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PERSPECTIVES

Genetic Causes of Renal Lithiasis

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Abstract

The great majority of renal stones are made of calcium, phosphate, oxalate or uric acid. The frequency of familial cases of renal stones and studies of nephrolithiasis occurrence in monozygote and dizygote twins suggest that genetic factors contribute significantly to renal stone formation. Disorders that alter ion transport in the kidney or in the intestine or that are associated with impaired bone formation may augment the risk of renal stone formation by increasing urine saturation. Recent data indicate that in most cases, renal stones form at the tip of the loop of Henle and then grow at the surface of the papilla by heterogeneous nucleation. Increasing knowledge of physiology and the targeted disruption of genes in mice have facilitated the identification of mutations or rare polymorphisms in various genes in humans. In this review we consider the pathophysiology of renal stone formation and describe the genetic disorders associated with nephrolithiasis.
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Introduction

Renal lithiasis is a frequent and recurrent disorder that affects 6 to 12% of people during their lifetime (1). Renal stones induce acute painful episodes, but this is a chronic disorder that can progressively alter renal function. Most renal stones (85%) are made of calcium and are frequently associated with an inappropriate control of calcium or phosphate balance that can lead to bone demineralization (2). Environmental factors, diet in particular, may increase the risk of renal stone formation, but familial aggregates of nephrolithiasis suggest that genetic factors also predispose to stone formation (3-5). Comparisons of renal stone occurrence in monozygote and dizygote twins further supports the role of genetic factors in renal stone formation (6;7). Over the past 10 years the causes of several genetic disorders associated with nephrolithiasis or bone demineralization have been identified and have greatly improved our knowledge of the mechanisms of renal stone formation and of calcium and phosphate homeostasis. In this review we consider genetic disorders associated with renal stone formation and focus on calcium and phosphate disorders.

General Mechanisms of Kidney Stone Formation

The main risk factors for renal stone formation that have been identified are: low urine output, excretion of excessive amount of various poorly soluble substances (such as calcium, phosphate, oxalate, and uric acid) and the pH of urine. These factors are partially determined by individual genetic characteristics.

Low urine volume excretion increases urine saturation, and slows urine flow rate, two conditions that facilitate crystal deposition and stone formation. Urinary output depends on fluid intake. It is unknown whether genetic factors can directly influence the amount of fluid ingested in humans, by

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modifying the feeling of thirst, for instance, but the ability of the kidneys to concentrate urine and consequently fluid output and intake partially depends on genetic characteristics. Low urine output can augment the number of new stones formed or their growth rate. Recent data suggest that the risk of renal stone formation is probably dependent as much on urine saturation in the thin limb of the loop of Henle as on saturation of final urine. Indeed, in idiopathic calcium stone formers, crystallization takes place in the thin limb of the loop of Henle where urine concentration is maximal due to water retrieval in the descending limb. Urine saturation in this part of the tubule is largely independent of final urine density but depends strongly on calcium, phosphate, oxalate, uric acid and in pathological conditions amino acid concentrations in the primary urine, all ions that are reabsorbed in the proximal tubule. Biopsies performed in idiopathic calcium stone formers have revealed that calcium-phosphate crystals (hydroxyapatite) form in the thin limb of the loop of Henle and then spread through the interstitium to the papilla and form plaques where heterogeneous nucleation will allow the growth of calculi by calcium oxalate deposits (8) (Fig. 1). Hence, disorders that prevent these substances from being reabsorbed in the proximal tubule may increase the risk of renal stone formation. An excess of oxalate in the final urine can increase the risk of transformation of crystals into stones and accelerate stone growth. Calcium hydroxyapatite and uric acid crystal solubility vary with pH, and genetic disorders that alter proton excretion and urine pH are associated with renal stone formation.

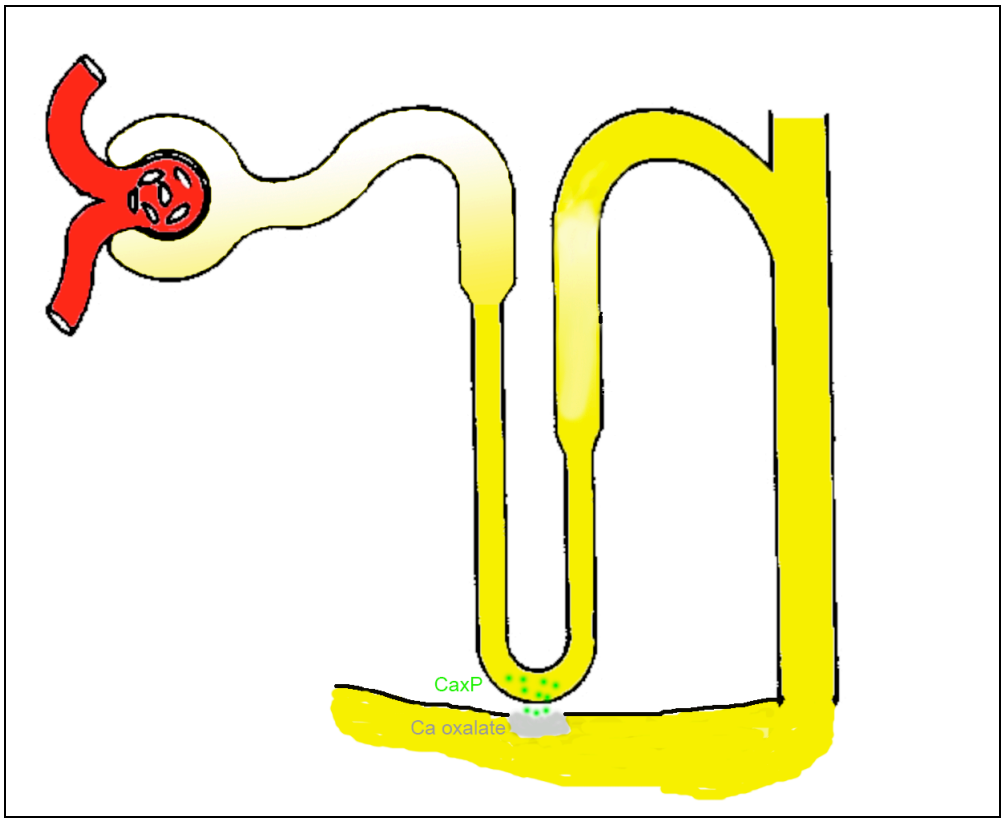

Fig. 1. Mechanism of formation and growth of renal stones. Urine concentration increases along the descending limb of the loop of Henle because of water retrieval. Ion concentration increases, and calcium-phosphate crystals can form and precipitate at the tip of the loop of Henle. Crystals spread through the interstitium to the papilla. Calcium oxalate present in the final urine is poorly soluble and can aggregate to calcium-phosphate crystals initiating the formation and the growth of renal stones.

Hypercalciuria Associated with Genetic Disorders

Urinary calcium excretion depends on calcium intake and intestinal calcium absorption. Genetic factors may influence calcium uptake by intestinal cells. In the intestine, calcium is absorbed by two mechanisms: passive paracellular and active transcellular pathways. Calcium absorption through the paracellular pathway is directly correlated with diet calcium content while the active pathway is hormonally regulated. Active calcium absorption involves specific calcium channels (TRPV5, TRPV6) expressed at the cell surface of enterocytes, intracellular calcium-binding proteins 9k and 28k, calcitriol and the vitamin D receptor. Mutations of these proteins might modify intestinal calcium absorption and consequently renal calcium excretion. The targeted disruption of TRPV6 in mice decreases intestinal calcium absorption by 60%, however, these mice are hypercalciuric because of the deletion of TRPV6 in the kidneys that also alters urinary calcium reabsorption (9). Bone mineral density is low in these mice but it has not been reported whether they had renal lithiasis. The targeted disruption of TRPV5 in mice increases intestinal calcium absorption because of high serum calcitriol concentration secondary to urinary calcium loss and PTH stimulation (10;11).

Increased intestinal calcium absorption might be due to hypersensitivity to calcitriol or to an overproduction of calcitriol. Several studies have looked for mutations in the genes encoding the vitamin D receptor or 1 α-hydroxylase in hypercalciuric stone formers (12;13). No significant associations have been reported in large populations for the 1 α-hydroxylase gene, however, this may be due to heterogeneity of subject phenotypes. Polymorphisms in the vitamin D receptor gene associated with renal stone formation have not been identified thus far (14).

Hypercalciuria Can Be Primary Due to Inappropriate Calcium Reabsorption by Renal Tubules

Plasma calcium that is not bound to proteins is filtered at the glomerulus. The proximal tubule reabsorbs sixty percent of the filtered calcium. Calcium transport is driven by water and osmole reabsorption through a paracellular pathway. Proximal tubulopathies impair calcium reabsorption inducing hypercalciuria. In Wilson's disease nephrolithiasis is not an uncommon finding and can be a presenting sign.

In the thick ascending limb of the loop of Henle, calcium is reabsorbed by a sophisticated mechanism (Fig. 2). At this site, calcium reabsorption is driven by a lumen-positive transepithelial potential generated by sodium-potassium-chloride transport. The decrease in sodium chloride reabsorption in this part of the nephron lowers calcium transport as observed in Bartter syndrome. This disorder can be due to loss-of-function mutations in the Na-K-2Cl transporter, the potassium channel ROMK, the chloride channel (ClCKa-b) or an associated protein (Barttin) (15-19). Patients have hypercalciuria associated with nephrolithiasis. Activating mutations of the calcium-sensing receptor (CaSR), which controls ROMK activity, also decrease renal calcium reabsorption, inducing hypocalcemia with hypercalciuria and renal lithiasis (19). Polymorphisms in the CaSR gene also modify the risk of renal stone formation (20).

The selective permeability of the paracellular pathway to calcium and magnesium is due to the expression of paracellin or claudin 16. This protein acts as a specific gate for calcium and magnesium. Mutations in paracellin abolished the permeability of the paracellular pathway to calcium, and are a rare cause of hypercalciuria, hypomagnesemia and calcium renal stones (21).

Variants in the gene encoding claudin 14 have recently been associated with kidney stones and low bone mineral density in a genome-wide association study performed

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in patients from The Netherlands, Iceland and Denmark (22). Claudin 14 is a tight junction protein expressed in the proximal tubule and in the loop of Henle (23). The mechanism by which these variants are associated with renal stones is unclear since they were not associated with calcium or phosphate concentration in plasma and urine. However, they were significantly associated with serum PTH and bone marker concentrations, which may explain the reduced bone mineral density.

Ten percent of the calcium filtered by the glomerulus is reabsorbed in the distal tubule by a mechanism similar to that present in the intestine. Calcium is actively reabsorbed by a transcellular pathway that requires TRPV5, TRPV6 and calbindin protein expression. Abolition of expression of these proteins in mice induces hypercalciuria, and on this basis, genomic DNA of hypercalciuric humans has been screened for mutations in these proteins, but the results are negative thus far (24).

Excessive bone resorption releases calcium and phosphate and induces hypercalciuria associated with hyperphosphaturia. Bone resorption can be induced by an overproduction of PTH or calcitriol. This is the case in primary hyperparathyroidism. Abnormal bone resorption can also be

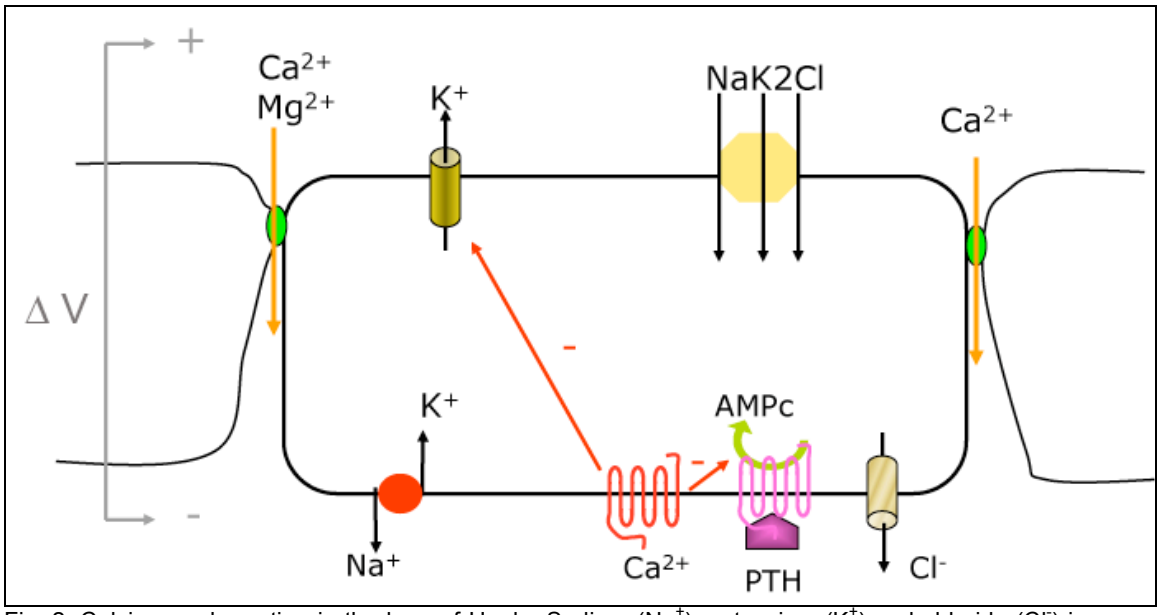

Fig. 2. Calcium reabsorption in the loop of Henle. Sodium (Na^+), potassium (K^+) and chloride (Cl^-) ions are reabsorbed from urine through the Na-K-2Cl transporter. K^+ returns into the tubule lumen through the potassium channel ROMK. The recycling of K^+ generates a lumen-positive transepithelial potential (ΔV) that drives calcium and magnesium paracellular transport. Cl^- leaves the cells at the basolateral domain through a chloride channel. Selective reabsorption of Ca^{2+} and Mg^{2+} is due to paracellin expression in the tight junction complex. Ca^{2+} reabsorption is controlled by the calcium-sensing receptor (CaSR) and parathyroid hormone (PTH) that modify ROMK and Na-K-2Cl activities. Inhibition of NaCl reabsorption decreases the transepithelial voltage and the reabsorption of Ca^{2+}.

observed in primary bone diseases. An increase in urinary excretion of calcium of bone origin can be observed in various forms of osteogenesis imperfecta and in McCune-Albright syndrome, which is due to postzygotic mutation of a small G-protein (GNAS1), however, nephrolithiasis is rare in these disorders.

Several studies have reported lower bone mineral density in renal calcium stone formers than in controls. The mechanism underlying this finding is not clear, but it may involve hyper-responsiveness to calcitriol or to PTH or bone abnormalities. However, low bone mineral density in calcium stone formers has not been associated with

increased bone resorption or with mutations or polymorphisms.

Abnormal Renal Phosphate Reabsorption

Phosphate can combine easily with calcium and form insoluble crystals. In the kidneys, phosphate is reabsorbed exclusively in the proximal tubule mainly through two sodium-phosphate cotransporters: NPT2a and NPT2c. Phosphate uptake is inhibited by two hormones: PTH and fibroblast growth factor 23 (FGF23) (25). Several lines of evidence, in human and in animal models, support the role of increased phosphate urinary excretion in calcium renal stone genesis. An inappropriate decrease in the capacity of the kidney to reabsorb phosphate in the absence of hormonal dysfunctions, leading to hypophosphatemia and hyperphosphaturia, is observed in 20% of stone formers when they are no longer suffering from their renal colic (26). In spontaneously hypercalciuric rats, decreasing urinary phosphate excretion by a low phosphate diet markedly decreases nephrolithiasis formation while urinary calcium excretion is further increased (27). The targeted disruption of the NPT2a gene in mice impairs renal phosphate reabsorption and induces calcium stone formation (28;29). Heterozygous inactivating mutations in NPT2a in humans induce hypophosphatemia, renal phosphate loss and nephrolithiasis or bone demineralization (30). A similar phenotype has been observed in patients with mutations in NPT2c (31-33). Surprisingly, NPT2c knockout mice are hypercalciuric but have normal serum phosphate concentrations, and urinary phosphate excretion, and do not have renal lithiasis (34).

In Jansen's syndrome, gain-of-function mutations of the PTH receptor type 1 (PTHR1) increase cAMP production in the absence of PTH, induce hypercalcemia, hypercalciuria, hyperphosphaturia, nephrolithiasis and also bone deformations (35). In this disorder, hypercalciuria is due to bone resorption and hyperphosphaturia to low phosphate uptake in the proximal tubule due to PTHR1 signaling in the absence of PTH.

Recently, mutations in the NHERF1 protein have been identified in patients with renal phosphate loss and nephrolithiasis or bone demineralization (36). NHERF1 is a protein with two PDZ domains that can interact with the carboxy terminal extremity of PTH1R and NPT2a. *In vitro* studies carried out in cells in culture showed that co-expression of NHERF1 with PTHR1 blunts PTH-induced cAMP synthesis. The targeted disruption of NHERF1 in mice impairs renal phosphate reabsorption and results in hypophosphatemia and nephrolithiasis (37). In human kidneys, NHERF1 is expressed exclusively in the proximal tubule (38). By screening patients with normal or decreased capacity of the kidney to reabsorb phosphate, we have found various mutations in the NHERF1 gene in patients with impaired phosphate renal reabsorption (36). These patients had increased urinary excretion of cAMP contrasting with normal plasma PTH concentrations. Expression of the NHERF1 mutants in renal cells in culture revealed that the mutations suppressed the inhibitory role of NHERF on cAMP production in response to PTH. Hence, the identified mutations induced a hyperresponsiveness of the renal proximal tubule to PTH. The patients with the mutations were not hypercalcemic and had no bone deformities, which is explained by the restricted co-expression of NHERF1-PTH1R to renal proximal tubular cells. Interestingly, one of the NHERF1 mutants identified seems to be a rare functional polymorphism, suggesting that mutations in the NHERF1 gene may not be a rare finding among stone formers with renal phosphate leak.

The risk of renal stone formation induced by renal phosphate loss seems to be influenced by serum calcitriol concentration and urinary calcium excretion. Hence the disruption of the 1α-hydroxylase gene in NPT2a knockout mice markedly reduces nephrolithiasis formation (39). Overexpression of FGF23, which inhibits NPT2a and NPT2c, induces marked renal phosphate leak and decreases 1α-hydroxylase expression and plasma calcitriol concentration, and does not induce renal stone formation except when patients are treated with high doses of calcitriol. We

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have also observed that in subjects with renal phosphate loss, urinary calcium excretion and serum calcitriol concentration were significantly higher in patients with renal lithiasis than in those with no lithiasis (40) (Fig. 3). Hence the consequences of renal phosphate leak may depend on the capacity of patients to increase calcitriol concentration in response to hypophosphatemia.

Impaired renal phosphate reabsorption is almost constant in proximal tubulopathies and is often associated with hypercalciuria and nephrolithiasis. This is the case in Dent's disease, caused by mutations in the chloride/proton exchanger ClC-5. These mutations may impair endocytosis of PTH present in the primary urine by proximal tubular cells. PTH that remains in urine may stimulate apical PTH1R and reduce NPT2a expression (41). The resulting hypophosphatemia would stimulate calcitriol synthesis, intestinal calcium absorption and consequently would increase urinary calcium excretion.

Wilson's disease associates hypercalciuria, hyperphosphaturia and renal stones or osteoporosis. Similar findings are observed in tyrosinemia type 1, glycogen storage disease type 1a or Lowe occulocerebrorenal syndrome.

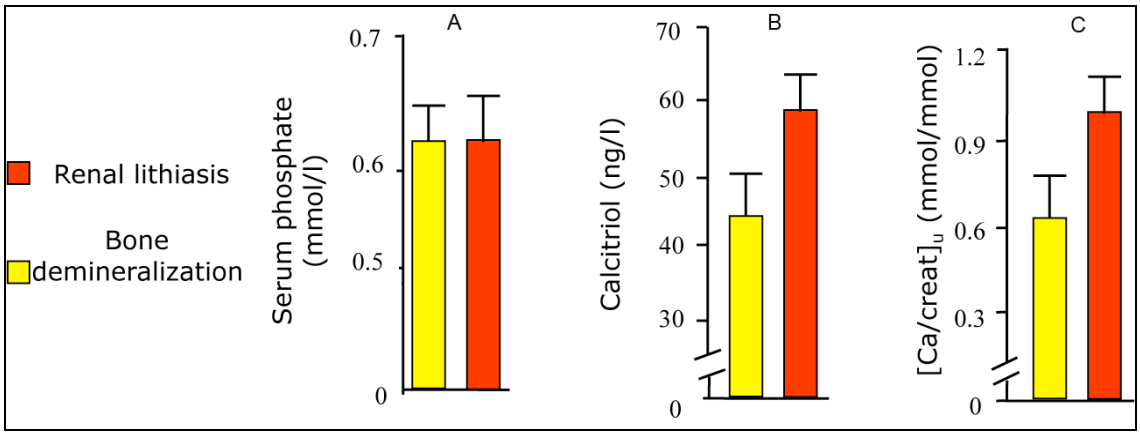

Fig. 3. Comparison of serum calcitriol concentration and urinary calcium excretion in patients with renal phosphate leak and renal lithiasis or bone demineralization. Serum concentration of phosphate was similarly low in patients with renal phosphate leak or bone demineralization (A). Serum calcitriol concentration (B) and urinary calcium excretion expressed as the ratio of calcium to creatinine in urine (C) were significantly higher in renal stone formers than in subjects with bone demineralization.

Increased Excretion of Oxalate

Elevated urinary oxalate excretion is critical for the growth of renal stones. Oxalate comes from the diet and is produced by the liver and erythrocytes from glyoxalate. It is filtered freely at the glomerulus and probably reabsorbed and then secreted in the proximal tubule. In the intestine, oxalate is also absorbed and secreted, but absorption exceeds secretion. Enzymatic defects (primary hyperoxalurias) can induce oxalate overproduction. The SLCA26A6 gene encodes an oxalate-chloride exchanger that is expressed in the intestine and in the renal proximal tubule (42). The disruption of this gene in mice results in an increase in oxalate plasma concentration, hyperoxaluria and renal calcium oxalate stone formation (43). The role of SLC26A6 is probably to secrete oxalate in feces. Its role in the proximal tubule is not clear. Mutations in this gene have not been identified in humans. In the vast majority of calcium stone formers, oxalate plasma concentration is normal and urinary oxalate excretion is not markedly increased, however, intermittent moderate levels of oxalate in urine may promote renal stone growth.

Uric Acid

Uric acid stones are less frequent than calcium stones and they represent 5 to 10% of nephrolithiasis. Uric acid is the final breakdown product of purine metabolism and it also derives from amino acid catabolism. Two-thirds of uric acid production are eliminated by the kidneys in humans. Uric acid is filtered at the glomerulus and then it is almost completely reabsorbed in the initial part of the proximal tubule (S1) by at least two transporters, URAT1 (SLC22A12) and GLUT9 (SLC2A9) (44;45). A member of the ATP-binding cassette family (ABCG2) is expressed in proximal tubular cells and secretes urate in the urine (46). Two factors increase the risk of uric acid stone formation: low pH and hyperuricosuria. Genetic disorders can increase uric acid production or alter urate tubular transport. An increase in uric acid production induces hyperuricemia, as is the case in hypoxanthine-guanine phosphorybosyl transferase or in glucose 6 phosphatase deficiencies, and in phosphorybosyl pyrophosphate synthetase over-activity. In contrast, mutations in urate transporters result in hyporuricemia and hyperuricosuria. Hence loss-of-function mutations in the URAT1 transporter decrease urate reabsorption in the proximal tubule (47). Genome-wide association studies have identified a link between polymorphisms in the gene encoding SLC2A9 and uric acid plasma concentration. Functional experiments showed that SLC2A9, which is expressed at the apical and basolateral sides of proximal tubular cells, transports urate, and that polymorphisms decrease urate uptake increasing uric acid excretion in urine (48). Inactivating mutations in the ABCG2 gene have been identified and they increase uric acid plasma concentration and are a cause of gout but are not associated with nephrolithiasis (46).

Renal Acidosis

Urinary pH determines the solubility of various substances in urine. Low pH decreases uric acid solubility but prevents calcium-phosphate crystal formation in contrast to a pH ≥ 7 that augments urate solubility but precipitates calcium-phosphate salts. Urinary pH depends on the proton load in the diet and on the ability of kidney to buffer free protons in urine. Renal acidosis is due to a defect of the renal tubule in secreting protons while buffers are normally produced, resulting in urinary pH > 5.5 and in metabolic acidosis. Patients with renal acidosis frequently have hypercalciuria and hyperphosphaturia. This may be due to calcium and phosphate release from bone because of proton buffering by bone. Nephrolithiasis and nephrocalcinosis are frequent in these disorders. Distal renal acidosis is due to mutations in the chloride-bicarbonate exchanger or in proton ATPase subunits (49).

Cystinuria

Cystine solubility in urine is low and increases as the pH increases. In the proximal tubule cystine is reabsorbed by the amino acid transporter B^0AT1. This transporter is a heterodimer composed of a light chain subunit, amino acid transporter and a heavy chain subunit (rBAT) that is mandatory for the correct targeting of the transporter to the brush border membrane (50). Mutations in each subunit have been identified in patients with cystinuria. Maintaining a daily urinary output > 4L with an alkaline pH, reducing cystine intake in the diet and using substances that form soluble dimers with cysteine reduce the risk of stone formation and of deterioration of renal function.

Conclusion

Many genetic disorders increase the risk of renal stone formation. In many cases renal stone formation requires the association of genetic and environmental factors. In about 10% of renal lithiasis a genetic disorder can be identified. We probably underestimate this frequency because patient phenotypes are not thoroughly studied. Furthermore, many still unidentified genes can contribute to altering calcium or phosphate transport in the kidneys, intestine or bone. Genome-wide association studies or linkage studies can both contribute to the identification of these

genes; a comparison of the advantages and limitations of these methods has been published recently (51).

Conflict of Interest: None reported.

Peer Review: This article has been peer-reviewed.

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