What is nephrocalcinosis?

Linda Shavit[1], Philippe Jaeger[2] and Robert J. Unwin[2]

[1]Adult Nephrology Unit, Shaare Zedek Medical Center, Jerusalem, Israel and [2]UCL Centre for Nephrology, Royal Free Campus and Hospital, University College London, London, UK

The available publications on nephrocalcinosis are wide-ranging and have documented multiple causes and associations of macroscopic or radiological nephrocalcinosis, most often located in the renal medulla, with various metabolic and genetic disorders; in fact, so many and various are these that it is difficult to define a common underlying mechanism. We have reviewed nephrocalcinosis in relation to its definition, genetic associations, animal models, and putative mechanisms. We have concluded, and hypothesized, that nephrocalcinosis is primarily a renal interstitial process, resembling metastatic calcification, and that it may have some features in common with, and pathogenic links to, vascular calcification.

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Correspondence: *Robert J. Unwin, UCL Centre for Nephrology, Royal Free Hospital and Campus, University College London, Rowland Hill Street, London NW3 2PF, UK. E-mail: robert.unwin@ucl.ac.uk*

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Strictly, the term 'nephrocalcinosis' refers to the generalized deposition of calcium oxalate (CaOx) or calcium phosphate (CaPi) in the kidney. However, in most cases, deposition seems to be interstitial, and this is what nephrocalcinosis is now generally taken to mean. Although some authorities may limit the definition of nephrocalcinosis to the deposition of mainly interstitial CaPi crystals, this is not universally acknowledged, and thus for the purposes of this review we have retained the broader definition of nephrocalcinosis to include both CaPi and CaOx deposition. When high-resolution Fourier transform infrared microspectroscopy and electron diffraction have been used to investigate the composition of Randall's plaque (areas in the renal papillae containing interstitial apatite deposits that can serve as a nidus for urothelial surface CaOx deposition), CaPi crystals are detected as their major component.[1] However, CaOx calculi overlie and adhere to Randall's plaque in up to 50% of stone formers.[2] Therefore, concurrent deposition of both hydroxyapatite and CaOx crystals may occur in the same patient with nephrocalcinosis. CaPi is present as crystalline apatite, but it is not known whether amorphous deposits of CaPi also occur.

A variety of inherited and acquired diseases have been associated with nephrocalcinosis and recognized as potential causes. Nephrocalcinosis can be classified in three ways that represent increasing degrees of severity of renal involvement:[1] *molecular or chemical*, often observed in patients with overt hypercalcemia and which is usually reversible when hypercalcemia is corrected;[2] *microscopic*, which in most cases is a precursor to macroscopic nephrocalcinosis and is diagnosed by identification of mineral deposits on light microscopy of renal tissue;[3] and *macroscopic*, in which calcification is visible on either a plain abdominal X-ray or ultrasound scan and/or confirmed by a computed tomography scan, is the well-known clinical and diagnostic feature of nephrocalcinosis. Although the clinical presentation and outcomes of these forms of nephrocalcinosis can be different, in clinical practice there is often some overlap.

Nephrocalcinosis usually involves the renal medulla (in 97% of patients) or, less often, the cortex. Cortical nephrocalcinosis has been described in patients with renal cortical necrosis (typically, and originally described, following postpartum hemorrhage), chronic glomerulonephritis or pyelonephritis, primary and secondary oxalosis (which are more often causes of medullary nephrocalcinosis), autosomal recessive polycystic disease, chronic renal allograft rejection, and benign nodular cortical nephrocalcinosis.[3]

In this review, we try to summarize the extensive literature on multiple causes of macroscopic medullary nephrocalcinosis, and their implication in promoting clinically significant renal injury. We review the recent studies that have investigated some novel pathogenic mechanisms and the genetic background to progressive renal calcification. A review of molecular nephrocalcinosis due to overt hypercalcemia and its consequences is beyond the scope of this review.

ETIOLOGY OF NEPHROCALCINOSIS

Several novel genetic disorders have been described in association with metabolic abnormalities that predispose to the development and progression of nephrocalcinosis. Epithelial cell and paracellular disturbances in calcium transport resulting in hypercalciuria seem to be the most important, along with an increase in phosphate or oxalate, and decrease in urinary citrate excretion. In addition, in some cases specific anatomical abnormalities predispose to the development of nephrocalcinosis, for example, in medullary sponge kidney (MSK).

Recent advances in genetics have helped identify a number of transporters, channels, and receptors that are involved in regulating renal tubular reabsorption of calcium and phosphate (Table 1). Several genes involved in rare monogenic disorders have been associated with hypercalciuric nephrolithiasis with nephrocalcinosis (that is, *CLCN5*, *CASR*, *CLDN16*, *CLDN19*, *ADCY10*, *SLC34A1*, *SLC9A3R1*, *GLUT2*, *HSPG2*, and *FN1*), whereas variants of uromodulin and fetuin seem to be protective.[4–12] For example, mutations with loss of function of the calcium-sensing receptor (CaSR) have been reported in the hypercalcemic disorders of familial benign hypocalciuric hypercalcemia, neonatal severe primary hyperparathyroidism, and familial isolated hyperparathyroidism, whereas gain-of-function CaSR mutations result in autosomal dominant hypocalcemia with hypercalciuria and Bartter syndrome type V.[4,13–16] However, modest hypercalcemia *per se*, when not accompanied by hypercalciuria, seems to be insufficient to trigger nephrocalcinosis, for example, in patients with familial benign hypocalciuric hypercalcemia; only those patients with significant hypercalciuria appear to be at risk of developing renal calcium deposition.

Several additional mutations have been identified in Bartter syndrome, which usually presents with hypokalemic alkalosis, renal salt wasting, hyperreninemic hyperaldosteronism, hypercalciuria, and hypocitraturia (presumed to be secondary to hypokalemia and potassium depletion): mutations in genes encoding the loop diuretic-sensitive Na–K–2Cl (NKCC2) cotransporter, the renal outer medullary potassium (ROMK) channel, the voltage-gated chloride channel, CLC-Kb, and the CLC-Kb β-regulatory subunit, barttin.[12,17,18] Nephrocalcinosis has been described as a clinical feature in Bartter syndrome types I, II, and V (mutations in NKCC2, ROMK, and CaSR) (Table 1).

Another hereditary disorder associated with nephrocalcinosis, which is X-linked and characterized by low-molecular-weight proteinuria, hypercalciuria, and nephrolithiasis, is Dent's disease (now known as Dent-1) that is caused by a mutation in the gene for the chloride/proton antiporter 5, *CLC–5*, that regulates proximal tubular cell endocytosis.[5] In addition, the X-linked recessive disease known as the oculocerebrorenal syndrome of Lowe, or just Lowe syndrome, which is due to a mutation in the *OCRL* gene, a phosphatidylinositol 4,5-bisphosphate-5- phosphatase involved in actin polymerization, and that presents typically with congenital glaucoma, cataracts, mental retardation, as well as multiple reabsorption defects in the proximal tubule, is also associated with nephrocalcinosis and renal stones; similar to Dent-1, it can lead to renal failure. There is also a clinical variant of Lowe syndrome known as Dent-2 that presents predominantly with a renal phenotype and is similar to Dent-1.[5]

Familial hypomagnesemia with hypercalciuria and nephrocalcinosis is an autosomal recessive renal tubular disorder that is frequently associated with progressive kidney failure and recurrent urinary tract infections: it was originally linked to mutations of the claudin-16 gene (also known as paracellin-1), a member of the claudin family of membrane proteins that form the intercellular tight junction barrier in a variety of epithelia, including the thick ascending limb of the loop of Henle, the site of the defect in this disorder; although other claudin mutations (claudin-19) have also been described.[8,9]

Several disorders have been associated with homozygous and compound heterozygous inactivating mutations of the solute carrier family 34, member 3 *SLC34A3*, the gene encoding the sodium (Na^+)-dependent phosphate cotransporter 2c (NPT2c). Hereditary hypophosphatemic rickets with hypercalciuria is an autosomal recessive renal phosphate-wasting disorder leading to hypophosphatemic rickets, bowing of the legs, short stature, as well as appropriately elevated $1,25(OH)_2$ vitamin D levels, often with hypercalciuria, renal calcification, and kidney stones.[19–21] Recent studies have revealed that individuals with mutations affecting both *SLC34A3* alleles have a significantly increased risk of kidney stone formation or medullary nephrocalcinosis (46% compared with 6% observed in healthy family members carrying only the wild-type *SLC34A3* allele).[22] Renal calcification was also more frequent in heterozygous carriers compared with the general population, and it was more likely to occur in homozygous and compound heterozygous and heterozygous individuals with decreased serum phosphate, decreased tubular reabsorption of phosphate, and increased serum $1,25(OH)_2$ vitamin D levels;[22] however, there was no correlation between genotype and urinary calcium excretion.

Various genetic causes have been identified in patients with fibroblast growth factor-23–dependent hypophosphatemic disorders that usually present with significant hypophosphatemia, a decreased tubular reabsorptive threshold for phosphate, growth retardation, rickets or osteomalacia, inappropriately normal or suppressed $1,25(OH)_2$ vitamin D levels, normal serum levels of calcium, normal-to-high parathyroid hormone levels, and normal urinary calcium