] (FIG. 6). Uromodulin can inhibit crystal formation in the lumen of distal tubules; however, it also contributes to the matrix of interstitial crystal plaques.

Tubule plugs in Bellini ducts and inner medullary collecting ducts are also sites of stone formation (brushite and hydroxyapatite stones) because urine concentration reaches its maximum in this segment of the renal tubule (FIG. 7). Such plugs occur in patients that form stones owing to procedures such as bariatric surgery, small bowel resection and ileostomy, or systemic diseases such as primary hyperparathyroidism, primary hyperoxaluria and cystinuria[124] (FIG. 6).

Kidney stone formation involves several additional pathomechanisms. The supersaturation of lithogenic substances in the distal loop of Henle leads to crystallization of calcium oxalate, calcium phosphate, uric acid and cystine. Crystal nucleation and growth are, however, limited by the presence of inhibitors of crystal aggregation such as magnesium and uromodulin in the urine[58,132]. Using a computer model, two studies have shown that crystals nucleated close to the wall flow at lower velocities than fluid in the central axis of the tubule and hence interact with the injured epithelium for longer than the surrounding fluid[133,134].

Crystal nucleation can also occur in the tubular lumen of healthy kidneys; however, the healthy tubular epithelium does not present a crystal-binding surface, which

Tubule plugs
Cast-like plugs of crystals that form inside the lumen of renal tubules.

Brushite
Phosphate mineral in complex with calcium ($CaHPO_4{\cdot}2H_2O$).

Hydroxyapatite
Crystals of calcium phosphate usually present in bones, kidney stones, and vascular calcifications.

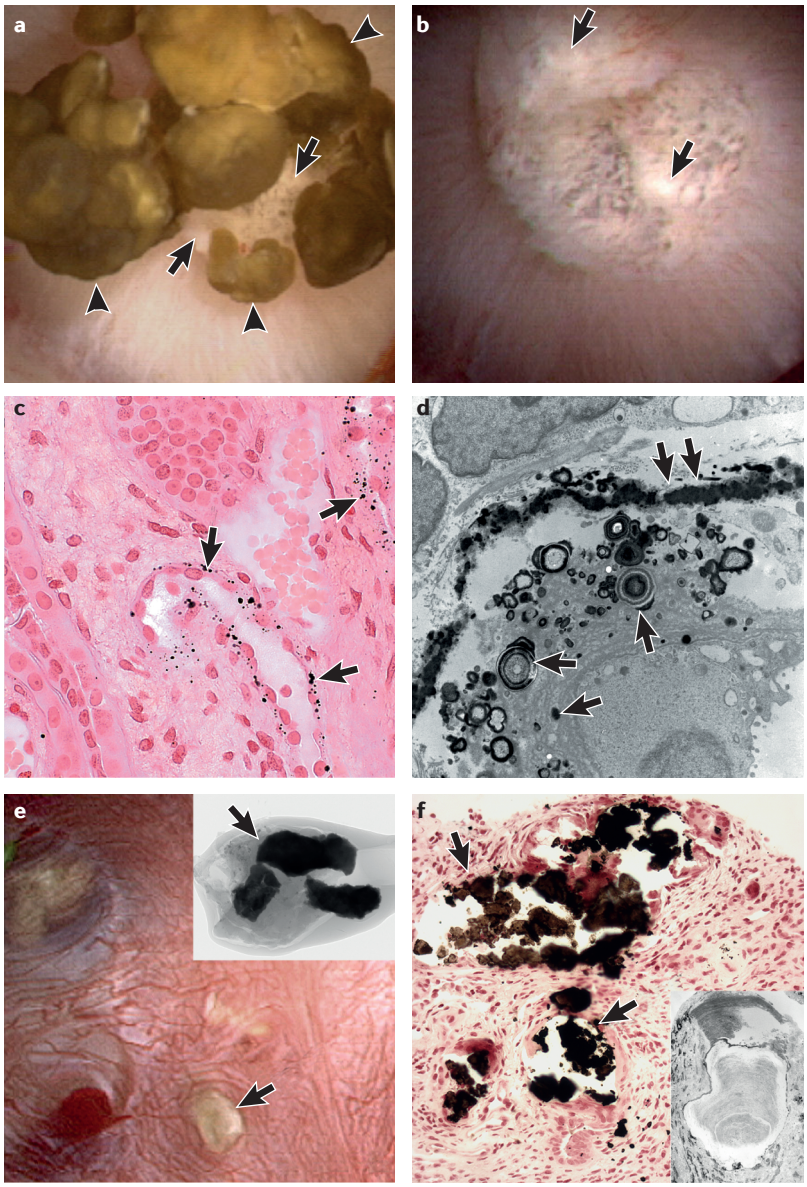


Figure 6 | **Endoscopic and histopathologic changes in papillary biopsy samples from stone formers. a** | Idiopathic calcium oxalate stone formers (ICSFs) with hypercalciuria have calcium oxalate stones (arrowheads) attached to a white Randall's plaque (arrows). **b** | The white, suburothelial sites of the interstitial plaque (arrows) are easily visible after the attached stones have been removed using percutaneous nephrolithotomy or ureteroscopic lithotripsy. **c** | The initial formation sites of Randall's or interstitial plaques are in the basement membranes of thin loops of Henle (arrows). **d** | The plaque forms as spherical deposits of alternating layers of crystals (electron lucent) and matrix (electron dense) materials (arrows). The interstitial plaque appears as islands of crystals and matrix (double arrows) in the interstitial space. **e,f** | Another histopathologic change that occurs in most stone formers except ICSFs with hypercalciuria is the presence of intraluminal plugs usually in the ducts of Bellini (panel **e**, arrow) and inner medullary collecting ducts (panel **f**, arrows, von Kossa staining), as seen in this stone former with primary hyperparathyroidism. The insert in panel **e** shows several inner medullary collecting duct plugs seen by micro-computed tomography. The insert in panel **f** shows an inner medullary collecting duct plug seen by transmission electron microscopy. Panels **a** and **b** reproduced with permission from Elsevier © Evan A. *et al.*, *Kidney Int.* **69,** 1313–1318, (2006). Panels **c** and **d** reproduced with permission from Springer Link © Evan A. P. *et al.*, *Urolithiasis* **43,** 19–32, (2015). Panels **e** and **f** reproduced with permission from Elsevier © Evan, A.E. *et al.*, *Kidney Int.* **74,** 223–229, (2008).

prevents crystal adhesion in the lumen[58,134,135]. Loss of epithelial integrity after an injury and the absence of inhibitors of aggregation enhances crystal adhesion to the tubular epithelium[58,134]. Using a murine model of hyperoxaluria-associated kidney stone disease[136], we recently showed that TNFRs mediate the adhesion of calcium oxalate crystals to the tubular epithelium by inducing the expression of crystal adhesion molecules at the luminal surface[118] (FIG. 5). In mice deficient in TNFR1 or TNFR2 the expression of adhesion molecules was not induced in tubular cells and intrarenal calcium oxalate crystal deposits were not formed despite severe hyperoxaluria[118]. In addition, Randall plaques which as mentioned above can form in the basement membrane of the thin limbs of the Loop of Henle and the vasa recta in the papilla in vascular crystal nephropathies[128,137], serve as precursors for calcium oxalate stones[126], although the process of by which calcium oxalate stones eventually grow on Randall plaques and Randall plugs in the ducts of Bellini, remains poorly understood.

The injury induced by apatite stones fosters calcium oxalate crystal attachment to the tubule basement membrane, which supports the 'free and fixed particle' theories, according to which stone development requires crystal formation in the tubular fluid and subsequent crystal retention and accumulation in the renal pelvis[138–140]. Other factors can also control crystal growth on plugs; for example, the composition of the plug itself, urine flow, urine supersaturation and urine molecules deposited on the plug[140,141].

Stone-induced renal injury

Several studies have shown that oxalate or calcium oxalate crystals induce oxidative stress, which is involved in the development of calcium oxalate-induced nephrolithiasis[142–145]. The inhibition of the NADPH oxidase family of enzymes, which catalyse ROS production, with antioxidants such as apocynin or free radical scavengers such as vitamin E, reduced calcium oxalate crystal deposition and subsequent renal injury in hyperoxaluric rat kidneys[144,146,147]. NADPH oxidase-mediated production of ROS is proposed to regulate the urinary macromolecular mediators of stone formation such as matrix Gla protein, adhesion molecules and uromodulin[148]. In addition, the renin–angiotensin system activates NADPH oxidase and is involved in the development of tubulointerstitial lesions caused by calcium oxalate crystals[149–151]. Interestingly, although supplementation with the antioxidant potassium citrate reduced oxidative stress in patients with renal stones, it did not reduce renal damage[152].

Therapeutic options

Treatment of acute renal colic focuses on immediate pain relief, stone passage or stone removal. Current treatment options for urolithiasis are chemolitholysis or active stone removal. Oral chemolitholysis is used for renal stones that are composed of uric acid[153]. The main principle is alkalization of the urine using oral alkaline citrate or sodium bicarbonate preparations to adjust the pH of urine to 7.0–7.2 (REF. 153). Procedures for active stone removal include extracorporeal shock wave lithotripsy (SWL)[154],

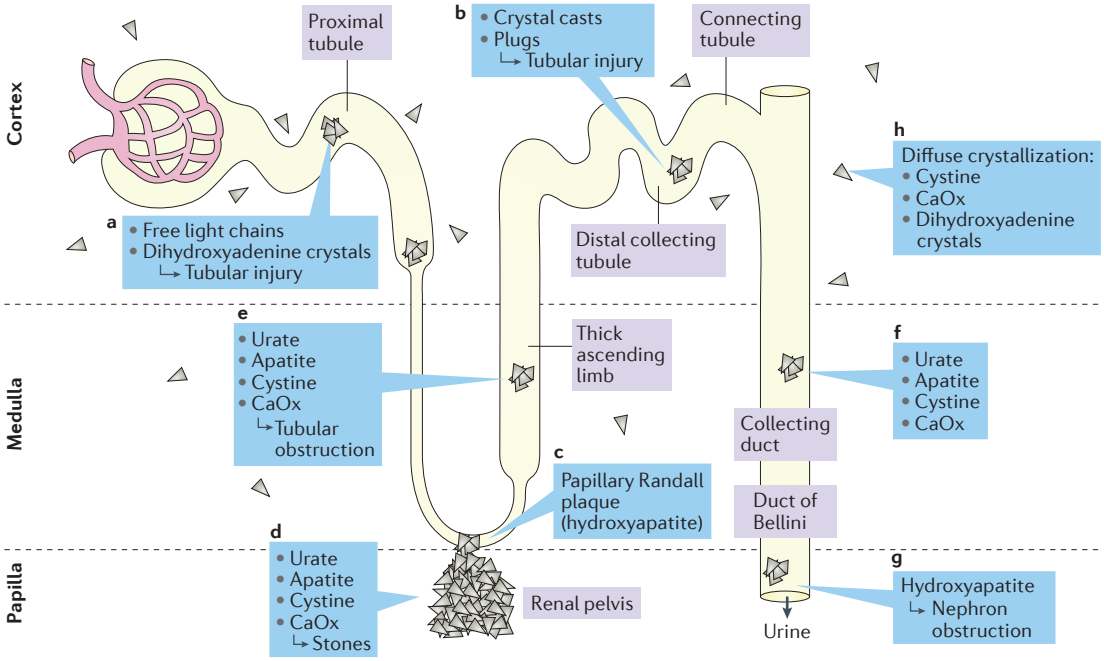


Figure 7 | **Overview of crystal deposition in the different compartments of the kidney and segments of the nephron. a** | Particles such as free immunoglobulin light chains enter the proximal tubule in the ultrafiltrate. They are taken up by proximal tubular cells and can lead to proximal tubule injury. **b** | Cystal or plug formation in the distal collecting tubule also cause tubular injury. **c** | Interstitial hydroxyapatite deposits at the inner medulla around the tips of the loops of Henle can form Randall plaques, which serve as a papillary nidus for the formation of calcium oxalate (CaOx), urate, apatite or cystine stones inside the renal pelvis (panel **d**). **e** | The thick ascending limb of the loop of Henle is the site of Tamm–Horsfall protein (uromodulin) secretion, which promotes the formation of casts and crystal plugs at this site. Such plugs and casts can lead to tubule obstruction further downstream in the nephron. **f** | Urine concentration and acidification in the collecting ducts promotes crystallization of many minerals as well as uric acid. **g** | The duct of Bellini — the terminal part of the collecting duct — is a preferred site of hydroxyapatite plug formation, which obstructs the outflow of numerous of nephrons that feed into this collecting duct. **h** | Diffuse crystallization with formation of microcrystals can occur in the interstitial compartment and can also affect the cortex. This process activates interstitial dendritic cells to produce inflammatory mediators.

percutaneous nephrolithotomy (PCNL)[155], ureterorenoscopy for renal stones[156] and open laparoscopic surgery for removal of renal stones[157]. The choice of technique usually depends on the size of stone. For example, PCNL is preferred for stones >20 mm diameter, SWL for stones 10–20 mm diameter, whereas stones <10 mm diameter are treated using either SWL or retrograde intrarenal surgery. For the management of ureteral stones, percutaneous antegrade ureteroscopy[158] and SWL[159] can be used. When SWL fails, the stone is removed using ureteral laparoscopy[160].

Conclusions

Crystalline particles can cause kidney injury through different mechanisms depending on their size and the renal compartment in which they form or are present (FIG. 7). The classification of crystal nephropathies proposed here follows the classical concept of prerenal, intrarenal, and postrenal kidney injury because crystals that obstruct vascular flow into the kidney, the tubules or the renal outflow along the urinary tract cause different clinical presentations, have different underlying molecular mechanisms, and need different diagnostic or therapeutic management strategies. The link between these seemingly disconnected disorders is the shared biology of crystal handling by parenchymal and immune cells. A better understanding of crystal biology will eventually help to improve patient outcomes by defining novel cellular and molecular targets to limit nephron loss and to maintain renal function.

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