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Calcium Phosphate Stones and Renal Tubular Acidosis

Viewed as a group, patients with calcium phosphate stones, or those with mixed calcium oxalate-calcium phosphate stones, tent to have a higher urinary pH than those with pure calcium oxalate stones. In addition, those with calcium phosphate stones, pure or mixed with calcium oxalate, tend to have a lower urinary citrate, hypercalciuria, and experience more frequent stone events. Some may have an "incomplete" form of distal renal tubular acidosis (dRTA), characterized by an abnormal urinary acidification response to an acid load but lacking systemic acidosis.

The ambient pH has a profound effect on the supersaturation with calcium phosphate. The dissociation to PO_4^{3-} is 11.6. PO_4^{3-} is a constituent of amorphous calcium phosphate and hydroxyapatite (HA), whereas HPO_4^{2-} is a constituent of BR. Therefore, calcium phosphate crystallization is strongly favored by a pH of 6.5 or greater, although mixed calcium oxalate/BR calcification can occur at lower pH values if the calcium concentration is high, and when the pH is 6.5 or greater even slight hypercalciuria strongly promotes BR crystallization. Above a pH of 6.8, mixtures of BR and carbonated apatite form. HA is usually formed via conversion from amorphous mixtures of BR and octacalcium phosphate, which are thermodynamically less stable precursors; conversion to HA is strongly favored by a pH of 6.9 or greater. If carbonate ions are available, as is invariably the case in urine, carbonate is incorporated into the crystalline phase, resulting in carbonated hydroxyapatite. The solubility of calcium phosphate crystals is also pH-dependent and greatly increased at pH of 6.2 or less. In general, BR is much more soluble than HA or octacalcium phosphate.

Given these considerations, it is not surprising that calcium phosphate stones are most commonly seen in patients with dRTA, a condition caused by specific defects in renal tubular hydrogen ion secretion. However, because of the solubility characteristics discussed above, stones that form in patients with dRTA often are not pure calcium phosphate but commonly contain calcium oxalate. Causes of dRTA can be hereditary, idiopathic, or secondary to a variety of conditions. The most common secondary causes are autoimmune diseases, including Sjögren's syndrome or systemic lupus. Factors that favor calcium phosphate crystallization in dRTA include the abnormally alkaline urine, hypercalciuria, and low urinary citrate concentration. The defect in urinary acidification can be incomplete, characterized by a high urinary pH and low urinary citrate but a lack of systemic acidosis. The low urinary citrate is thought to result from a combination of a decreased filtered load of citrate and increased proximal tubular reabsorption of citrate, presumably driven indirectly by the urinary loss of base. Hypokalemia and hypomagnesaemia, often associated with RTA, also stimulate proximal tubular reabsorption or citrate. Hypercalciuria can result from a systemic acidosis, if present, although idiopathic hypercalciuria is common and in many cases it may exist as a compounding independent trait (presumably in addition to the dRTA). In fact, in certain individuals, it has been proposed that hypercalciuria is a cause of a secondary dRTA, perhaps because nephrocalcinosis damages distal tubules. An incomplete form of proximal RTA has also been described in patients with hypercalciuria and stone disease, characterized by abnormal bicarbonaturia in response to a bicarbonate load. In these patients, it is speculated that transient bicarbonaturia, especially if other risk factors such as hypercalciuria are present, promotes favorable conditions for the formation of a calcium phosphate nidus.

Nephrolithiasis is common in patients with dRTA (up to 59% in on series), and conversely patients with dRTA make up a sizable percentage of those seen in stone clinics (up to 8% in one large clinic). In certain patients with dRTA, the stone formation rate can be accelerated. Nephrocalcinosis is also common, affecting as many as 55% in certain familial cases. The treatment is oral potassium citrate to indirectly increase urinary citrate excretion; a large clinical trial confirms the efficacy of this approach. In a group of dRTA patients treated with citrate, the relative supersaturation for BR increased because of a rise in urinary pH, whereas the supersaturation for calcium oxalate fell because of an increase in urinary citrate levels. Because stones associated with dRTA often contain some calcium oxalate, these data suggest that supersaturation with respect to calcium oxalate may be an important pathogenic factor in the stones that form. Urinary calcium excretion may fall with citrate administration; if not, this risk factor can be treated independently by addition of a thiazide diuretic. Urinary acidification via chronic ammonium chloride or L-methionine administration has been proposed for refractory patients with incomplete dRTA and without evidence for systemic acidosis (who typically present with pure brushite stones) because a fall in urinary pH from 6.5 to 5.5 will markedly decrease BR supersaturations. Because of concerns about long-term effects on bone, this strategy has not been widely used but is probably worthy of careful research protocols in those specific patients who do not respond well to citrate.

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